CONFIDENTIAL

A Phase 3, Multi-Arm Multi-Stage Covariate-Adjusted Response-Adaptive Randomised Trial to Determine Optimal Early Mobility Training after Stroke (AVERT DOSE)

Protocol No: 001-1
Version 5.0
Date: 15 June 2025

SPONSOR

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STUDY ACKNOWLEDGMENT/CONFIDENTIALITY

By signing this Protocol, the Principal Investigator acknowledges and agrees:

The Protocol contains all necessary details for conducting the study. The Investigator will conduct this study as detailed herein, in compliance with Good Clinical Practice[1] (GCP) and the applicable regulatory requirements, and will make every reasonable effort to complete the study within the time designated.

The Protocol and all relevant information on the treatment relating to prior clinical experience, provided by The Florey (Sponsor), will be made available to all personnel who participate in the conduct of this study. The Principal Investigator will discuss this material with all staff to assure that they are fully informed regarding the conduct of the study.

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The Florey will have access to any source documents from which Case Report Form information may have been generated. The Case Report Forms and other data pertinent to this study are the sole property of The Florey, which may utilise the data in various ways, such as for submission to government regulatory authorities, or in publication of the results of the study.

The conduct and results of this study will be kept confidential until the results of this study are published. Upon completion of the Study, it is the intention of the parties to prepare a joint publication regarding or describing the Study and all the results, and both parties shall co-operate in this regard. Where it is the intention of The Florey to file for a patent or other intellectual property right protection, publication may be deferred at the option of The Florey for up to twelve months from the date of completion of the proposed joint publication to allow The Florey to make all filings it deems appropriate.

Investigator Signatory:

PRINCIPAL INVESTIGATOR NAME AND TITLE **Signature:**

Date:

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THE FLOREY SIGNATORY NAME AND TITLE **Signature:**

Chief Investigator

Date: 15 June 2025

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Addendum 15 June 2025 Preamble

The circumstances surrounding the Covid 19 pandemic resulted in significant disruption to study recruitment to this trial. Sponsor funding is to be terminated 31 Dec 2025. Due to the complex nature of the trial and the unforeseen circumstances of the pandemic, the initial recruitment target cannot be reached. This has necessitated an apriori review of the protocol and a revised statistical analysis approach.

*This protocol will be marked up accordingly with the **addendum** details boxed and in italics to clearly describe the new approach throughout the document.*

1 Abbreviations and Definitions of Terms

ADL	Activities of Daily Living
AE	Adverse Event
AIHW	Australian Institute of Health and Welfare
AUD	Australian Dollars
AVERT	Phase 3 randomised controlled, blinded outcome trial of very early mobilisation versus standard care in acute stroke patients.[1]
BP	Blood Pressure
°C	Degrees Celsius
CFS	Clinical Frailty Scale
CT	Computed Tomography (non-contrast)
CTA	Computed Tomography Angiography
CTP	Computed Tomography Perfusion
CTRA	Clinical Trial Research Agreement
CARA	Covariate-Adjusted, Response-Adaptive
CRG	Collaborative Research Group
CRIq	Cognitive Reserve Index questionnaire
CUA	Cost Utility Analysis
DNA	Deoxyribonucleic Acid
DSMC	Data Safety and Monitoring Committee
ECR	Endovascular Clot Retrieval
eCRF	electronic Case Report Form

EQ-5D-5L	EuroQol, 5 dimensions, 5 levels questionnaire
FAC	Functional Ambulation Classification
FAS	Fatigue Assessment Scale
FMA	Fugl-Meyer Assessment
FMA-UL	Fugl-Meyer Assessment of Upper Limb
FMA-LL	Fugl-Meyer Assessment of Lower Limb
GBP	Great British Pounds
GCP	Good Clinical Practice
GISCOME	Genetics of Ischaemic Stroke Functional Outcome
GWAS	Genome Wide Association Study
HADS	Hospital Anxiety and Depression Scale
HR	Heart Rate
ICER	Incremental Cost Effectiveness Ratio
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IME	Important Medical Event
ITT	Intention to Treat
IQR	Inter-Quartile Range
LOC	Level of consciousness
MAMS	Multi-Arm Multi-Stage
MAP	Mean Arterial Pressure
MEP	Motor Evoked Potential
MEP+	Motor Evoked Potential present
MEP-	Motor Evoked Potential absent
MBS	Medical Benefits Schedule
mmHg	millimetre of Mercury
mmt	manual muscle test
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
MSAS	Mobility Scale for Acute Stroke
NZD	New Zealand Dollars

rTICI	Revised Thrombolysis in Cerebral Infarction scale
NACDC	National Aged Care Data Clearing House
NDI	National Death Index
NEADL	Nottingham Extended ADL scale
NHMRC	National Health and Medical Research Council
NIHSS	National Institute of Health Stroke Scale
NZ	New Zealand
OR	Odds Ratio
PK	Pharmacokinetic
PM	Project Manager
QALY	Quality Adjusted Life Year
QID	Four times a day
QOL	Quality of Life
RACF	Residential Aged Care Facility
RCT	Randomised Clinical Trial
REDCap®	Research Electronic Data Capture
RM	Malaysian Ringgit
SADQ-H 10	Stroke Aphasic Depression Questionnaire - Hospital Version 10 items
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGD	Singaporean Dollar
SGPALS	Saltin-Grimby Physical Activity Level Scale
SURE	Secure Unified Research Environment
SRRR	Stroke Recovery and Roundtable
SWAT	Studies within a Trial
TIA	Transient Ischaemic Attack
TMS	Transcranial Magnetic Stimulation
TOAST	Trial of ORG 10172 in Acute Stroke Treatment. (Stroke subtype Classification)
TWD	Taiwan Dollar
UK	United Kingdom
UTN	Universal Trial Number

VAS	Visual Analogue Scale
10MWT	Ten Metre Walk Test

2 Synopsis

Study Title:	A Phase 3, Multi-Arm Multi-Stage Covariate-Adjusted Response-Adaptive Randomised Trial to Determine Optimal Early Mobility Training after Stroke (AVERT DOSE)
Protocol Number:	001-1
Development Phase:	Phase 3
Indication:	Acute Stroke
Study Intervention:	Participants are randomised to one of four different prespecified Mobility training regimens. (functional task-specific sessional mobility training), provided by physiotherapists and nurses and to commence within 48 hours of stroke and for 14 days or until discharge from acute care.
No. Participants:	2,700 with potential adaptive sample size re-estimation for up to the maximum of 3,600
Addendum 15 June 2025:	
No. Participants:	*Approximately 650 mild strata 350 moderate strata (approx. 1000 total)*
No. Centres:	Approximately 50
Study Duration:	5+ years
Objectives of the Study:	To define the optimal early intervention regimens for people with ischaemic stroke of mild and moderate severity. **Primary Hypothesis** Against a pre-specified reference group, the optimal dose intervention regimen(s) will result in more participants experiencing no or little disability at 3 months post stroke. **Secondary Hypotheses** Against a pre-specified reference group, the optimal dose intervention regimen(s) will result in: • Fewer deaths at 3 months

	• Participants experiencing fewer and less severe complications during the intervention period • Increased unassisted walking 50 metres and walking speed at 3 months • Better quality of life at 3 months *and* • More cost-effective care at 6 months
Study Endpoints:	**Primary Outcome** Proportion of participants achieving a favourable outcome of no or little disability (mRS[2] score 0-2) at 3 months post stroke. **Secondary Outcomes** *Safety/medical complications.* All complications during 14-day intervention period Immobility-related and stroke-related complications up to 3 months Serious Adverse Events up to 6 months *mRS outcome at 3 months across the full ordinal scale.*[3] *Recovery of unassisted walking 50 metres and walking speed* *Quality of life* The EQ-5D at 3 and 6 months *Economic evaluation* Unit costs will be obtained from each participating country and applied to patient-level data collected within that country.
Study Design:	Multi-Arm Multi-Stage Covariate-Adjusted Response-Adaptive Randomised Trial of 4 acute mobility training regimens in the first 14 days post randomisation. Blinded outcome analysis.
Addendum 15 June 2025:	
Study Design	*Multi-Arm, Covariate-Adjusted Response-Adaptive Randomised Trial of 4 acute mobility training regimens in the first 14 days post randomisation. Blinded outcome analysis.*
Eligibility Criteria	**Inclusion** Patients admitted to a stroke unit with: • Ischaemic stroke (first ever or recurrent) • Aged ≥ 18 years

	• Ability to be enrolled within 48 hours of the onset of stroke symptoms. • Mild (NIHSS 0-7) or moderate stroke severity (NIHSS 8 ≤ 16) • Pre stroke mRS of 0 – 2 • Participants are medically stable at time of recruitment • Participants may receive thrombolytic and/or ECR **Exclusion** • Pre-stroke mRS of 3, 4 or 5 (indicating moderate to severe pre-morbid disability) • Diagnosis of haemorrhagic stroke or transient ischaemic attack • Severe stroke (NIHSS > 16) • Co-morbid progressive neurological conditions • Severe heart failure, unstable coronary condition or any other condition that is judged by the investigator to impose a hazard to the participant if involved in the trial (Including COVID 19). • Concurrent diagnosis of rapidly deteriorating disease (e.g. terminal cancer) • Deterioration following admission, resulting in palliation or immediate surgery • A lower limb fracture/disability resulting in the participant unable to take part in mobility training • Patients with no evident mobility problems • Patients expected to be discharged within 3 days post enrolment. • Current participation in a drug or other intervention trial
Study Procedures:	Baseline assessments and trial interventions provided during acute hospitalisation post stroke. Patients will be followed up at 3 and 6 months by an assessor who has been blinded to treatment arm and may occur in the clinic, the community or by telehealth if required.
Sample Size Determination:	Using the probabilities of favourable outcome observed in AVERT data for the different doses proposed in this study, extensive simulations have been run for Mild and Moderate stroke severity strata to identify the sample sizes to yield 80% power to observe 10% absolute treatment effects or larger compared to a pre-specified reference group in both severity strata (assuming 70% incidence of favourable

	outcome in a pre-specified reference group in both severity strata assuming Bonferroni corrected one-sided alpha family-wise threshold p=0.025 per stratum. Recruiting 1300 participants in Mild stratum and 1400 participants in Moderate stratum would yield 80% power. Adaptive sample size re-estimation will be undertaken for individual strata using Mehta and Pocock promising zone methodology with a potential increase of up to the maximum of 1600 participants for Mild stroke stratum and 1900 participants for Moderate stroke stratum.
Addendum 15 June 2025:	
Sample size determination	*Given significant disruption to study recruitment, current recruitment numbers and termination of funding, (31 Dec 2025) there will be insufficient numbers of participants to execute the pre-planned adaptive sample size re-estimation and/or achieve the pre-planned sample size. Recruitment to the study will proceed until to the 30 November 2025 when recruitment will be terminated.*
Statistical Analyses:	**Primary** The mRS scores at 3 months will be dichotomised, with scores of 0-2 reflecting 'favourable outcome' and scores of 3-6 reflecting 'poor outcome'. In our primary analysis we will use the randomisation-based analysis with permutation test of the difference between the single intervention arm selected to proceed to Stage 2 and the pre-specified reference arm individually for each stratum (stratum-specific one-sided family-wise p=0.025). The non-parametric permutation or randomisation tests used for analysis in proposed adaptive design, test the null hypothesis that the assignment of treatments has no effect on the responses (outcome) of the participants in the study. The effect sizes will be reported as risk differences between the probabilities of a favourable outcome. In case the same treatment regimen appears optimal in both strata, a pooled risk difference measure will be derived using Mantel-Haenszel method. **Secondary** analyses will be conducted using regression modelling. Despite the adaptive nature of the randomisation used in AVERT DOSE, maximum likelihood estimations using, e.g.Wald test, can be applied if the appropriate correction for potential estimation bias is undertaken. Full dose-response exploratory analyses will be conducted across all dose regimens.
Addendum *15 June 2025*:	

Statistical Analyses:	***Primary*** *The mRS scores at 3 months will be dichotomised, with scores of 0-2 reflecting 'favourable outcome' and scores of 3-6 reflecting 'poor outcome'. In our primary analysis we will use the randomisation-based analysis with permutation tests of the differences between every individual intervention arm and the pre-specified reference arm for each stratum. According to FDA Guidance for Industry for Master Protocols[85], the use of multiplicity adjustments to strongly control Type I error across the multiple comparisons of different treatments to the control in an umbrella or platform trial is not recommended, hence within each stratum comparisons of every individual intervention arm and the pre-specified reference arm will be conducted independently. The non-parametric permutation or randomisation tests used for analysis in proposed adaptive design, test the null hypothesis that the assignment of treatments has no effect on the responses (outcome) of the participants in the study. The effect sizes will be reported as risk differences between the probabilities of a favourable outcome. In addition, frequentist confidence for benefit and for lack of meaningful benefit (futility) compared to the reference arm will be estimated for every individual intervention arm[86]* *Secondary analyses will be conducted using regression modelling. Full dose-response exploratory analyses will be conducted across all dose regimens.*
Sub Analyses	Genetics (in selected countries) Data Linkage (in selected countries) Cognitive Reserve (Countries with CRIq validation only)

3 Introduction and Background

Stroke is a major cause of severe adult disability. It is also the second most common cause of death worldwide with 85% of all strokes now occurring in low- to middle-income countries.[4] For treatments to have any major impact on the burden of stroke, they must be widely accessible, appropriate, safe, effective and cost-effective in the vast majority of patients.[5]

Effective stroke treatments applicable to most people with stroke include early aspirin for ischaemic stroke followed by care in a stroke unit. Effective interventions that are only applicable to selected populations include thrombolysis (applicable to about 20% of patients) and, very recently, intra-arterial clot retrieval (applicable to about 10% of these patients). Whilst these acute interventions can dramatically improve outcomes in selected patients, rehabilitation remains the most broadly applicable treatment for all stroke survivors regardless of where they live in the world, particularly in the early post acute phase (<14 days). Yet the evidence base for rehabilitation is inadequate. As a consequence there are major differences among international guidelines.[6] In current National Stroke Care Standards[7], no specific type or dose of rehabilitation could be set as a national standard. We urgently need to know the most effective and safe rehabilitation intervention to recommend for the vast majority of people disabled by acute stroke.

Mobility-focused rehabilitation (often referred to as mobilisation) is aimed at promoting return of walking function, prevention of immobility-related complications and secondary negative changes, such as loss of cardiovascular fitness, muscle wasting and reduced respiratory function.[6] It is a relatively simple, broadly applicable intervention that can be started soon after stroke, making it suitable for adoption in both high and low-to middle-income countries. Further, it is biologically plausible that an early start to intervention will promote better recovery due to the existence of a period of heightened brain plasticity early post stroke.[8] In our 2015 comprehensive review of evidence and practice in this field[6] we found that while 'early rehabilitation/mobilisation' (starting from ≤72 days versus >3 days, or ≤7days or > 7 days) was recommended in 22 global clinical practice guidelines, the recommendations were underpinned by low level evidence, varied widely and lacked detail, with the dose (amount and frequency) of intervention rarely noted. Before AVERT there was no reliable large RCT evidence to underpin recommendations in the acute phase of care.

3.1 A Very Early Rehabilitation Trial (AVERT)

In 2015, we completed the first global randomised controlled early stroke rehabilitation trial (AVERT), to define the effect of commencing a more intensive (both more frequent, up to 8 times daily; and greater amount, up to 20 minutes/session) mobility intervention, very early (<24 hours post stroke) which had shown promising early results in small phase II trials. AVERT was a pragmatic, investigator-led, phase III trial conducted in 5 countries (Australia, New Zealand (NZ), United Kingdom (UK), Malaysia, Singapore), and included 2104 participants. The inclusion criteria for AVERT were kept deliberately broad to increase generalisability[9] and led to recruitment of a highly representative patient sample which included 26% of participants over the age of 80 years, 45% with moderate and severe stroke, and 24%

treated with thrombolysis.[10] Participants were randomised to receive either usual care (not standardised), or the high intensity mobility training (mobilisation) *in addition to usual care* (termed 'Very Early Mobilisation'). The intervention was guided by a written protocol and delivered by trained physiotherapy and nursing staff. The intervention lasted 14 days or until discharge, whichever was sooner. All mobilisation activities were recorded and the data quality from the trial was exceptional with low drop outs (<1% at 3 months). The trial contributed the first high quality, reliable evidence to help guide us toward evidence-based early treatment. The AVERT results provided vital new knowledge about what we should not do (high intensity, high amount of mobilisation - see below), and generated important questions about how to apply the intervention, and who should be targeted to receive intervention early after stroke onset. These questions are highly relevant to participants and clinicians and are essential to answer definitively in order to establish clear intervention protocols and evidence-based clinical guidelines.

3.2 Top line AVERT results and how they inform AVERT DOSE

The primary AVERT results showed evidence that a very early *intensive program in addition to usual care* reduced the odds of a favourable outcome (modified Rankin Scale, mRS 0-2) at 3 months.[10] Our pre-specified dose-response analyses[11] showed that frequency of sessions and amount of mobility training, not hours post stroke that rehabilitation started, were the most important considerations in treatment early after stroke. The pre-specified sub-group analysis, although underpowered, showed signal of harm mainly in participants with severe stroke (National Institutes of Health Stroke Scale[12], NIHSS > 16) and those with intracerebral haemorrhage (ICH).

The pre-specified safety analysis[13] for AVERT showed that while the number of deaths from stroke were low in the first 14 days (3.8%), 16 more deaths occurred in the early intensive mobility training group compared to usual care[14] which was significant, with deaths occurring earlier with early intensive mobility training.[14] These findings could be due to harmful instability of the cardiovascular system in a sub-group of patients and highlighted the importance of developing clear, safe treatment protocols in this early time period.

It found that lower dose training, started within 48 hours post stroke and delivered over more sessions was associated with increased odds of less disability (mR0-2), and reduced odds of death.[11] For example, increasing the amount (every 5 additional minutes) of mobilisation per day reduced the odds of a good outcome (OR 0.94, 95% CI 0.91- 0.97, p<0.001), while increased daily frequency of out of bed sessions, improved the odds of a favourable outcome (OR 1.13, 95% CI 1.09-1.18, p<0.001).[17] This knowledge informs the intervention regimens proposed for AVERT DOSE (see Section 7).

Our data indicate that patients with severe stroke are not the target for early mobility rehabilitation and they appear to respond best to a more conservative, individualised approach. These patients will be excluded from AVERT DOSE. Patients with haemorrhagic stroke will also not be recruited. These represent a small proportion of

stroke patients (12%) and add heterogeneity due to differing pathology and outcomes. The trial outcome may lack clarity if these patients are included.

4 What is the Most Important Current Challenge?

The results of AVERT radically changed our understanding about early intervention and the potential outcomes for patients if we get the treatment right (or wrong). The robust findings of AVERT strongly suggest that the current 'more is better' mantra advocated by many[15, 16] may not apply early post stroke. Furthermore, given that 22 clinical practice guidelines now recommend early rehabilitation (but without clear evidence informed to inform these) it is quite possible that harmful early protocols are already the norm in some countries.[17]

We now need to fully define the intervention regimens that provide most benefit. Because of the size, scope and detailed nature of the data collected in AVERT, we have the opportunity to determine the optimal treatment regimens for those who will benefit most from standardised early treatment protocols: patients with mild to moderate stroke severity. Importantly, we now have novel trial techniques whereby this can be achieved within our established global clinical trial network.

5 Aims and Hypotheses

5.1 Primary

The main **aim** of this study is to define the optimal early intervention regimens for people with ischaemic stroke of mild and moderate severity.

We **hypothesise** that against a pre-specified reference group, the optimal dose intervention regimen(s) will result in:

- More participants experiencing **favourable outcome** (mRS 0-2) at 3 months.

5.2 Secondary

We **hypothesise** that against a pre-specified reference group, the optimal dose intervention regimen(s) will result in:

- Fewer deaths at 3 months
- Participants experiencing fewer and less severe complications during the intervention period (< 14 days post randomisation)
- Increased unassisted walking 50 metres and walking speed at 3 months
- Better quality of life at 3 months *and*
- More cost-effective care at 6 months

5.3 Tertiary

Five studies within a trial (SWAT) will also be conducted alongside the main trial. These studies will examine: Genome Wide Association analysis and stroke recovery (Appendix A); long term stroke service usage using data linkage (Appendix B); and prior cognitive reserve and favourable outcome (Appendix C);

6 Study Design

The study is an international, multi-centre, dose-finding, **Multi-Arm** (three intervention arms and a pre-specified reference group), **Multi-Stage, Covariate-Adjusted, Response-Adaptive (MAMS CARA) randomised trial with blinded outcome assessments at 3 and 6 months post stroke.** The trial is adequately powered to identify the best intervention regimen for individuals with both mild and moderate stroke severity.

6.1 Multi-Arm Multi-Stage Covariate-Adjusted Response-Adaptive Randomised Trial

The MAMS CARA design is outlined in detail below and illustrated in Figure 1. The design allows us to test multiple promising intervention regimens at trial start, with the treatment effects (favourable outcome, mRS 0-2) of each intervention regimen dynamically informing the probability of allocation of participants to subsequent interventions as the trial progresses in an automated and pre-specified manner.[18] In the final analysis, the best identified intervention regimen is compared to the reference group. Assessment will be blinded and analysis will be intention to treat.

Adaptive designs are both ethical and efficient and ideally suited to this study in which we aim to identify the optimal intervention regimen(s) from four treatment regimens. While AVERT DOSE represents the first use of the design in rehabilitation (and one of a handful of such trials in stroke), it has been used very successfully in other populations including cardiovascular disease and cancer.[19] An adaptive design uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial.[18, 20] These designs differ from conventional RCTs where there is a fixed randomisation proportion.[21] Adaptive design methods have greater flexibility without compromising trial rigour.[19, 22] MAMS CARA RCTs integrate three separate components: the Multi-Arm Multi-Stage component, Covariate-Adjusted Randomisation component, and the Response-Adaptive Randomisation component.

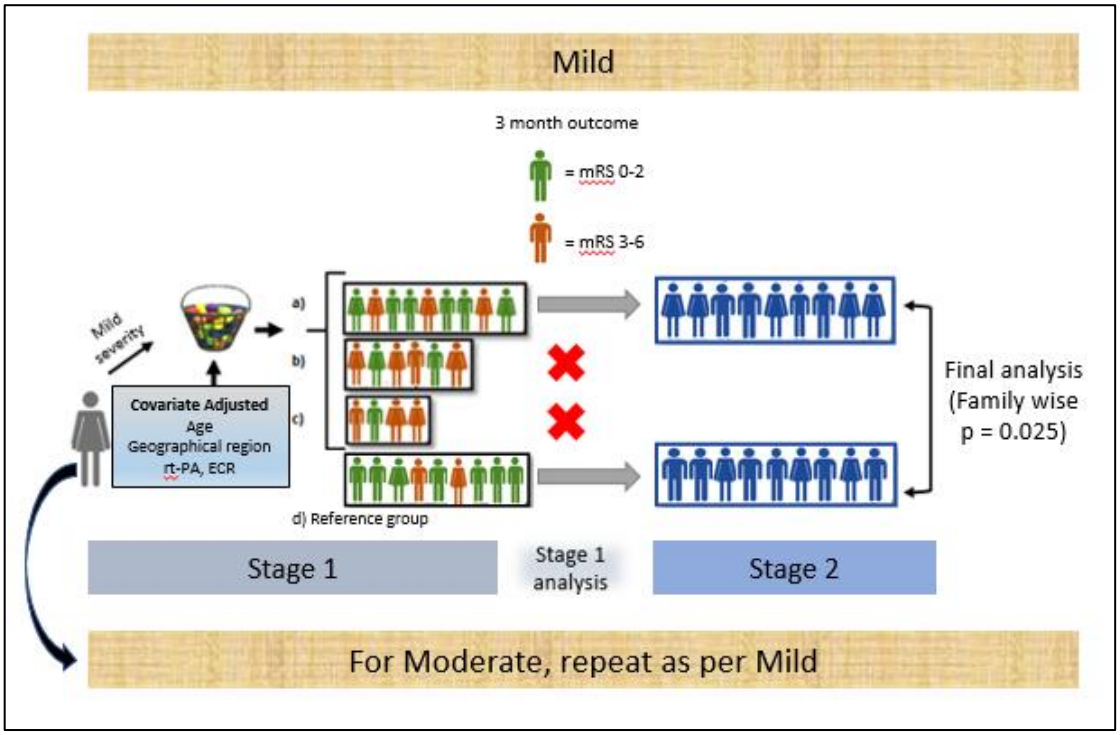

Figure 1. In this figure good outcome on the mRS is shown in Stage 1 with green figures, poor outcomes with red figures. In this example, treatment (a) is more beneficial in outcome (more participants achieve mRS 0-2; no or little disability at 3 months) and so the number of participants allocated to this group is increased. This process occurs iteratively as new outcomes become known. Following Stage 1 analysis, the best performing group will be compared to the reference group in Stage 2.

6.1.1

Multi-Arm Multi-Stage Component

The Multi-Arm Multi-Stage design (originally proposed by Royston et al [23, 24] has a number of benefits over more conventional approaches to treatment evaluation in the situations where multiple treatment arms are evaluated with the intention to eliminate poorly performing contenders at a first stage. AVERT-DOSE will use the two-stage design, where only the single treatment arm demonstrating the highest proportion of favourable outcome at the first stage will be allowed through to the second stage of patient accrual, culminating in the comparison against reference arm at the end of the trial. For both individual Mild and Moderate stroke severity strata, the end of the first stage is pre-defined as the time point when the primary outcome is available for 700 participants recruited into individual strata.

Addendum 15 June 2025:

6. Study Design

The study is an international, multicentre, dose finding Multi Arm (three intervention arms and a pre specified reference group), Covariate adjusted, response adaptive randomised trial with blinded outcome assessments at 3 and 6 months post stroke.

6.1 Multi Arm, Covariate Adjusted, Response Adaptive Randomised Trial

The amended Multi-Arm Single Stage CARA design is outlined below and illustrated in Figure 1a. The design allows us to test multiple promising intervention regimens at trial start, with the treatment effects (favourable outcome, mRS 0-2) of each intervention regimen dynamically informing the probability of allocation of participants to subsequent interventions as the trial progresses in an automated and pre-specified manner.[18] In the final analysis, within each stratum, every individual intervention regimen is compared to the reference group. Assessment will be blinded and analysis will be intention to treat.

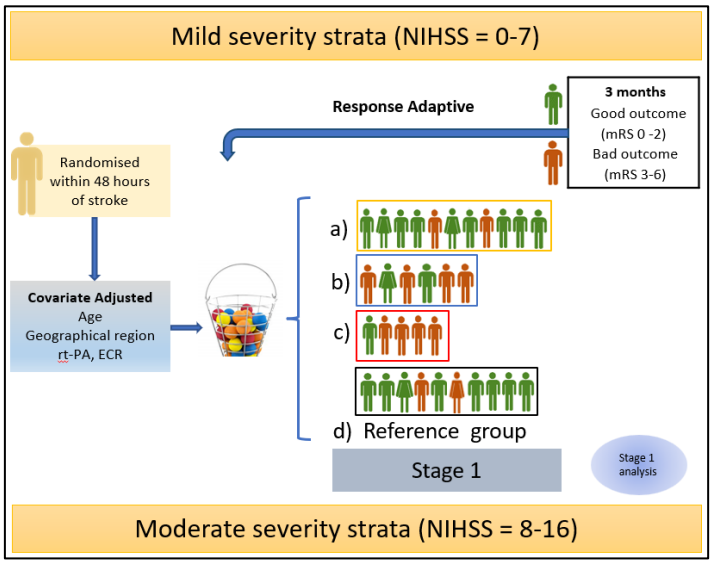

Figure 1a. *In this figure good outcome on the mRS is shown in Stage 1 with green figures, poor outcomes with red figures. In this example, treatment (a) is more beneficial in outcome (more participants achieve mRS 0-2; no or little disability at 3 months) and so the number of participants allocated to this group is increased. This process occurs iteratively as new outcomes become known.*

6.1.2

Covariate-Adjusted Randomisation Component

The covariate adjusted randomisation reduces the covariate imbalance of the treatment groups and is also known as *adaptive stratification*. There are four prognostic factors which are known *a priori* to influence stroke outcome: stroke severity, age, geographic region of care and reperfusion interventions (thrombolytic, Endovascular Clot Retrieval (ECR)). Because of the utmost importance of stroke severity, our trial is designed to explicitly stratify participants into mild (NIHSS 0-7) and moderate (NIHSS 8-16) stroke strata with individual power to identify the desired effect in both strata (see Section 13.2 Sample Size). Other three prognostic covariates of age, geographic region and reperfusion interventions will be used to inform the adaptive randomisation procedure that will be implemented as per Pocock-Simon's model (1975).[25] This model involves modifying the probability of the covariate adaptive randomisation over time according to the cumulative information about baseline covariates and treatment assignments.

Response-Adaptive Randomisation Component

Because of the dose-finding nature of AVERT DOSE, the trial will commence with three intervention arms and one reference arm per severity strata and the final comparison will comprise the best arm together with the reference arm.

6.1.3 ***Addendum 15 June 2025:***

6.1.3 Response – Adaptive Randomisation Component

Because of the dose-finding nature of AVERT DOSE, the trial will commence with three intervention arms and one reference arm per severity stratum.

Response-adaptive randomisation is an automated randomisation technique in which the allocation of participants to treatment groups is based on the 3 month response/outcome of previous participants (see Figure 1). It serves the very important and ethical purpose of providing the next participant to be randomised with better treatment based on the knowledge of the treatment effect at that moment. Assuming that some regimens are superior, a response-adaptive design reduces harm (and increases benefit) to participants in the trial compared to conventional fixed randomisation. This is because as data accrues, newly randomised participants are more likely to receive the dose arm that is achieving better outcomes, at that time of the trial. The rules for dynamically assigning more or fewer participants into specific intervention arms are fully pre-specified at the design phase. Some arms therefore become larger or smaller. Importantly these are treated algorithmically without the need of direct human involvement during the running of the RCT (as per Chang's Multi-Arm Response-Adaptive Randomisation with Binary Endpoints[18]). This means that the researchers are blind to treatment allocation and cannot influence trial conduct. An attractive feature of AVERT DOSE is that the proposed adaptation is based on responses collected at 3 months post stroke, thus generating a delay in adaptation. Since all response-adaptive randomisation procedures are dependent on estimation of unknown parameters, it is often proposed that a response-adaptive RCT would first randomise a given number of participants with equal allocation, and only then start the response-adaptive randomisation process.[22] Our 3 month delay in response-adaptation for AVERT DOSE will perform the function of such a proposed stability buffer, reducing the possibility of major changes to the recruitment patterns very early in the running of the trial and allowing for a reasonable number of participants to be recruited in all groups (i.e. keeping all groups open early in the trial) before any adaptation is commenced.

The design strongly minimises the following potential biases:[26]

(1) accrual bias: when volunteers delay their involvement in a study to take advantage of improved outcome.[27] This is not possible with AVERT DOSE in which we recruit participants ≤48 hours of stroke;

(2) accidental bias: due to unbalanced treatment assignments. This is minimised by the covariate-adaptive randomisation model selected for AVERT DOSE;

(3) selection bias: is introduced into studies when an investigator can guess, and influence, the treatment assignment of future participants. In our design, selection bias is not possible (see above).

Randomisation Method

6.1.4 The Florey Institute of Neuroscience and Mental Health is an institutional partner with Research Electronic Data Capture (REDCap®),[28] a secure, web-based application designed to support data collection and management for research studies, that will be used for this trial. A separate adaptive randomisation module algorithmically combining covariate adjustment with response adaptation in intervention arms was implemented within REDCap®'s Application Programming Interface and tested through extensive simulations to ensure adequate between-arms balance is achieved. For both Mild and Moderate stroke severity strata, at the first stage of the trial, 25% of patients will be randomised into a reference arm, while the randomisation into intervention arms will be guided by the adaptive algorithm. At the second stage of the trial, randomisation into the reference arm and the single selected intervention arm will be guided by the adaptive algorithm.

Allocation Concealment

6.1.5 Allocation concealment will be achieved using REDCap®. If the site experiences a problem accessing REDCap® a centralised randomisation can be performed by contacting the trial manager who will arrange a remote manual randomisation to occur.

6.1.6 **Blinding**

Participants will be allocated to one of the four groups of mobility training without the knowledge of what the reference group comprises. Participants and family/carers will not be told of the group allocation. Trial physiotherapists and nurses will be aware of their group allocation as they are delivering the interventions but they will be blinded to which group comprises the reference group and which is the predicted optimal group. Other ward staff will not be told of group allocation so as to not bias usual processes of care. Trial staff will not record the daily dose schedule on the participant's medical record. Blinding of the outcomes assessor will be maintained by using off-site trained assessors to collect all outcome data.

6.1.7 All MAMS CARA processes and thresholds are fully pre-specified. An independent unblinded statistician from Florey Statistics and Decision Analysis Program, different to the study statistician, will monitor the performance of the randomisation process. As the trial progresses, trial staff will not be able to identify reference or optimal group as adaptive randomisation will occur by region, not by site. The Data Safety and Monitoring Committee will be unblinded.

Contamination

Contamination of stroke unit physiotherapy and nursing practice will be minimised as details of the intervention protocol will not be made publicly available. The Intervention

Protocol (001-2) is confidential and only available to staff responsible for delivering and monitoring the trial intervention.

7 Intervention

Once screening, consent and baseline assessments are complete, participants will be randomly allocated with the CARA method into one of four groups within the mild or moderate stroke severity strata, one of which in each strata will be the reference group.

- Participants stratified to the mild stroke severity will be those with a baseline NIHSS score (at the time of randomisation) of 0-7.
- Participants stratified to the moderate stroke severity will be those with a baseline NIHSS score (at the time of randomisation) of 8-16.

7.1 Description of Intervention

Interventions will commence at the time of randomisation (within 48 hours of stroke onset) and continues for 14 days or until discharged, whichever is sooner for each participant. Interventions will be provided by trained physiotherapists and nurses who will work together to provide mobility training sessions during the intervention period. Intervention regimens are detailed in the AVERT DOSE Intervention Protocol 001-2. The Intervention Protocol will only be provided to trial nurses, physiotherapists and where needed for trial evaluation (e.g. ethics committees). The underlying principles of the mobility training interventions delivered in this trial are: functional and task-specific mobility training, characteristics of training approaches with the most evidence of benefit.[29] Interventions will mostly be applied at or near the bedside and within the stroke unit or surrounds.

Interventions will be recorded on the electronic Case Report Forms (eCRF) in REDCap®. Data collected will include number and type of staff involved, time session commenced, type of mobility training activity, therapy intensity of therapy provided and minutes in therapy. Data will also be submitted each time a session cannot be provided.

All intervention regimens will be delivered as per protocol for all enrolled participants, instead of what would normally be provided as usual care**,** i.e. the allocated trial intervention becomes the mobility training regimen for the participant. One of the mobility training treatment groups is a pre specified reference dose informed by AVERT trial data. The AVERT DOSE intervention will be delivered in conjunction with mobility for personal hygiene purposes (e.g. showering, toileting) but not on top of any other type of routine mobility interventions provided by physiotherapists/ nurses.

The replacement of usual physiotherapy mobility training with AVERT DOSE training regimens provides us with the best chance of identifying the optimal treatment approach in this trial. The intervention will be deeply integrated with other routine ward care.

7.2 End of Intervention

The intervention will continue until the participant is discharged from the stroke unit or 14 days post randomisation, whichever is earlier. The participant may be discharged from the stroke unit to home, transferred to inpatient rehabilitation, or transferred to another ward, hospital or residential care. Contact details for the participant will be collected prior to the end of intervention, to allow the blinded assessor to follow up the participant at their place of residence.

Other reasons for end of intervention may include palliation or death. End of intervention information will be collected, with the reason for end of intervention documented. All available information will be documented and submitted. Participation in the trial intervention may be terminated if consent is withdrawn, or if the participant's safety is deemed to be at risk by the investigators. A participant may dropout of the treatment phase, but will continue to be followed up in the trial unless the participant also withdraws consent for follow up. If a participant cannot be contacted (lost to follow up), health care data will be retrieved from the participants GP and or medical files.

7.3 Dose Considerations

Our dose-response analyses[11] showed that frequency of sessions and amount of mobility training were the most important considerations in treatment safety and efficacy early after stroke. This can be conceptualised as finding different treatment effects of the 'therapy drug' when given once a day in a higher or lower dose, given in a bolus (all at once) or given 4 times a day (QID). We analysed data from 1813 AVERT participants with mild and moderate stroke severity and examined the probability of having no or little disability (mRS 0-2) at 3 months post stroke as a function of intervention dose (average minutes of total therapy per day) and frequency (average number of therapy sessions per day). These analyses, together with the results of the pre-specified dose-response analyses, which included CART[11], provided a solid foundation to select the dose regimens for this trial.

7.4 Comparator Justification

The reference dose is based on an extensive analysis of intervention and outcome data from the AVERT trial (unpublished). The comparator or reference dose has been chosen, documented and secured prior to trial commencement by the trial Statistician. The reference dose will remain confidential and will not be known to any investigators during the trial (blinded comparator).

7.5 Unblinding

As a single blind trial, group allocation will be known to the therapists and nurses. Allocation of treatment will be known by selected members of the research team including the statistician.

7.6 Therapy Fidelity

Evaluation of intervention fidelity is an important aspect of the trial protocol.[30] We will report two components of intervention fidelity. Firstly, the component delivered by the

researchers education and training of staff, and secondly, the adherence by therapists and nurses to the planned intervention by group.

A record of all education and training provided to relevant physiotherapists and nurses will be maintained.

For all staff involved in mobility training with participants, a peer reviewed assessment will be undertaken by the main investigator or delegate. The staff member will complete the training session with the participant and complete the therapy recording form for the session. The main investigator/delegate will observe the training session and complete a therapy recording form for the session. These will be submitted to the research team for review and feedback to the staff. Throughout the trial, peer assessment will be randomly undertaken with the goal of monitoring 5% of all therapy sessions.

All mobility sessions will be documented in detail on a therapy recording form, for the time, type and intensity of the session which is subsequently transcribed into REDCAP®. These data will be centrally reviewed for adherence to the protocol and feedback provided to site staff on a regular basis. The trial monitors will visit sites on a regular basis and where issues with fidelity are identified, additional training and peer reviewed sessions will be conducted.

8 Study Population

8.1 Number of participants

Using the probabilities of mRS 0-2 outcome observed in AVERT data for the different doses proposed in this study, extensive simulations have been run for Mild (National Institute of Health Stroke Scale[12] (NIHSS), 0-7) and Moderate (NIHSS 8-16) stroke severity strata to identify the sample sizes to yield 80% power to observe 10% absolute treatment effects or larger compared to a pre-specified reference group in both severity strata (assuming 70% incidence of mRS0-2 in a pre-specified reference group in Mild stroke stratum and 30% incidence of mRS0-2 outcome in a pre-specified reference group in Mild stroke stratum).

Recruiting 1300 participants in Mild stratum and 1400 participants in Moderate stratum would yield 80% power to identify individual within-strata absolute effects of this magnitude assuming Bonferroni corrected one-sided alpha family-wise threshold, p=0.025 per stratum.

Adaptive sample size re-estimation will be undertaken for both individual strata using Mehta and Pocock[31] promising zone methodology at the end of Stage 1 (i.e. once the mRS0-2 at 3 months outcomes of 700 patients from a given stratum become available) based on the comparison between the reference group and the single intervention group selected to proceed to Stage 2, with a potential increase of up to the maximum of 1600 participants for Mild stroke stratum and 1900 participants for Moderate stroke stratum.

Addendum 15 June 2025:

8. Study Population

Given significant disruption to study recruitment, current recruitment numbers and termination of sponsor funding on 31 Dec 2025 it is not anticipated that the study will recruit sufficient numbers of participants to execute the pre-planned adaptive sample size re-estimation and/or achieve the pre-planned sample size. Therefore, recruitment to the study will proceed until the 30 November 2025 when recruitment will be terminated (Last Patient First Visit). The outcomes for all recruited participants will be included in the analyses based on the ITT principles.

8.2 Region of participants

Participants will be recruited from various geographic regions including Australasia, UK/Europe, South America, India and South East Asia. Our aim is to recruit no more than 40% of the total number of participants from any one region to ensure generalisability of results.

Hospitals with a geographically located stroke unit will be selected for participation in this study.

8.3 Inclusion Criteria

Patients admitted to stroke unit with:

- Ischaemic stroke (first ever or recurrent)
- Aged ≥ 18 years
- Ability to be enrolled within 48 hours of the onset of stroke symptoms. (Stroke onset is defined as the date and time the patient was known to be symptom free)
- Mild (NIHSS 0-7) or moderate stroke severity (NIHSS 8 ≤ 16)
- Pre stroke mRS of 0 – 2
- Participants are medically stable at time of recruitment (i.e. meet physiological criteria: (participant rousable, SBP > 120 mmHg and < 180 mmHg, O_2 saturation > 92%, HR > 40 and < 100, and temperature < 38.5ºC).

8.4 Exclusion Criteria

Patients with:

- Pre-stroke mRS of 3, 4 or 5 (indicating moderate to severe pre-morbid disability)
- Diagnosis of haemorrhagic stroke or transient ischaemic attack
- Severe stroke (NIHSS > 16)
- Co-morbid progressive neurological conditions
- Severe heart failure, unstable coronary, or any other condition that is judged by the investigator to impose a hazard to the participant if involved in the trial (including COVID 19)
- Concurrent diagnosis of rapidly deteriorating disease (e.g. terminal cancer)
- Deterioration following admission, resulting in a documented clinical decision for palliative treatment, or immediate surgery

- A lower limb fracture or other disability which deems the participant unable to participate in mobility training
- Patients with no evident mobility problems
- Patients expected to be discharged within 3 days of trial enrolment
- Current participation in a drug or other intervention trial

Notes.

- Participants may receive thrombolytic and/or ECR by 48 hours post stroke
- Participants may be included in observational trial/s (i.e. no intervention provided) with approval by the trial sponsor.
- Participants can be included if they are admitted via intensive care or other hyper acute unit as long as there are plans for transfer to the acute stroke unit within 48 hours of stroke.
- Time of onset for wake up strokes will be taken from when the patient was last seen well.

9 Study Assessments and Procedures

The schedule for trial assessments is located in Appendix F. All collected data will be entered via the eCRF using REDCap®.

9.1 Screening Evaluation

All patients with a clinical diagnosis of ischaemic stroke, with mild or moderate stroke severity (NIHSS 0-16) admitted within 48 hours will be screened for trial eligibility. The reason why a patient is not eligible according to the exclusion criteria will be collected for trial reporting purposes. Minimal details relating to the reason why the patient was not recruited will be collected on the screening logs to enable reporting of generalisability of the study population. Screening data collected will be non identifiable. Where a patient is deemed eligible and has provided informed consent, they will be enrolled in the study and proceed to baseline.

9.2 Study Procedures

Baseline Day 0-3 (0-72 hours post stroke)

Baseline stroke and demographic data will be collected including date of birth and time of stroke onset and admission to hospital, geographical region, treatment with thrombolytic and or ECR, current stroke data, and previous medical history. These baseline data will be entered on AVERT DOSE Online prior to randomisation. Randomisation will occur using REDCap®. Assessments include:

- Baseline NIHSS assessment (Appendix G) will be performed by an investigator holding current certification.
- Admission NIHSS assessment (Appendix G) obtained from the medical record at the time of admission to hospital (retrospective) will be performed by an investigator holding current certification.

- Pre-morbid and baseline mRS scores (Appendix H) will be assessed by an investigator currently certified to perform this assessment.
- The Mobility Scale for Acute Stroke (MSAS, Appendix I)[32]
- For participants who have received thrombolytic or have had ECR, the revised Thrombolysis in Cerebral Infarction (rTICI, Appendix J) score will be recorded.
- Other clinical information such as side of stroke, first or recurrent stroke, risk factors for stroke and other conditions and premorbid walking status will be obtained from the medical records.
- Demographic information such as living arrangements and formal education will be collected from the participant.
- The motor component for the Fugl-Meyer Assessment (FMA) of Upper Limb (FMA-UL, Appendix K) and Lower Limb (FMA-LL, Appendix L) will be performed in patients recruited prior to 1 July 2024
- Participant will be asked to complete Trail Making A[33] and Line Bisection[34] to assess attention and neglect (Appendix W) in patients recruited prior to 1 July 2024.
- Physiological measurements for first mobility session will be conducted according to the AVERT DOSE Intervention Protocol 001-2.

9.2.2 Intervention Period (Up to 14 days post randomisation or discharge)

- All routinely ordered imaging data undertaken during the intervention period will be acquired for participants recruited prior to 1 July 2024. This may include computed tomography (CT), computed tomography angiography (CTA), perfusion (CTP) and magnetic resonance imaging (MRI).
- Physiotherapists and nurses will provide the intervention training according to group allocation, from the time of randomisation up until day 14 post randomisation or discharge, whichever is earlier.
- For the first three days of mobility training post randomisation, physiological measures of temperature, blood pressure, mean arterial pressure (MAP), heart rate and oxygen saturation will be taken prior to, during and after mobility training for the first session of the day. The use of beta blockers, calcium channel blockers and angiotensin-converting enzyme inhibitors will be recorded. If the participant has mobilised out of bed prior to consent and randomisation, these will be documented. If the participant is medically unstable and mobility training cannot commence, the pre training measures will be taken and recorded. Assessments will continue each day, until there are three days of physiological observations. Further details can be found in the AVERT DOSE Intervention Protocol 001-2.
- If applicable, the date that the participant was able to walk 50 metres unassisted will be recorded.
- Pre stroke physical activity measured using the Saltin-Grimby Physical Activity Level Scale (SGPALS, Appendix M).[35, 36]
- The participants Pre morbid Clinical Frailty Score will be assessed (Appendix X)
- MSAS (walking section) assessment will be performed on day of discharge (Appendix I).
- The Ten Metre Walk Test (10MWT)[37] will be performed on participants who are supervised or independent walkers on the day of discharge.

- TOAST (classification of subtype of acute ischaemic stroke)[38] will be obtained (Appendix N)
- Contact details will be obtained in order for the blinded assessor to follow up the participant, including details of a relative or friend who does not live in the same household as the participant. This maximizes the potential to follow-up participants who may have moved house.
- **For Genetics sub analysis participants only (additional consent required)**: Participants will be asked to provide a sample of saliva prior to discharge. Samples will be labelled and stored on site at ambient temperature.

- **For Cognitive Reserve Sub analysis participants only**: Cognitive Reserve Index questionnaire (CRIq) may be completed with participant or proxy prior to discharge (Appendix V) for participants recruited prior to 1st July 2024.

3 month Follow Up

9.2.3 Follow up assessment visits will be performed face to face by the blinded outcome assessor and are anticipated to take approximately 90 minutes. If a face to face assessment is not practical, a Voice over Internet Protocol (voice or video) or telephone service will be used to collect maximum available data with the participant and/or carer. Data from participant medical records will also be sourced. If a participant or carer cannot be located, the country death register will be searched to determine whether the participant has died.

Assessments required at the 3 month follow up visit include:

- Disability using the mRS (Appendix H) [2, 39, 40]
- Walking independence: Days to 50 metre walk unassisted if not achieved prior, comfortable 10MWT[37] and Functional Ambulation Classification (FAC, Appendix O)[41]
- Motor recovery will be measured using the FMA-UL and FMA-LL[42] (Appendix K, L) for participants recruited prior to 1 July 2024 Motor recovery will be measured using the FMA-UL and FMA-LL[42] (Appendix K, L) for participants recruited prior to 1 July 2024 [42]
- Participant will be asked to complete Trail Making A[33] and Line Bisection[34] and to assess attention and neglect (Appendix W) for participants recruited prior to 1 July 2024.
- Nottingham Extended ADL measure (NEADL, Appendix U)[43]
- Health related quality of life using the EQ-5D-5L(Appendix P)[44]
- Anxiety and Depression will be measured using the HADS[45] (Appendix Q), and for participants with aphasia (as defined by score of 1,2 or 3 on item 9 of the NIHSS), the SADQ-H 10[46] (Appendix R) will be utilised as an alternative.
- Resource Use Questionnaire
- COG-4[47], and Montreal Cognitive Assessment (MoCA, Appendix S)[48]
- Fatigue using the Fatigue Assessment Scale (FAS)[49] (Appendix T)
- Patient Centred Outcome Measures after Stroke[50]
- Collection of IMEs and Serious Adverse Events
- **For Cognitive Reserve Sub analysis participants only**: CRIq collected with participant or proxy if not collected whilst participant was in hospital (patients recruited prior to 1 July 2024 only).

6 month Follow Up

Visit to be conducted as per 3 months.

Assessments required at the 6 month follow up visit include:

- Disability using the mRS (Appendix H)[2, 39, 40]
- Walking independence: Days to 50 metre walk unassisted if not achieved prior, comfortable 10MWT[37] and Functional Ambulation Classification (FAC)[41] (Appendix O)
- Nottingham Extended ADL measure (NEADL, Appendix U).[43]
- Health related quality of life using the EQ-5D-5L[44] (Appendix P)
- Anxiety and Depression will be measured using the HADS[45], (Appendix Q) and for participants with aphasia (as defined by score of 1,2 or 3 on item 9 of the NIHSS), the SADQ-H 10[46] (Appendix R) will be utilised as an alternative.
- Resource Use Questionnaire
- Fatigue using the Fatigue Assessment Scale (FAS)[49] (Appendix T)
- Patient Centered Outcome Measures after Stroke[50]
- Collection of Serious Adverse Events

9.2.4

9.3 Baseline and Outcome Assessments

9.3.1 National Institute of Health Stroke Scale (NIHSS)

Baseline stroke severity will be scored using the NIHSS[12](Appendix G). For randomisation, patients will be grouped as mild (NIHSS 0-7) or moderate (NIHSS 8-16)[51] stroke severity. Admission NIHSS will be obtained retrospectively from the medical record[52]. Staff assessing NIHSS must hold current certification.

9.3.2

Mobility Scale for Acute Stroke (MSAS)

The Mobility Scale for Acute Stroke is a reliable measure of mobility status in the acute stroke phase (Appendix I).[32] The amount of assistance required for 5 mobility tasks is scored at baseline. At discharge, the walking component (Item 5) is assessed.

9.3.3

Toast Classification of Subtypes of Acute Ischaemic Stroke (TOAST)

The TOAST classification is an effective and easy to use tool to classify ischaemic strokes into 5 broad categories and subcategories representing the most common causes of ischaemic stroke (Appendix N).[38]

9.3.4

Revised Thrombolysis in Cerebral Infarction (rTICI)

The TICI grading system was described in 2003 by Higashida et al.[53] as a tool for determining the response of thrombolytic therapy for ischaemic stroke. In neuro-interventional radiology it is commonly used for patients post endovascular revascularisation. Like most therapy response grading systems, it predicts prognosis.

The TICI has been revised (rTICI) to standardise and improve sensitivity of scoring of distal perfusion (Appendix J).[54]

Modified Rankin Scale (mRS)

9.3.5 The mRS is the Stroke Recovery and Roundtable (SRRR) consensus recommended stroke global disability outcome measure.[55] The mRS is scored from 0-6, where 0 is no disability, 5 corresponds to fully dependent, requiring constant care[2, 56] and death is scored as 6 (Appendix H). The participant or carer can be interviewed to obtain a score. Inter-observer reliability is improved by using a structured questionnaire during the interview process [57, 58] and by raters undergoing a multimedia training process.[59] All mRS assessors will be certified every 12 months.

Comfortable Ten Metre Walk Test (10MWT)

9.3.6 This outcome is the SRRR consensus recommended measure of walking.[55] The ten metre walk test (10MWT) is a valid and reliable measure of walking ability.[37] Participants able to walk with supervision or independently, with or without a gait aid will be asked to walk at a comfortable pace for 10 metres and timed over the central six metres. Standardised instructions are used. The time taken and type of gait aid are recorded. If the person cannot perform the walk, it will be recorded as unable.

9.3.7 **Days to 50 Metre Walk**

The date the participant achieves walking 50 metres unassisted (independently or supervised) after stroke will be recorded.[10] This will be assessed at relevant time points throughout the study (e.g. discharge and follow up visits).

9.3.8

Functional Ambulation Classification (FAC)

9.3.9 The Functional Ambulation Classification is a validated measure of community ambulation(Appendix O).[41]

Nottingham Extended ADL Scale (NEADL)

The Nottingham Extended ADL scale is a 22 item questionnaire developed to assess stroke patients living in the community (Appendix U).[43] The 22 ADL activities cover four sections and include mobility (six items), kitchen (five items), domestic (five items) and leisure (six items) activities. Each item is scored on the response to four options: no (0 points), with help (0 points), on my own with difficulty (1 point), on my own (1 point).

9.3.10

Fugl-Meyer Assessment (FMA)

The Fugl-Meyer Assessment (motor section) was recommended in the SRRR consensus guidelines for administration at acute, early sub-acute and late sub-acute time points.[55] The FMA is a stroke-specific, performance-based impairment index.[42, 60] It is used in research to determine severity and describe motor recovery. We will use the motor section of the upper limb (Appendix K) and lower limb assessment (Appendix

L) in participants recruited prior to 1 July 2024. Staff assessing Fugl-Meyer will be trained and certified by the research team.

EuroQol 5 dimensions, 5 levels (EQ-5D-5L)

This outcome is the SRRR consensus recommended stroke quality of life outcome measure.[55] The EuroQol, 5 dimensions, 5 levels questionnaire (EQ-5D-5L) is a standardised instrument developed by the EuroQol Group (https://euroqol.org/) as a

9.3.11 measure of health-related quality of life that can be used in a wide range of health conditions and treatments.[44] The EQ-5D-5L consists of a descriptive system, as well as the Visual Analogue Scale (VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with five levels of severity (Appendix P). The VAS records the participant's self-rated health on a vertical visual analogue scale. The scores on these five dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preferability compared to other health profiles.[61] For this trial, modes of administration will be completion by the participant (self-complete) or by the carer (EQ-5D-5L Proxy Version 1).

A user guide is provided on how to use the EQ-5D-5L instrument.[62] The EQ-5D-5L has more than 150 official translations for languages other than English for use for non-English speaking participants and/or carers.

Trail Making A and Line Bisection

9.3.12 Attention will be assessed using Trail Making Part A for participants recruited prior to 1 July 2024. [33] Participants are asked to connect numbers presented randomly on a page by a single line following an example completed with the assessor. The participant is asked to work as fast as they can, and the time taken to complete is recorded in seconds from the point at which the patient starts.

For ease of administration neglect will be identified using an abbreviated form of the Line Bisection Test for participants recruited prior to 1 July 2024. In keeping with a review by Parton et al[34] and with other neglect bisection tests that include multiple lines, a 20cm line is presented to the participant horizontally across a landscape A4 page. The participant is asked to mark the midpoint or centre of the line and will be scored as a

9.3.13 distance in mm, either left or right, from the true midline. Measurement is taken in mm from the left end of the line to determine the score.

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a self-administered measure used to screen for the presence of depression and anxiety (Appendix Q).[45] The HADS was developed to provide clinicians with an acceptable, reliable, valid and easy to use practical tool for identifying and quantifying depression and anxiety. The HADS can be used in a variety of settings (e.g. community, primary care, in-hospital, and psychiatry). The HADS is not intended as a complete diagnostic tool, but as a means for identifying general hospital patients who need further psychiatric evaluation and assistance.

Stroke Aphasic Depression Questionnaire (SADQ-H 10)

9.3.14 The Stroke Aphasic Depression Questionnaire (SADQ-21) was developed to detect depressed mood in clients with stroke and significant aphasia living in the community. It is a 21-item questionnaire developed based on observable behaviours thought to be associated with depressed mood. It is completed by the client's caregiver on behalf of the client. A shortened version of the SADQ has been developed (SADQ-10), which is comprised of 10 questions that best differentiate those with high scores on depression questionnaires from those with low scores. A revised version of the scale has also been developed for clients in hospital to be completed by hospital staff (SADQ-H 10, Appendix R). [46]

Montreal Cognitive Assessment Scale (MoCA)

9.3.15 The Montreal Cognitive Assessment (MoCA) is a valid and reliable assessment as a a rapid screening instrument for the detection of mild cognitive impairment.[63] The MoCA assesses the following cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation (Appendix S). The measure can be used for but is not limited to patients with stroke. The blind version of the assessment will be used if the participant is followed up by phone. (MoCA Blind - Appendix Y)

Fatigue Assessment Scale (FAS)

9.3.16 The FAS is quick and easy for participants to complete.[49] The FAS has proven to be a valid questionnaire to assess fatigue in participants with chronic diseases. It is a 10-item general fatigue questionnaire with five questions evaluating physical fatigue and 5 questions (questions 3 and 6-9) mental fatigue (Appendix T).

9.3.17

Clinical Frailty Scale

9.3.18 Frailty is a judgement of decreased physiological reserve and ability to respond to and recover from stressors. The Canadian Study of Health and Aging 2008 Clinical Frailty Scale (CFS) requires clinical judgement to rate the participants pre-stroke state of vulnerability. The scale uses a written description with visual chart for each level (Appendix X). This scale is a practical and time efficient scale to administer with information taken from the participant or person responsible.

Saltin-Grimby Patient Activity Level Scale

9.3.19 The Saltin-Grimby Physical Activity Level Scale (SGPALS, Appendix M).[35, 36] is a four-level questionnaire to assess leisure time physical activity The concurrent validity, with respect to aerobic capacity and movement analysis using objective measurements has been shown to be good, as has the predictive validity with respect to various risk factors for health conditions and for morbidity and mortality.

Patient Centered Outcome Measures

A consensus stroke measure standard set was developed by Salinas et al.[50] Using an international expert panel a set of patient reported outcomes were identified. The

majority of recommended outcomes are included in the study outcomes. Several additional questions regarding stroke recovery, and prior driving are included.

Resource Utilisation

Resource use will be collected using standardised methods and tools across multiple hospital sites within the participating countries. Country-specific Resource Use eCRFs will be used to reflect local stroke service provision and any differences in terminology.

9.3.20 Data will be collected to calculate resource use for participants in all arms of this study. During the acute phase, additional resources utilised in the delivery of Mobility Training interventions will also be recorded using data submitted on the Mobility Training eCRF by nursing and physiotherapy staff.

At the three and six month follow up visits the blinded assessor will use the Resource Use eCRF to capture changes to employment (paid/unpaid) and services utilised as a result of the stroke including: length of acute hospital stay; discharge destination; inpatient and outpatient rehabilitation; emergency department presentations, stroke related hospital re-admissions; community and health care service use; respite and informal care services; and carer employment. If a participant dies during the trial, the Resource Use eCRF will be completed to capture resources used prior to death by a review of the participant medical records and discussion with the proxy where possible.

9.3.21 **Adverse Events**

All Adverse Events (serious and non serious) will be collected by the research staff during the intervention period (from consent until acute discharge or 14 days post randomisation). Important Medical Events will be collected from consent to 3 months from date of stroke at the 3 month follow up visit. Serious Adverse Events will be collected from the time of consent until 6 months post stroke. Relationship to treatment will be assessed by the blinded assessor. Events will be recorded in REDCap® and reported to local HRECs as required. See Section 10 for details.

9.3.22

In Brazilian sites only:

A rehabilitation package will be provided to participants prior to discharge. It will contain information about stroke, include basic stroke information, a selected suite of exercises with images and instructions, the 'Take Charge'[84] intervention adapted to the Brazilian context, an exercise diary, and information about local stroke resources.

Participants will be asked to report if they received the package, if they used the package and if so, what aspects they found useful. This will help provide some preliminary pilot data about the value of such a package.

10 Adverse Events (AEs), Important Medical Events (IMEs) and Serious Adverse Events (SAEs)

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) and an important medical event (IME). AEs and IMEs may be serious (SAE) or not serious. During the study, when

there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs, IMEs and SAEs, as detailed in this section of the protocol. The blinded assessor will question the patient and review the medical files at six months to ensure all reportable events have been identified and documented.

10.1 Definition of an Adverse Event (AE)

Any untoward medical occurrence in a participant, temporarily associated with the use of a therapy, whether or not considered related to that therapy.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with a therapy whether or not considered related to the therapy.

Examples of an AE **include**:

- Exacerbation of a chronic or intermittent pre-existing condition including an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after therapy administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction with therapy.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of a medicinal product.
- Abnormal laboratory assessments that are clinically significant.

Examples of an AE **do not include**:

- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE.

10.2 Reporting an Adverse Event (AE)

Adverse Events should be documented in the participant's medical record or clinic notes. AEs will be recorded from the time of consent until the end of intervention (discharge or Day 14 post randomisation). These events will be reported on the Adverse Event form in REDCap®.

For each adverse event, start and stop dates, action taken, outcome, intensity and relationship to study treatment (causality) must be documented. If an AE changes in frequency or intensity during a study, a new entry of the event must be made in the eCRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In the absence of a diagnosis, the individual signs/symptoms should be documented.

10.3 Definition of an Important Medical Event (IME)

An IME is an adverse event that is of particular interest and/or is an important outcome measure for this trial.

IMEs include:

- Falls - with no soft tissue injury
  - with soft tissue injury
  - with bone fracture or head injury
- Recurrent stroke (defined as a new stroke in a new territory)
- Neurological deterioration related to the initial stroke that occurs during the intervention period.– Classified as a increase in NIHSS score of greater than or equal to four points on the scale.[64]
- Deep Vein Thrombosis / Pulmonary Embolism
- Angina/Myocardial Infarct
- Urinary Tract Infection
- Pressure Sores
- Pneumonia
- Depression
- Seizures
- TIAs

10.4 Reporting of Important Medical Events (IMEs)

Important medical events should be documented in the participant's medical record or clinic notes. IMEs will be recorded from the time of consent until the 3 month follow up visit. These events will be reported on the Adverse Event form in REDCap®.

For each important medical event, start and stop dates, outcome, intensity and relationship to study treatment (causality) must be documented. If an IME changes in frequency or intensity during a study, a new entry of the event must be made in the eCRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In the absence of a diagnosis, the individual signs/symptoms should be documented.

10.5 Definition of a Serious Adverse Event (SAE)

A Serious Adverse Event is any untoward medical occurrence that, at any dose:

a) results in death

b) is life-threatening

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.

c) requires hospitalisation or prolongation of an existing hospitalisation.

Note: In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs.

If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

Hospitalisation for planned elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) results in disability/incapacity, or

Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions.

e) Other important medical event

Note: Medical and scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or abuse. This includes diagnosis of COVID 19 during the participants involvement in the study.

10.6 Reporting of a Serious Adverse Event

Serious Adverse Events should be documented in the participants' medical record or clinic notes.

SAEs will be recorded from the time of consent until the 6 month follow up visit for the participant.

These events will be reported on the Adverse Event form in REDCap®, with supplemental medical record information provided in the form of de identified support documentation.

When an event occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostic reports) relative to the event. The investigator will then record all relevant information in to the eCRF.

For each event, reason for serious, start and stop dates, action taken, outcome, intensity and relationship to study treatment (causality) must be documented.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In the absence of a diagnosis, the individual signs/symptoms should be documented.

Details of any treatments initiated due to the adverse event should be recorded.

10.7 Prompt Reporting of SAEs to Sponsor

Once an investigator becomes aware that an SAE has occurred in a study participant, the study monitor will be contacted via REDCap® to notify them of the event. The SAE form must be completed as thoroughly as possible on REDCap® with all available details of the event, signed by the investigator (or qualified designee), and forwarded to the monitor, within 24 hours of becoming aware of the event. If all information

regarding the SAE is not available initially, the initial report will be completed and sent as soon as possible. The form will be updated when additional information is received.

A blinded investigator will provide an assessment of causality at the time of the initial report as described in Section 10.10.2. If data obtained after reporting indicate that the assessment of causality is incorrect, then the SAE form may be appropriately amended, signed and dated, and resubmitted.

In accordance with local IEC requirements, the investigator must also notify their Ethics Committee of any SAEs according to the guidelines of the Ethics Committee.

The investigator, and others responsible for participant care, should institute any supplementary investigations of serious adverse events based on their clinical judgement of the likely causative factors. This may include seeking further opinion from a specialist in the field of the adverse event. If a participant dies, any post-mortem findings, including histopathology will be provided when available.

10.8 Expeditable Events

Expeditable events are those adverse events that are **CAUSALLY** (see Section 10.10.2) related to the study treatment, **AND** that are both **SERIOUS** (see Section 10.5) and **UNEXPECTED** (see Section 10.10.3). Such events are expedited in the reporting to the Data Safety and Monitoring Committee.

10.9 Time Period, Frequency, and Method of Detecting Events

Each participant will be monitored regularly by the investigator and study personnel for events occurring during the trial. The investigator will enquire about potential events the participant may have experienced by asking the participant and/or next of kin, non-leading questions and enquiring about any trips to see the general practitioner/ physician, specialist or hospital presentations. Further information may be required from medical records.

10.10.1

10.10 Evaluating AEs, IMEs and SAEs

Assessment of Severity

The investigator will make an assessment of severity for each event reported during the study. The assessment will be based on the investigator's clinical judgement. The intensity of each event recorded in the eCRF should be assigned to one of the following categories:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event which is incapacitating and prevents normal everyday activities.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets one of the pre-defined outcomes as described in Section 10.5.

Assessment of Causality

10.10.2 The blinded assessor will assess the relationship between therapy and the occurrence of each AE/SAE. They will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the therapy will be considered and investigated.

The causal relationship to the study therapy should be assessed using the following classifications:

Not Related	In the assessor's opinion, there is not a causal relationship between the study treatment and the adverse event.
Unlikely	The temporal association between the adverse event and study treatment is such that the study treatment is not likely to have any reasonable association with the adverse event.
Possible	The adverse event could have been caused by the study participant's clinical state or the study treatment.
Probable	The adverse event follows a reasonable temporal sequence from the time of study treatment, abates upon discontinuation of the study treatment and cannot be reasonably explained by the known characteristics of the study participant's clinical state.
Definitely	The adverse event follows a reasonable temporal sequence from the time of study treatment administration or reappears when study treatment is reintroduced.

10.10.3 There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always makes an assessment of causality for every event prior to transmission of the SAE form to The Florey. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE form accordingly. The causality assessment is one of the criteria used when determining safety reporting requirements.

Assessment of Expectedness

Expected	An adverse event, the nature or severity of which is consistent with the clinical condition of the subject and or known information about the study treatment.

Unexpected An adverse event, the nature or severity of which is not consistent with the clinical condition of the subject and/or known information about the study treatment.

10.11 Follow-up of AEs, IMEs and SAEs

After the initial AE/IME/SAE report, the investigator is required to proactively follow each participant and provide further information on the participant's condition.

All events documented at a previous visit/contact and designated as ongoing, will be reviewed at subsequent visits/contacts.

All events will be followed until resolution, until the condition stabilises, until the event is otherwise explained, or until the participant is lost to follow-up.

New or updated information will be recorded on the originally completed SAE form, with all changes signed and dated by the investigator.

11 Participant Completion and Discontinuation

11.1 Participant Completion

Participants are deemed to have completed the trial if they have completed the intervention and have follow up visits at 3 and 6 months completed. If a participant dies during the course of the study, relevant information will be collected and recorded for the visit scheduled to occur after the death. This will include data on resources used, Serious Adverse Event information and the mRS.

11.2 Stopping Rules / Discontinuation Criteria

In line with the MAMS CARA trial design, a number of decision points for trial modification are pre-specified, however no formal stopping rules are required. In the unlikely event that a similar trial completes prior to this trial and yields definitive results, the Data Safety and Monitoring Committee will be notified. There is no similar, known trial at this point in time.

11.3 Participant Withdrawal

Participants may withdraw from the study at any time if they wish. They may withdraw consent to continue treatment and/or follow-up, or the investigator may need to withdraw the participant from the study for safety reasons such as an adverse event. If the participant is withdrawn from the study, already collected samples and trial data will remain as part of the study, unless the participant expressly wishes these data to be removed. Randomised participants will not be replaced. The central study team will be notified as soon as possible of any potential withdrawal.

11.4 Early Termination of the Study

The study may be terminated prematurely by the principal investigator or his/her designee and the sponsor if:

- The number and/or severity of adverse events justify discontinuation of the study
- New data become available which raise concern about the safety of the study treatment, so that continuation might cause unacceptable risks to participants.

In addition, The Florey reserves the right to discontinue the trial prior to inclusion of the intended number of participants, but intends only to exercise this right for valid scientific or administrative reasons.

After such a decision, the Investigator must contact all participants within two weeks, and written notification must be sent to the Ethics Committee.

12 Electronic Case Report Form (eCRF)

An electronic Case Report Form (eCRF) will be completed for each study participant summarising all clinical screening and study data. Participants will only be referred to in the eCRF by their participant number and initials in order to retain participant confidentiality.

The completed original eCRF data is to be submitted via REDCap® online to the Sponsor as soon as practical after completion. A copy of each completed eCRF is to be retained by the Investigator for a period of time as determined by local regulations.

13 Data Analysis and Statistical Considerations

13.1.1 **13.1 Outcomes**

Primary Outcome

The primary outcome is the proportion of participants *achieving a favourable outcome of no or little disability* (mRS[2] score 0-2) *at 3 months post stroke*. The mRS enables categorisation of participants based on 7 levels (0-6), ordered for dependency and the
13.1.2 ability to look after themselves in daily life, with death included as an outcome. It is used as the primary outcome in large stroke clinical trials.[39]

Secondary Outcomes

The final 6 month end point is selected to evaluate the effects of intervention at the end of the peak phase of stroke recovery.[65]

13.1.2.1 Safety/medical complications

Deaths at 3 months

All complications will be recorded during the 14-day intervention period classifying them as serious or not serious, immobility-related and stroke-related. Serious Adverse Events (SAEs) will be monitored up to 3 and 6 months. This follows the same design as our successful AVERT model.

13.1.2.2 mRS outcome at 3 months across the full ordinal scale.[3]

13.1.2.3 Increased unassisted walking 50 metres and walking speed at 3 month will be recorded.

13.1.2.4 Quality of life

The EQ-5D will be repeated at the 3 and 6 month endpoints, to assess overall quality of life and will be utilised.[66, 67]

13.1.2.5 Economic evaluation

13.1.2.6 Valuation of resources used

Unit prices will be applied to all resources that are used, with 2022 as the reference year. Where the 2022 unit price is not available, adjustment to the real price in the reference year will be made using the appropriate country-specific health sector price inflator.

Unit costs will be obtained from each participating country (Australia, Malaysia, Singapore, United Kingdom, Republic of Ireland, India, and Brazil etc.) and applied to patient-level data collected within that country. It will not be practical to collect centre-specific unit costs because of the large number of centres likely to be involved in the trial. Nominal prices (which will be adjusted to real prices if needed) will be used to value the resource use taken from published sources such as national datasets (e.g. Independent Hospital Pricing Authority, IHPA, Australia; National Health Service, NHS, UK) and fee schedules (Australian Medicare Benefits Schedule, MBS). Centre-specific unit costs will only be used where national data were not available.

Where there are insufficient data, unpublished unit prices or unit prices from countries with similar economic status/health care system will be obtained and used for pragmatic reasons. The source of unpublished prices will vary and not be limited to hospital financial records or provider specific fee schedules/invoicing. The health economics team will be assisted in sourcing unit costs by trial collaborators from each individual participating country. Where there is a large variation in the unit prices for a specific item, a mean cost will be applied and a range around the mean cost will be tested in the uncertainty analysis. Informal care will be valued as an opportunity cost by the proxy good method based on the country-specific hourly wage rate of a professional carer.

13.1.2.6.1 Currency, price data and conversion

Unit prices will be converted to a common currency using the Purchasing Power Parity (PPP)[68]. The Australian Dollar (AUD) is most relevant to use, but the final currency chosen may be decided at a later stage when a target journal is selected for publication of the economic evaluation results. Where specific analysis is undertaken by country, results will also be reported in local currencies as follows: AUD Australia; RM Malaysia; SGD Singapore; GBP United Kingdom; INR India; BRL Brazil and EURO Ireland.

13.1.2.6.2 Productivity losses

The human capital approach (HCA) (assigns a monetary value to the lost economic productivity due to ill health, disability, or premature mortality based on the present

value of expected future earnings)[69] will be utilised to measure the productivity gains/losses.

13.2 Sample Size

Using the probabilities of mRS 0-2 outcome observed in AVERT data for the different doses proposed in this study, extensive simulations in C and R software have been run for Mild (National Institute of Health Stroke Scale[12] (NIHSS), 0-7) and Moderate (NIHSS 8-16) stroke severity strata to identify the sample sizes to yield 80% power to observe 10% absolute treatment effects or larger compared to a pre-specified reference group in both severity strata assuming Bonferroni corrected one-sided alpha family-wise threshold p=0.025 per stratum.

For the **mild stroke stratum**, in order to observe the difference between proportions of good outcome being 0.7 in the reference arm and 0.8 in the best intervention group with power of 80%, the 50,000 simulations based on the integrated covariate and response adaptive randomisation algorithm (Pocock and Simon's covariate adaptive algorithm[25] and Chang's M-Arm Response-Adaptive Randomisation with Binary Endpoints[18]) yields the expected total within-stratum sample size of 1300 participants.

For the **moderate stroke stratum**, to observe the difference between proportions of good outcome of 0.3 in the reference arm and 0.4 in the best intervention arm with 80% power, the 50,000 simulations yield the total within-stratum sample size of 1400 participants distributed between four groups.

Adaptive sample size re-estimation will be undertaken for both individual strata using Mehta and Pocock[31] promising zone methodology at the end of Stage 1 (i.e. once the mRS0-2 at 3 months outcomes of 700 patients from a given stratum become available) based on the comparison between the reference group and the single intervention group selected to proceed to Stage 2, with a potential increase of up to the maximum of 1600 participants for Mild stroke stratum and 1900 participants for Moderate stroke stratum. The effect sizes are clinically important, similar to current effective, but limited[5] stroke treatments.

Addendum 15 June 2025:

13.2 Sample size

Given significant disruption to study recruitment, current recruitment numbers and termination of sponsor funding on 31 Dec 2025 it is not anticipated that the study will recruit sufficient numbers of participants to execute the pre-planned adaptive sample size re-estimation and/or achieve the pre-planned sample size. Therefore, recruitment to the study will proceed until to the 30 November 2025 when recruitment will be terminated (Last Patient First Visit). The outcomes for all recruited participants will be included in the analyses based on the ITT principles.

13.3 Statistical Analyses

All analyses will be based on intention-to-treat (ITT) principles.

Primary Efficacy Analysis

13.3.1 The mRS scores at 3 months will be dichotomised, with scores of 0-2 reflecting 'favourable outcome' and scores of 3-6 reflecting 'poor outcome'. In our primary analysis we will use the randomisation based analysis with permutation test of the difference between the single intervention arm selected to proceed to Stage 2 and the pre-specified reference arm individually for each stratum (stratum-specific one-sided family-wise p=0.025). The non-parametric permutation or randomisation tests used for analysis in proposed adaptive design, test the null hypothesis that the assignment of treatments has no effect on the responses (outcome) of the participants in the study.[21] The effect sizes will be reported as risk differences between the probabilities of a favourable outcome. In case the same treatment regimen appears optimal in both strata, a pooled risk difference measure will be derived using Mantel-Haenszel method.

Addendum 15 June 2025:

13.3.1 Primary Efficacy Analysis

The mRS scores at 3 months will be dichotomised, with scores of 0-2 reflecting 'favourable outcome' and scores of 3-6 reflecting 'poor outcome'. In our primary analysis we will use the randomisation-based analysis with permutation tests of the differences between every individual intervention arm and the pre-specified reference arm for each stratum. According to FDA Guidance for Industry for Master Protocols, the use of multiplicity adjustments to strongly control Type I error across the multiple comparisons of different treatments to the control in an umbrella or platform trial is not recommended, hence within each stratum comparisons of every individual intervention arm and the pre-specified reference arm will be conducted independently. The non-parametric permutation or randomisation tests used for analysis in proposed adaptive design, test the null hypothesis that the assignment of treatments has no effect on the responses (outcome) of the participants in the study.

The effect sizes will be reported as risk differences between the probabilities of a favourable outcome. In addition, frequentist confidence for benefit and for lack of meaningful benefit (futility) compared to the reference arm will be estimated for every individual intervention arm. The procedure for the definition of the lack of meaningful benefit (futility) threshold will be presented in detail in the Statistical Analysis Plan finalized prior to the study data lock. This will include gaining independent expert opinion of lack of meaningful benefit via a short survey.

13.3.2

Secondary Efficacy Analysis

The secondary analyses will be conducted using regression modelling. Despite the adaptive nature of the randomisation used in AVERT DOSE, maximum likelihood estimations using, e.g.Wald test, can be applied if the appropriate correction for potential estimation bias is undertaken.[22, 27] Full dose-response exploratory analyses will be conducted across all dose regimens. We will publish a detailed Statistical Analysis Plan,[13] and Economic Evaluation Plan[70] prior to close out of the trial.

Addendum 15 June 2025:

13.3.2 Secondary Efficacy Analysis

Secondary analyses will be conducted using regression modelling. Full dose-response exploratory analyses will be conducted across all dose regimens.

We will publish a detailed Statistical Analysis Plan,[13] and Economic Evaluation Plan[70] prior to study data lock.

Secondary Cost Effectiveness Analysis

The primary economic evaluation will be cost-effectiveness analysis using the favourable outcome (mRS score 0-2) at six months (primary outcome of the trial), combined with resource utilisation data collected for the period baseline to month six.

13.3.3 Incremental cost-effectiveness ratios will be reported as cost per favourable mRS outcome and cost per Quality Adjusted Life Years (QALYs) gained (based on the EQ-5D-5L).

Cost Utility Analysis (CUA)

Cost Utility Analysis (CUA) will be performed based on health-related quality of life,

13.3.4 measured as QALY gains over the six month period. The QALY gains over the trial duration will be computed in two different ways: 1) using the mapped utility from the baseline mRS; 2) score using the baseline EQ-5D-5L utility score. The QALY gains calculated using the first approach will be adopted in the primary analysis, while the second approach will be tested in the sensitivity analysis to examine the robustness of primary analysis results.

Incremental cost effectiveness ratios (ICER) will be calculated to jointly assess costs and outcomes (i.e. the probability of achieving a favourable mRS score and QALY gains). The additional cost/savings of the intervention compared to the reference group will be expressed as a ratio by dividing the net benefits derived and reported as the: incremental cost per unit increase in the probability of achieving a favourable outcome at six months (mRS 0-2); and incremental cost per QALY (i.e. QALY gains calculated using mapped utility based on baseline mRS score). The final ICER will be reported with and without productivity costs. Any assumptions made during the analysis will be documented and reported alongside the economic evaluation results.

In terms of the primary analysis, data will be aggregated for the identified optimal intervention regimens across all countries and results will be reported as single ICERs with respect to each stroke severity group (i.e. mild and moderate). Any reporting of separate ICERs for individual country/region will be dependent on participant numbers and will be determined at the time of analysis.

13.3.4.1 Uncertainty analysis

Bootstrapping (a non-parametric technique which involved large number of repetitive computations to estimate the shape of a statistic's sampling distribution empirically[71]), of costs and benefits (i.e. probability of achieving a favourable outcome in terms of mRS score and QALY gains) will be undertaken to assess the degree of uncertainty around reported ICERs. Multivariate sensitivity analysis will be carried out to test various assumptions.

Results will be plotted on a cost-effectiveness plane to illustrate the distribution of cost and effect iterations. A cost-effectiveness acceptability curve will be drawn to assess the degree of uncertainty around the result using commonly used, appropriate cost-effective threshold (i.e. AUD 50,000 for Australia[72]; GBP 20,000-30,000 for UK[73], etc.).

Tertiary Analyses

Additional Exploratory Sub Analyses will be detailed in the Statistical Analysis Plan.

14 Data Management

13.3.5 RedCap® provides 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The platform complies with regulatory requirements and is developed, deployed and maintained according to industry guidelines and standards that apply to computerised systems in healthcare, including audit trails, electronic signatures and documentation for software and systems. It is compliant to the Good Clinical Practice guidelines for clinical trials.

Using our proven processes that delivered high quality data in AVERT, any missing data will be returned to the assessor or site investigator for follow up. Data checks will be performed and the data verified as necessary and these will be reported to the trial management group.

An electronic Case Report Form (eCRF) will be completed for each study participant summarising all clinical screening and study data. REDCap® is accessed by investigators by a secure username and password.

All data entered on the eCRF will have supporting source data located at the study site in the participant's medical record. Data allowed to be recorded directly in to the eCRF (i.e. no prior written or electronic record of data), will be discussed and documented with the Sponsor at the commencement of the trial. The completed eCRF's will be submitted according to data timelines, and as soon as practical after completion and review. A copy of each completed eCRF will be printed and retained by the Investigator for at least 7 years from the end of the study.

Monitoring of the data will be performed by the study team and will occur using the data query function of the REDCap® system. A risk based approach to on site monitoring will be implemented.

15 Monitoring and Quality Assurance

The task of the Study Monitor is to guarantee the best conduct of the study through frequent contacts by phone and in person with the responsible sites, in accordance with a documented Monitoring Plan. These site visits will enable the Monitor to maintain current, personal knowledge of the study through review of the records, comparison with source documents, and observation and discussion of the conduct of the study with

the Investigator. The Monitor is responsible for monitoring adherence to the Protocol and completion of the eCRF, and for the relationship between the Investigator and The Florey.

The organisation, monitoring, supply of study materials and quality assurance of the present clinical study is the responsibility of The Florey.

In order to ensure the accuracy of data, direct access to source documents by the Study Monitor and any regulatory authorities is mandatory. Anonymity of the participant will be maintained at all times.

15.1 Curriculum Vitae and Other Documentation

In order to comply with regulatory requirements, all Investigators signing the Protocol and all trial staff should provide a current, signed and dated Curriculum Vitae (CV) to be filed by The Florey. The CV should include name, title, occupation, education, research experience and present and former positions. An authorised Staff Signature List is required for Principal Investigators to delegate study tasks to members of the local teams.

16 Investigator Responsibility

Except where the Principal Investigator's signature is specifically required, it is understood that the term 'Investigator' as used in this Protocol and on the eCRF refers to the Principal Investigator or an appropriately qualified member of the staff that the Principal Investigator designates to perform specified duties of the Protocol. The Principal Investigator is ultimately responsible for the conduct of all aspects of the study.

Each Investigator will comply with the local regulations regarding clinical trials and the Investigator responsibilities outlined in the International Conference on Harmonisation (ICH) GCP guidelines.[74]

17 Study Report

At the conclusion of the study the findings will be published in peer review journals and at relevant conferences in compliance with NHMRC and other relevant governance requirements. The final study report will be prepared by the executive management team with input from relevant sub committees. Results of the study will also be provided to participants via the research staff at each site. A lay summary of the results will be made available for this purpose. Following publications participants de-identified data will be opened to other researchers for analysis, including stroke big data registries such as Virtual International Stroke Trials Archive (VISTA).

18 Administrative Procedures

18.1 Ethical Considerations

This study will be carried out according to the Declaration of Helsinki, the NHMRC National Statement on Ethical Conduct in Research Involving Humans (1999) and the Notes for Guidance on Good Clinical Practice as adopted by the Australian Therapeutic Goods Administration (2000) (CPMP/ICH/135/95) and the ICH GCP Guidelines.[74]

18.2 Ethical Review Committee

The Protocol will be submitted for approval to appropriate Independent Ethics Committees (IECs), and written approval obtained, before volunteers are recruited and participants are enrolled. The Investigators will receive all the documentation needed for submitting the present Protocol to the Ethics Committee. A copy of the respective approval letters will be transmitted to the Sponsor before starting the study. The composition of the Ethics Committee will also be provided. If approval is suspended or terminated by the Ethics Committee, the Investigator will notify the Sponsor immediately.

It is the responsibility of the Investigator to report study progress to the local Ethics Committee as required or at intervals not greater than one year.

The Principal Investigator, or his/her nominee, will be responsible for reporting any Serious Adverse Events to the Ethics Committee as soon as possible, and in accordance with the guidelines of the Ethics Committee.

18.3 Regulatory Authorities

In agreeing to the provisions of the Protocol, these responsibilities are accepted by the Investigator.

18.4 Informed Consent

Before recruitment and enrolment into the study, each prospective, eligible candidate will be given a full explanation of the nature and purposes of the study, and a copy of the Participant Information Sheet to review. Once the essential study information has been provided, and the Investigator is assured that each individual volunteer understands the implications of participating in the study, the participants will be asked to give consent to participate in the study by signing the informed consent form. The consent forms shall be signed and dated by the appropriate parties. A notation that written informed consent has been obtained will be made on the participant's CRF and in the medical record. The completed information sheet and consent forms will be retained by the Investigator and a copy of these will be provided by the Investigator to the participant. Where a participant does not have capacity to consent for themselves, a person responsible in the jurisdiction will be asked to provide acknowledgement of consent on behalf of the participant. A person responsible information and consent form will be signed and dated by appropriate parties depending on the law in the jurisdiction, documentation of the consent process will be made, and copies of the consent will be retained by the investigator and the person responsible.

Witness consent also available for those who have capacity, but unable to sign the consent themselves.

18.5 Participant Reimbursement

Participants will be reimbursed for out of pocket expenses relating to trial involvement. It is unlikely that participants will encounter out of pocket expenses as they will be visited during hospitalisation and at their place of residence for follow up visits, but follow up clinic visits will also be reimbursed where staff are unable to visit the residence.

18.6 Emergency Contact with Investigators

All participants will be provided with details of whom to contact in the case of an emergency.

18.7 Notification of Primary Care Physician

With the consent of the participant, it is the Investigator's responsibility to notify the primary care physician of the participant's participation in the study, provided that such a physician can be identified for the participant. A letter will be sent to the physician stating the nature of the study, expected benefits or adverse events. A copy shall be retained by the study site for verification.

18.8 Investigator Indemnification

The study is being conducted by a collaborative research group (CRG). The CRG is an academic non-commercial collaborative research group responsible for sponsoring, initiating, managing, developing and coordinating the study. The Sponsor and the study sites are each liable for its acts and omissions in relation to the conduct of the study

Each party must maintain such insurances as are reasonably available and necessary to provide indemnity to it in relation to any liability which it may incur in conducting the study or performing its obligations under the executed collaborative clinical trial agreement.

18.9 Financial Aspects

The conduct of the study is participant to a Clinical Trial Research Agreement (CTRA) between The Florey and the participating sites.

18.10 Protocol Amendments

Neither the Investigator nor The Florey will modify the Protocol without first obtaining the concurrence of the other in writing. Protocol modifications that impact on participant safety or the validity of the study will be approved by the Ethics Committee.

No amendments to the Protocol may be implemented without prior approval from the Sponsor and the relevant Ethics Committee. If a Protocol amendment requires changes

to the Informed Consent Form, the revised Informed Consent Form, prepared by the Investigator, must be approved by the Ethics Committee.

Once the final Protocol has been issued and signed by the Investigator and the authorised signatories, it shall not be informally altered. Protocol amendments are alterations to a legal document and have the same legal status. Therefore, they must pass through appropriate steps before being implemented. In general, any important change that theoretically increases risk to participants constitutes an amendment. Minor changes are administrative changes and need documentation without approval.

It is the responsibility of the Investigator to submit the amendment to the Ethics Committee for their approval; written approval should be obtained and a copy provided to the Sponsor. The Sponsor is responsible for determining whether or not the local regulatory authority must be notified of the Protocol change.

The original signed copy of amendments will be kept in the Study File with the original Protocol. It should be noted that where an amendment to the Protocol substantially alters the study design or the potential risks to the participants, each participant's consent to continue participation should be obtained.

18.11 Protocol Compliance

The instructions and procedures specified in this Protocol require diligent attention and must be followed. Should there be questions or consideration of deviation from the Protocol, clarification will be sought from the Study Monitor. Any participant treated in a manner that deviates from the Protocol, or who is admitted into the study but is not qualified according to the Protocol, may be ineligible for analysis and thereby compromise the study.

Only when an emergency occurs that requires a departure from the Protocol for an individual will there be such a departure. The nature and reasons for the Protocol violation shall be recorded in the CRF.

The Investigator and designees will comply with all applicable federal, state and local laws.

18.12 Archives: Retention of Study Records

All source documents, copies of eCRFs and trial documentation will be kept by the Investigator for the appropriate retention period as stipulated by local regulations and ICH-GCP[1].

18.13 Archives: Retention of Other Study Specific Samples

All source documents, CRFs and trial documentation will be kept by and are the responsibility of the Investigator for the appropriate retention period as stipulated by local regulations. Currently this regulation is 7 years. Electronic de-identified data may be kept indefinitely to allow comparisons with future studies in this developing area of research.

For participants agreeable to providing a saliva sample, additional consent will be sought.

The sample will have DNA extracted which will then be given a different non identifiable code which will be used for the analysis. The saliva sample and DNA will be destroyed by routine secure, bio sample destruction techniques.

De identified samples will be sent to, stored analysed and destroyed at Clinical Research Laboratory and Biobank

Hamilton Health Sciences - General Hospital Site

David Braley Cardiac, Vascular & Stroke Research Institute

237 Barton St. E.

Hamilton, ON L8L 2X2

The DNA results will be kept indefinitely for potential further research into stroke recovery. Any further research that may occur using the sample, will be overseen by an appropriate Human Research Ethics Committee.

18.14 Publication Policy

The reporting of results is the primary role of the principal investigators and sponsor and the intellectual property remains the sole property of the research team.

It is possible that there will be opportunities for collaborators to participate in the reporting, presenting and/or publishing of results related to this trial. However, all abstracts, reports, presentations and publications must be coordinated through the Sponsor in the first instance and prior written approval is required.

The main efficacy results of this study will be published on behalf of the trial collaboration.

Appendix A: Genetics Sub Analysis

Research Team Affiliations and Contact Details

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Background

A deeper understanding of the biology of stroke recovery is needed to identify new therapeutic targets. Genome Wide Association (GWA) analysis and whole exome sequencing may provide clues to biological mechanisms underlying recovery. Mendelian randomisation studies,[75] based on GWA, may moreover provide evidence on causal influences of common clinical factors on recovery (e.g. diabetes, depression, obesity, educational attainment). GWA studies also may provide information on the relative contribution of genetic versus environmental factors by heritability analysis. Preliminary evidence from individual candidate gene studies suggests that genetic factors, in addition to clinical and radiological factors, may assist in understanding functional recovery after stroke. A recent GWA identified a common polymorphism influencing stroke recovery as measured using modified Rankin Scale (mRS).[76] To date, there is a lack of prospective efforts internationally to explore the contribution of genetic markers to stroke recovery. Ongoing efforts are retrospective and largely restricted to general recovery as measured by mRS.

Aim and Hypothesis

Our ***primary aim*** is to understand the contribution of genetic factors in the recovery of upper and lower limb function after stroke.

We ***hypothesise*** that common and rare variants will contribute to recovery after stroke.

Population

All participants will be asked for additional consent for saliva/spit tests

Additional Exclusion Criteria

No additional exclusion criteria.

Study Procedures

Saliva Collection

Prior to discharge participants will be asked to provide a five ml saliva specimen by spitting into the specifically designed container provided. A link to instructional videos and procedural documents will be provided to train the personnel to obtain saliva.

Specimen will be labeled with participant study number and site number. Specimens will be stored at ambient temperature at site in a secure location and shipped to the central coordinating centre at intervals determined by the study team. Deoxyribonucleic Acid (DNA) will be collected by extracting DNA from leucocytes derived from saliva in all participants at baseline.

Outcomes

The primary outcome for the genetic analysis will be the FMA at 3 months with adjustment made for age, sex and baseline stroke severity (as assessed by the NIHSS).

Clinical measures will include baseline NIHSS, baseline mRS, premorbid mRS, Neuroimaging data will include the assessment of routine clinical CT/MRI scans to confirm lesion location and lesion volume.

Statistical Analyses

A standard genome-wide analysis will be run, validation of associations will be performed in independent samples. We will contribute de-identified data to the Genome Wide Association Study (GWAS), an international data repository to perform appropriately powered analyses.

We will control for demographics, baseline characteristics, and risk factors per Genetics of Ischaemic Stroke Functional Outcome network (GISCOME), with a minimum dataset requirement of age, sex, stroke severity within 48-hours of stroke onset.

Principal component analysis will be used to account for population-specific variations in allele distribution on the single nucleotide polymorphisms

Appendix B: Data Linkage Sub Analysis

Research Team Affiliations and Contact Details

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Background

Mobility and functional independence are important for long-term recovery, community re-integration, the ability to live independently and the prevention of future cardiovascular events following stroke. Mobility status following acute stroke has been shown to influence discharge destination from hospital. However, there is limited information on how this influences long-term independence and living arrangements. The ability to mobilise safely is an important determinant of an older person's ability to remain living in their home. It is plausible that a mobility based intervention aimed at improving walking and physical function following stroke will have long-term individual and societal benefits not currently captured in the primary AVERT DOSE study. Providing data on outcomes such as delayed admission to a Residential Aged Care Facility (RACF) or reduced utilisation of community based supports would be of interest to policy makers and government funding bodies and provide useful information for post-trial implementation.

Aims and Hypothesis

Aims

1. Does an optimal dose regimen of mobility training following stroke increase time to admission to a Residential Aged Care Facility (RACF) in older people with stroke?
2. Does an optimal dose regimen of mobility training following stroke reduce utilisation of community based aged care support services in older people with stroke living at home?

Hypothesis. Older stroke patients (>65 years) who receive an optimal dose regimen of mobility training following stroke will live at home for longer and with fewer supports compared to the pre specified reference group.

Population

Trial data from all Australian participants recruited to the trial will be submitted for linkage with routinely collected data held by the Australian Institute of Health and Welfare (AIHW). Data will be obtained from one year prior to stroke, to at least five years post stroke depending on the availability of AIHW held data and when they are recruited to the study.

Additional Exclusion Criteria

Participants not in Australia.

Study Procedures

To answer the proposed research questions we will request linkages with the following datasets: Medical Benefits Schedule (MBS); the National Death Index (NDI); and the National Aged Care Data Clearing House (NACDC).

The MBS database contains transactional data related to all services that are subsidised by the Commonwealth Government under the Medicare scheme. Claims related to RACF attendances have specific item numbers that can be used to identify when a person has transitioned to this care type. Items for some community support programs such as Health Care Homes are also contained within the MBS dataset. The NACDC is a central independent repository (i.e. data warehouse) of national aged care data. It brings together data related to government-funded aged care programs that include: Residential Aged care; Home Care Packages Programme; Flexible Care; Aged Care Assessment Program; Aged Care Funding Instrument; and the Commonwealth Home Support Programme. The NDI provides reliable date and cause of death data for all Australians. Date of admission to a residential care will be determined using both MBS and NACDC data to maximise case ascertainment and allow cross-validation. Date and length of access to various aged care support schemes will also be obtained from these data sets. Data from 12 months prior to study commencement (to account for pre-stroke utilisation and living arrangements) to the latest possible will be requested. This will provide between one and four years of data depending on the date of recruitment to the trial e.g. those recruited in the first year will have up to four years of data whereas those recruited during the final year of the trial may only have one year of data.

A two stage separation model of data linkage will be used. This means that identifying data from Australian participants such as name, sex, residential address and date of birth will be submitted to the AIHW data linkage by AVERT DOSE site staff at each site. Probabilistic matching techniques will be used to ensure accurate matching with the administrative data. In our previous work patients' with acute stroke registered in the Australian Stroke Clinical Registry were matched to the NDI data with a sensitivity and specificity of >99% using these techniques. The content data (analysis variables) from both the administrative and AVERT DOSE datasets will be provided to the researchers in a de-identified format and will be stored and analysed in the Sax Institute's Secure Unified Research Environment (SURE). This remote-access computing environment or data safe haven must be used to access linked Commonwealth data so that data remain within the AIHW system. This complies with the highest possible standards of security and confidentiality. Content data will be merged using a project specific identification (ID) number.

At consent, the participant information sheet or the person responsible information sheet will detail that the AVERT DOSE study data may be linked with government held health data using a statement that is compliant with the AIHW ethics requirements. An information sheet will also be provided to the consenting clinician in case potential participants have questions about the security and use of their health data. Additional

ethics approval will also be sought through the AIHW HREC for these linkages and approval from the data custodians of the requested datasets obtained.

Outcome

The primary outcome is the time to admission to residential care in the first 1-4 years following stroke.

Secondary outcomes are:

(i) Number and type of support services utilised at 1, 2, 3 and 4 years following stroke.

(ii) Survival at 1, 2, 3, and 4 years following stroke.

Statistical Analyses

For the primary analysis multi-level multivariable statistical analysis (e.g. survival analyses) adjusted for the competing risk of death and other relevant covariates will be used. Data will be analysed taking into account the adaptive trial design. Participants will have varying timeframes of data depending on when they were recruited into the study. Therefore separate analyses will be performed for sub groups with 1, 2, 3 and 4 years of data.

For the secondary analysis:

(i) The support programs utilised by each group will be described and Poisson regression used to compare the number or rate of support programs utilised taking into account the competing risk of death at 1, 2, 3 and 4 years;

(ii) Multilevel survival analysis will be used to examine differences in time to death between groups up to 1, 2, 3 and 4 years following stroke accounting for the adaptive trial design.

Appendix C: Cognitive Reserve Sub Analysis

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Background

The cognitive reserve hypothesis proposes that pre-existing and effective cognitive processing strategies (neural reserve), and an increased ability of the brain to recruit alternate neural networks (neural compensation), may allow certain individuals' the ability to maintain effective cognitive performance despite high neuropathological burden or injury.[77] To date, cognitive reserve has been relatively unexplored in the context of acquired brain injury (for a selective review, see Nunnari et al., 2014)[78], particularly in conditions such as stroke, despite promising preliminary findings. Impairments in cognitive function are common following stroke, with between 30-50% of all stroke survivors experiencing long-term (chronic) single- or multi-domain deficits. Importantly, cognitive impairment has a significant negative impact on performance of activities of daily living and quality of life, with cognitive impairments often unmet in post-stroke rehabilitation programs. It is thus important to determine which factors might mediate cognition following stroke. Previous research has demonstrated that lifetime engagement in a combination of modifiable lifestyle factors (such as education, complexity of occupation, and engagement in physical, social and cognitive activities) may provide a 'cognitive reserve' and preserve cognitive function despite the presence of brain pathology/injury, such as that which occurs following stroke. The aim of this study is to assess whether cognitive reserve is associated with cognitive outcomes at 3 months following stroke. This study will provide additional insight into one of the key research aims developed from the 1st Stroke Recovery and Rehabilitation Roundtable, which emphasised the need for future research to attempt to characterise stroke recovery phenotypes.[79]

Aim and Hypothesis

Our primary aim is to investigate whether pre-morbid cognitive reserve mediates 1) cognitive and 2) disability outcomes at 3 months following stroke. We hypothesise that a higher pre-morbid cognitive reserve will be associated with better cognitive outcomes and lower disability (as measured by the MoCA and the mRS) at 3 months following stroke.

Population

Participants or person responsible (close relative or friend) will be asked to complete the Cognitive Reserve Index questionnaire (CRIq).

Additional Exclusion Criteria

Participants from some countries will be excluded, where the CRIq items of education, work and leisure have not been validated.

Study Procedures

COG-4[47], a subset of the NIHSS assessment will be used as an assessment of baseline cognitive function. Cognitive reserve will be assessed during the acute hospitalisation via the use of the CRIq (Appendix V).[80]

Outcome

Cognitive Reserve Index questionnaire (CRIq)

The CRIq is a standardised and validated multi-indicator questionnaire that compiles data regarding education, complexity of occupation, and engagement in physical, social, cognitive and leisure activities across the lifespan to form a composite measure of cognitive reserve. The questionnaire has a comprehensive psychometric profile, with established validity and reliability,[80] and has the added benefit of being able to be completely by proxy (by a close relative and/or friend) if an individual is unable to be interviewed for any reason (e.g. aphasia, cognitive impairment, fatigue). The CRIq may be completed at the 3 month follow-up if missed at baseline. Cognitive outcome at three months will be measured using the MoCA. Assessors will use the CRIq training instructions provided by the developers (http://www.cognitivereserveindex.org/).

Statistical analyses

To determine the association between cognitive reserve sub-groups (low, low-medium, medium, medium-high, and high cognitive reserve) and cognitive outcomes at 3 months following stroke, we will perform mixed effects modelling (regression modelling). We will control or model for demographics, pre-stroke physical activity using SGPALS (Appendix M)[35, 36], baseline characteristics (comorbidities including pre-existing neurological conditions), therapy group, baseline COG-4, with a minimum dataset requirement of age, sex, and stroke severity (NIHSS).

Appendix F. Study Schedule of Events

Assessment	Baseline	Intervention period	Follow up	
Timeline	**Day 0-2 post stroke**	**Days 0-14 post randomisation**	**3 Months +/- 7 days**	**6 Months +/- 7 days**
Screening/Eligibility	**X**			
Consent	**X[1]**			
Admission NIHSS (retrospective)	**X**			
Baseline NIHSS (includes COG-4)	**X**			
mRS	**X[2]**		**X**	**X**
TOAST		**X**		
rTICI score (for ECR participants only)	**X[12]**			
Mobility Scale for Acute Stroke	**X**	**X[16]**		
Line Bisection/ Trail Making A	**X[18]**		**X[18]**	
FMA-UL and FMA-LL	**X[18]**		**X[18]**	
Randomisation	**X**			
Demographics	**X**			
Past Medical History	**X**			
Routine CT/CTA/CTP/MRI/Carotid Duplex		**X[8]**		
SGPALS		**X[7]**		
Clinical Frailty Scale		**X[7]**		
Physiological Observations	**X[5]**	**X[6]**		
Intervention Protocol		**X[3]**		
Days to 50 Metre Walk		**X[10]**	**X[15]**	**X[15]**
10MWT		**X[10]**	**X**	**X**

Nottingham Extended ADL scale			**X**	**X**
Ambulation -FAC			**X**	**X**
Fatigue - FAS			**X**	**X**
EQ-5D-5L (participant or proxy)			**X**	**X**
COG-4			**X**	
MoCA			**X[17]**	
HADS or SADQ – 10 (aphasia pts)			**X**	**X**
Patient Centered Outcome Measures			**X**	**X**
Resource Use Questionnaire			**X**	**X**
Adverse Events/ IMEs/SAEs	**X**	**X**	**X[4]**	**X[13]**
Genetics only (selected sites)				
Saliva		**X[7]**		
Data Linkage only (Australia)				
AIHW				**X[14]**
Cognitive Reserve only (selected sites)				
CRIq		**X[11]**	**X[11]**	
Brazilian sites only				
Rehabilitation Package		**X**	**X**	

X[1] Participant, Person responsible as per local guidelines

X[2] Premorbid and baseline mRS

X[3] According to randomisation schedule. First mobility session to occur within 48 hours of onset of stroke

X[4] Adverse events meeting IME and SAE criteria only

X[5] First mobility protocol

X[6] First session for first 3 days post randomisation Measures of BP, temperature, HR, MAP, O^2, (pre, sitting, standing, post)

X[7] Prior to discharge. Can be collected at follow up visits if missed at baseline.

X[8] Routine scans and written reports performed prior to discharge collected for patients recruited prior to 1 July 2024.

X[10] At discharge or at 14 days post randomisation

X[11] To be done prior to discharge for participants recruited prior to 1 July 2024. If not completed before discharge, can be completed at 3 month visit. Can be completed by participant or person responsible.

X[12] Scores collected for participants that have had endovascular clot retrieval only.
X[13] Adverse events meeting SAE criteria only
X[14] Follow up for one to four years
X[15] If not achieved at earlier timepoint
X[16] At discharge, walking component only (item 5)
X[17] Blind version to be used if phone follow up
X[18] For participants recruited prior to 1 July 2024

Appendix G. National Institute of Health Stroke Scale (NIHSS)

Must be performed by a certified practitioner.

Category	Score/Definition
1a. Level of consciousness	☐ 0 = Alert, keenly responsive ☐ 1 = Not alert, but arousable with minimal stimulation ☐ 2 = Not alert, requires repeated stimulation or obtunded ☐ 3 = Responds only with reflex motor or automatic effects or totally unresponsive (see item 5)
1b. LOC questions (ask month and age)	☐ 0 = Answers both correctly ☐ 1 = Answers one correctly ☐ 2 = Both incorrect
1c. LOC commands (ask to open /close eyes and make a fist)	☐ 0 = Obeys both correctly ☐ 1 = Obeys one correctly ☐ 2 = Both incorrect
2. Best Gaze (horizontal eye movement)	☐ 0 = Normal ☐ 1 = Partial gaze palsy, Gaze abnormal in 1 or both eyes, but forced deviation or total gaze paresis not present ☐ 2 = Forced deviation or total gaze paresis not overcome with occulocephalic manoeuvre
3. Visual fields testing	☐ 0 = No visual field loss ☐ 1 = Partial hemianopia ☐ 2 = complete hemianopia, if participant has severely impaired consciousness (Q1=3), score 2 here ☐ 3 = Bilateral hemianopia, blind, including cortical blindness
4. Facial Palsy (ask subject to show teeth and raise eyebrows, and close eyes tightly)	☐ 0 = Normal symmetrical movement ☐ 1 = Minor paralysis or "mild" noted ☐ 2 = Partial paralysis (total or near total paralysis of lower face) ☐ 3 = Complete absence of movement in upper and lower face
5a. Motor Function **Right arm**	☐ 0 = No Drift (limb holds 90 or 45 degrees for 10 seconds ☐ 1 = Drift (limb hold 90 or 45 degrees but drifts down before 10 seconds, does not hit bed or support) ☐ 2 = Some effort against gravity ☐ 3 = No effort against gravity (limb falls) ☐ 4 = No movement ☐ 9 = Untestable
5b. Motor Function **Left arm**	☐ 0 = No Drift (limb holds 90 or 45 degrees for 10 seconds ☐ 1 = Drift (limb hold 90 or 45 degrees but drifts down before 10 seconds, does not hit bed or support) ☐ 2 = Some effort against gravity ☐ 3 = No effort against gravity (limb falls) ☐ 4 = No movement ☐ 9 = Untestable
6a. Motor Function **Right leg**	☐ 0 = No Drift (leg holds 30 degree position for 5 seconds) ☐ 1 = Drift ☐ 2 = Some effort against gravity ☐ 3 = No effort against gravity ☐ 4 = No movement ☐ 9 = Untestable

6b. Motor Function **Left Leg**	☐ 0 = No drift (leg holds 30 degree position for 5 seconds) ☐ 1 = Drift ☐ 2 = Some effort against gravity ☐ 3 = No effort against gravity ☐ 4 = No movement ☐ 9 = Untestable
7. Limb ataxia	☐ 0 = Absent (score 0 if unrecorded, participant unconscious, uncooperative or limb too weak to perform task) ☐ 1 = Present in one limb ☐ 2 = Present in two limbs (UL and LL)
8. Sensory (use pinprick to test arms, legs, trunk and face – compare sides)	☐ 0 = Normal ☐ 1 = Mild to moderate sensory loss (participant fells pin prick is less sharp or dull on affected side) ☐ 2 = Severe/total sensory loss (participant is unaware of being touched. Brainstem stroke with bilateral sensory loss)
9. Best language (describe picture, name items, read sentences)	☐ 0 = Normal (no aphasia) ☐ 1 = Mild to moderate aphasia (some loss of fluency, comprehension, however can make conversation) ☐ 2 = Severe aphasia (communication through fragmentary expression. Information exchange is limited) ☐ 3 = Mute, Global aphasia(no usable speech or auditory comprehension)
10. Dysarthria (read several words)	☐ 0 = Normal articulation ☐ 1 = Mild to moderate (slurring of words) ☐ 2 = Severe Dysarthria (Near unintelligible or unable to speak) ☐ 9 = Intubated or other physical barrier
11. Extinction/ inattention	☐ 0 = No abnormality ☐ 1 = Visual tactile auditory or personal inattention (or extinction to bilateral simultaneous in 1 of the sensory modalities) ☐ 2 = Profound hemi-inattention or inattention in more than 1 sensory modality. (Does not recognise own hand or orientates to one side of space)
Total Score ☐☐ (do not include items scores of '9' in total) **Assessed by:**_____	

Appendix H. Modified Rankin Scale (mRS) questionnaire

The modified Rankin Scale questionnaire[82] must be performed by a certified practitioner.

0	**No symptoms at all**; no limitations and no symptoms	☐
1	**No significant disability;** symptoms present but not other limitations. Question: Does the person have difficulty reading or writing, difficulty speaking or finding the right word, problems with balance or co-ordination, visual problems, numbness (face, arms, legs, hands, feet), loss of movement (face, arms, legs, hands, feet), difficulty with swallowing, or other symptoms resulting from stroke?	☐
2	**Slight disability;** limitations in participation in usual social roles, but independent for ADL. Questions: Has there been a change in the person's ability to work or look after others if these were roles before stroke? Has there been a change in the person's ability to participate in previous social and leisure activities? Has the person had problems with relationships or become isolated?	☐
3	**Moderate disability;** need for assistance with some instrumental ADL, but not basic ADL. Question: Is assistance essential for preparing a simple meal, doing household chores, looking after money, shopping or traveling locally?	☐
4	**Moderately severe disability;** need for assistance with some basic ADL, but not requiring constant care. Question: Is assistance required for eating, using the toilet, daily hygiene, or walking?	☐
	Severe disability; someone needs to be available at all times; care may be provided by either a trained or an untrained caregiver. Question: Does the person require constant care?	☐
6	**Dead**	☐

Appendix I: Mobility Scale for Acute Stroke (MSAS)

Each activity is scored using the rating scale below.[32]

Activities

1) Bridging from supine, buttocks clear of bed, return to supine.
2) Sitting from supine, legs over side of the bed, let the patient choose the side, return to supine.
3) Balanced sitting for 3 minutes, maximum base of support (feet on floor).
4) Sit to vertical stand from a standardised chair (height 43cm) with no arm rests.
5) Gait, assessed indoors on a level surface along a measured walkway of 10 metres, with or without a gait aid.

For activities 1, 2 and 4 the patient is asked to perform the activities three times and the best of three attempts is recorded. For activities 3 and 5 the overall assistance provide for the duration of the activity is recorded.

Rating Scale

1	Unable to do activity; patient makes no contribution to activity, or is unable to complete activity.
2	Maximum assistance of one to two people; patient makes minimal contribution to the activity.
3	Moderate assistance of one person, hands on assistance for most of the activity. The patient is able to perform a part of the activity independently.
4	Minimal assistance, hands on for part of the activity.
5	Supervised (verbal input, no hands on assistance, physiotherapist prepared to give assistance).
6	Unassisted and safe, no verbal input.

Appendix J: Revised Thrombolysis in Cerebral Infarction (rTICI)

Score	Modified TICI[54]
0	No perfusion or anterograde flow beyond site of occlusion
1	Penetration but not perfusion. Contrast penetration exists past the initial obstruction but with minimal filling of the normal territory
2	Incomplete perfusion wherein the contrast passes the occlusion and opacifies the distal arterial bed but rate of entry or clearance from the bed is slower or incomplete when compared with non-involved territories
2A	Some perfusion with distal branch filling of <50% of territory visualized
2B	Substantial perfusion with distal branch filling of ≥50% of territory visualized
2C	Near-complete perfusion except for slow flow in a few distal cortical vessels or presence of small distal cortical emboli
3	Complete perfusion with normal filling of all distal branches

Appendix K: Fugl-Meyer Assessment of Upper Limb (FMA-UL)

I Reflexes

1. Biceps	☐ 0 (No reflex)	☐ 2 (Reflex elicited)
2. Triceps	☐ 0 (No reflex)	☐ 2 (Reflex elicited)

II Flexor Synergy

Patient is asked to bring affected forearm fully supinated to ear of the affected side, elbow fully flexed, shoulder abducted to 90°/externally rotated/retracted/elevated. Ask patient to do with unaffected side first

3. Shoulder girdle retraction	☐ 0	☐ 1	☐ 2
	no scapular movement visualized or palpated	Any degree of retraction that is less than unaffected side	Equal to or greater retraction than the unaffected side
4. Shoulder girdle elevation	☐ 0	☐ 1	☐ 2
	no scapular movement visualized or palpated	Any degree of elevation that is less than unaffected side	Equal to or greater elevation than the unaffected side
5. Shoulder abduction	☐ 0	☐ 1	☐ 2
	No abduction	any degree of abduction less than 90°	equal to or greater abduction than 90°
6. Shoulder external rotation	☐ 0	☐ 1	☐ 2
	No external rotation	any degree of external rotation that is less than unaffected side	equal to or greater external rotation than the unaffected side
7. Elbow flexion	☐ 0	☐ 1	☐ 2
	No elbow flexion	any degree of elbow flexion that is less than	equal to or greater elbow

		unaffected side	flexion than the unaffected side

8. Forearm supination	☐ 0	☐ 1	☐ 2
	No forearm supination	any degree of supination that is less than unaffected side	equal to or greater supination than the unaffected side

III. Extensor Synergy

Starting in flexor synergy position (passively placed, if necessary), patient is instructed to bring hand towards opposite knee with forearm pronated. Can support elbow to avoid passive movement due to gravity. Ask patient to do unaffected side first

9. Shoulder adduction/internal rotation	☐ 0	☐ 1	☐ 2
	No adduction/internal rotation	any degree of add/int. rotation that is less than unaffected side	equal to or greater add/int. rotation than the unaffected side
10. Elbow extension	☐ 0	☐ 1	☐ 2
	No elbow extension	any degree of extension that does not reach 0° extension (even if contracture exists)	elbow extension that reaches 0° extension
11. Forearm pronation	☐ 0	☐ 1	☐ 2
	No pronation	any degree of pronation where palmar side of hand does not reach contralateral knee	palmar side of hand reaches contralateral knee in setting of full elbow ext and shoulder add/int. rot.

IV Movement Combining Synergies

12. Hand on Lumbar spine	☐ 0 No IP joint passes frontal plane defined by location of anterior iliac spine	☐ 1 ³1 IP joint passes frontal plane defined by location of anterior iliac spine	☐ 2 dorsal hand actively and completely reaches lumbar spine
13. Shoulder flexion to 90°, elbow fully extended, forearm in midposition b/w supination and pronation	☐ 0 cannot achieve starting position **or** deviation from starting position occurs at onset of shoulder flexion **or** no shoulder flexion occurs	☐ 1 while actively maintaining starting position, shoulder flexion does not reach 90°, **or** any deviation from starting position occurs following onset of shoulder flexion	☐ 2 actively maintains starting position and shoulder flexes to 90°
14. Pronation/Supination of forearm, elbow actively flexed to 90°, shoulder at 0°	☐ 0 cannot achieve starting position **or** deviation from starting position occurs at onset of shoulder flexion **or** no pronation or supination occurs	☐ 1 while actively maintaining starting position, any degree of supination or pronation that is less than unaffected side, **or** any deviation from starting position occurs after the onset of pronation or supination	☐ 2 achieves and maintains starting position, and pronation and supination is equal to or greater than unaffected side
V Movement out of Synergy			
15. Shoulder abduction to 90°, elbow fully extended throughout, forearm pronated	☐ 0 cannot achieve starting position **or** deviation from starting position	☐ 1 while actively maintaining starting position,	☐ 2 actively maintains starting position,

	occurs at onset of abduction **or** no shoulder abduction occurs	abduction does not reach 90°, **or** any deviation from starting position occurs following onset of abduction	and shoulder abducts to 90°
16. Shoulder Flexion, 90°-180°, elbow fully extended, forearm midposition b/w supination and pronation	☐ 0 cannot achieve starting position **or** deviation from starting position occurs at onset of shoulder flexion **or** no shoulder flexion >90° occurs	☐ 1 while actively maintaining starting position, shoulder flexion does not reach 180°, **or** any deviation from starting position occurs following onset of shoulder flexion >90°,	☐ 2 actively maintains starting position, and shoulder flexes to 180°
17. Pronation/Supination of forearm, elbow fully extended, shoulder kept b/w 30°-90°	☐ 0 cannot maintain starting position **or** deviation from starting position occurs at onset of pronation/supination **or** no pronation or supination occurs	☐ 1 while maintaining starting position, any degree of pronation **or** supination is less than the unaffected side, **or** deviation from starting position occurs following onset of pronation **or** supination	☐ 2 maintains starting position, and pronation and supination is equal to or greater than unaffected side

VI Normal Reflex Activities

If all previous items have achieved max score, evaluate biceps, triceps and finger flexion reflexes. Otherwise score 0.

18. Reflex activity	☐ 0 two or three reflexes are hyperactive, or score on last tests < maximum	☐ 1 one reflex is hyperactive	☐ 2 all 3 reflexes are present, none is hyperactive

VII Wrist

Can support patient at proximal forearm

19. Extension wrist, shoulder at 0°, elbow at 90°	☐ 0 cannot achieve starting position even with support provided to proximal forearm **or** deviation from starting position occurs at onset of wrist extension **or** cannot achieve wrist extension to 15°	☐ 1 achieves 15° wrist extension but with attempt to take resistance, subject deviates from starting position, **or** subject cannot maintain 15° wrist extension	☐ 2 maintains starting position while wrist is extended to 15° and slight resistance is taken (force equal to 3+/5 mmt)
20. Alternating extension/flexion, shoulder at 0°, elbow at 90°	☐ 0 cannot achieve starting position even with support provided to proximal forearm **or** deviation from starting position occurs at onset of wrist movement **or** no wrist movement occurs	☐ 1 any degree of wrist movement that is less than subject's passive ROM in flexion or extension **or** deviation from starting position occurs following onset of wrist movement	☐ 2 maintains starting position, and wrist flexion and extension is equal to passive ROM during 1 full flexion/extension cycle

21. Extension wrist, shoulder flexed 30°-90°, elbow extended to 0°	☐ 0 cannot achieve starting position even with support provided to proximal forearm **or** deviation from starting position occurs at onset of wrist extension **or** cannot achieve wrist extension to 15°	☐ 1 achieves 15° wrist extension but with attempt to take resistance, subject deviates from starting position, **or** subject cannot maintain 15° wrist extension	☐ 2 maintains starting position while wrist is extended to 15° and slight resistance is taken (force equal to 3+/5 mmt)
22. Alternating extension/flexion, shoulder at 30°-90°, elbow extended to 0°	☐ 0 cannot achieve starting position even with support provided to proximal forearm **or** deviation from starting position occurs at onset of wrist movement **or** no wrist movement occurs	☐ 1 any degree of wrist movement that is less than subject's passive ROM in flexion or extension **or** deviation from starting position occurs following onset of wrist movement	☐ 2 maintains starting position, and wrist flexion and extension is equal to passive ROM during 1 full flexion/extension cycle
23. Wrist Circumduction, shoulder at 30°- 90°, elbow extended to 0°	☐ 0 cannot achieve starting position even with support provided to proximal forearm **or** deviation from starting position occurs at onset of wrist movement **or** no circumduction is possible	☐ 1 maintains starting position, and any degree of wrist circumduction that is less than the unaffected side **or** deviation from starting position occurs following onset of wrist movement	☐ 2 maintains starting position, and wrist circumduction is equal to unaffected side, and is performed smoothly

VII Hand

Patient is instructed to perform following tasks with elbow at 90° (support elbow if necessary, but don't support wrist). Start with fingers in resting position except mass extension task

24. Finger mass flexion	☐ 0 No MCP or IP flexion occurs	☐ 1 any degree of MCP or IP flexion in any finger that <90°	☐ 2 MCPs and IPs flexion that is equal to or greater than the unaffected side
25. Finger mass extension Start with fingers flexed	☐ 0 No MCP or IP extension occurs	☐ 1 any degree of MCP or IP flexion in any finger that does not reach 0°	☐ 2 MCPs and IPs extension that is equal to or greater than the unaffected side
26. Hook Grasp (MCPs extended to 0° with PIPs and DIPs of digits 2-5 flexed to 45°)	☐ 0 Subject cannot achieve starting position	☐ 1 maintains starting position, but grasp cannot withstand resistance (equal to 4/5 mmt)	☐ 2 maintains starting position, and holds grasp against great resistance (equal to 4/5 mmt)
27. Thumb Adduction	☐ 0 Subject cannot achieve starting position **or** cannot grasp paper	☐ 1 maintains starting position, and grasps paper but cannot withstand resistance (equal to 4/5 mmt)	☐ 2 maintains starting position, and paper is held against great resistance (equal to 4/5 mmt)
28. Pincer Grasp	☐ 0 Subject cannot achieve starting position **or** cannot grasp pencil	☐ 1 maintains starting position, and pencil is kept in place but not against	☐ 2 maintains starting position, and pencil is held against great resistance (equal to 4/5 mmt)

		resistance (equal to 4/5 mmt)	

29. Grasp a Can

☐ 0	☐ 1	☐ 2
Subject cannot achieve starting position **or** cannot grasp can	maintains starting position, and can is kept in place but not against resistance (equal to 4/5 mmt)	maintains starting position, and can is held against great resistance (equal to 4/5 mmt)

30. Spherical Grasp

☐ 0	☐ 1	☐ 2
Subject cannot achieve starting position **or** cannot grasp ball volitionally	maintains starting position, and ball is kept in place but not against resistance (equal to 4/5 mmt)	maintains starting position, and ball is held against great resistance (equal to 4/5 mmt)

VIII Coordination/Speed

Ask patient to place tip of index finger from knee to nose, 5 times, in a rapid a succession as possible

31. Tremor

☐ 0	☐ 1	☐ 2
marked tremor, when present substantially interferes with coordination	slight tremor, when present mildly interferes with coordination	tremor is absent

32. Dysmetria

☐ 0	☐ 1	☐ 2
pronounced or unsystematic dysmetria (random error occurs)	slight and systematic dysmetria (same error of size and direction)	no dysmetria (index finger or MCP lands in area 1 cm squared to tip of nose)

33. Speed

☐ 0	☐ 1	☐ 2
at least 6 seconds slower than the unaffected side or subject unable to complete task	between 2-5 seconds slower than unaffected side	less than 2 seconds slower than unaffected side

Appendix L. Fugl-Meyer Assessment of Lower Limb (FMA-LL)

PART 1			
I. Reflexes With patient in the supine position elicit the following reflexes:			
1. Achilles or Patellar reflex	☐ 0 No reflex		☐ 2 Reflex elicitable
2. Knee flexor reflex	☐ 0 No reflex		☐ 2 Reflex elicitable
For efficiency in scoring Question 14 (Section V), note now if reflex activity is normal or hyperactive.			
II. Synergistic Movement: Flexor Synergy Instruct the patient to flex his hip, knee, and ankle joints fully while in supine position.			
3. Hip flexion	☐ 0 Cannot be performed	☐ 1 Partial motion	☐ 2 Full motion
4. Knee flexion	☐ 0 Cannot be performed	☐ 1 Partial motion	☐ 2 Full motion (Check to ensure that knee flexion is active)
5. Ankle dorsiflexion	☐ 0 Cannot be performed	☐ 1 Partial motion	☐ 2 Full motion
III. Synergistic Movement: Extensor Synergy From the position of full hip, knee, and ankle flexion, instruct the patient to extend and adduct his lower extremity against resistance. A score of '1' or '2' for these 4 questions requires active movement not just movement due to gravity.			
6. Hip extension	☐ 0 No motion	☐ 1 Weak motion	☐ 2 Almost full strength compared to normal
7. Hip adduction	☐ 0 No motion	☐ 1 Weak motion	☐ 2 Almost full strength compared to normal
8. Knee extension	☐ 0 No motion	☐ 1 Weak motion	☐ 2 Almost full strength compared to normal
9. Ankle plantarflexion	☐ 0 No motion	☐ 1 Weak motion	☐ 2 Almost full strength compared to normal

PART 2			
IV. Movement combining synergies Sitting with knees free of chair/bedside, there should be slight knee extension.			
10. Knee flexion beyond 90°	☐ 0 No active motion	☐ 1 From slightly extended position, knee can be actively flexed but not beyond 90°	☐ 2 Knee flexion beyond 90°
11. Ankle dorsiflexion	☐ 0 No active dorsiflexion	☐ 1 Partial active dorsiflexion	☐ 2 Normal dorsiflexion
V. Movement out of Synergy Standing with hip at 0°			
12. Knee flexion	☐ 0 No active movement or hip starts to flex at onset of knee flexion	☐ 1 Partial knee flexion or hip starts to flex during motion	☐ 2 Knee flexes to at least 90°
13. Ankle dorsiflexion	☐ 0 No active movement or hip or knee starts to flex at onset of ankle dorsiflexion	☐ 1 Partial ankle dorsiflexion, or hip or knee starts to flex during motion	☐ 2 Full ankle dorsiflexion compared to the other side
VI. Normal reflexes			
14. If above 2 tests, Questions 12 and 13, are faultless, evaluate achilles, patellar, and knee flexor deep tendon reflexes as below. Otherwise, do not perform this test and record a score of '0'.	☐ 0 2 out of the 3 (or all 3 out of 3) are markedly hyperactive	☐ 1 One reflex is hyperactive or two reflexes are lively	☐ 2 No more than one reflex lively

Appendix M: Saltin-Grimby Physical Activity Level Scale (SGPALS)

Pre-stroke physical activity and exercise. Mark only one option. [36, 83]

How much do you move and exert yourself physically during your leisure time? If your activity varies greatly between, for example, summer and winter, try to estimate an average. The question refers to the past year.

1. Physically inactive ☐
Almost completely inactive, reading, watching television, watching movies, using computers or doing other sedentary activities, during leisure time……

2. Some light physical activity ☐
Physically active for at least 4 hours/week, such as riding a bicycle or walking to work, walking with the family, gardening, fishing, table tennis, bowling etc.…….

3. Regular physical activity and training ☐
Spending time doing heavy gardening, running, swimming, playing tennis, badminton, calisthenics and similar activities, for at least 2-3 hours/week……..……

4. Regular hard physical training for competitive sports ☐
Spending time running, orienteering, skiing, swimming, playing football, handball etc. several times per week

Appendix N: TOAST Classification of Subtypes of Acute Ischemic Stroke

Aetiology

☐ Large Artery Atherosclerosis
- ☐ Extractranial atherosclerotic disease
- ☐ Intracranial atherosclerotic disease
- ☐ Other

☐ Cardio-embolism
- ☐ Left atrial thrombus
- ☐ Left ventricular thrombus
- ☐ Atrial Fibrillation
- ☐ Recurrent Myocardial Infarction (< 1 month)
- ☐ Valve disease
- ☐ Bioprosthetic/mechanical heart valve
- ☐ Dilated Myocardiopathy
- ☐ Endocarditis
- ☐ Other Cardio-embolic Source

☐ Small Artery Occlusion (lacune)

☐ Stroke of undetermined aetiology
- ☐ Multiple aetiologies seem likely
- ☐ Don't know despite thorough investigation
- ☐ Don't know, evaluation incomplete

☐ Other Determined aetiology
- ☐ Hypercoagulable state
- ☐ Iatrogenic
- ☐ Arterial Dissection (Carotid or Vertebral)
- ☐ Other

In the opinion of the clinical and based on available clinical and imaging information please indicate the aetiology of the ischaemic stroke.

☐ Embolic

☐ Lacunar (small vessel, 2 -20 mm non cortical infarcts, basal ganglia, internal capsule, corona radiate, pons)

☐ Another Cause

Appendix O. Functional Ambulation Classification (FAC)

Level 0 (non-ambulation): Absolute walking incapacity, even with external help.

Level 1 (non-functional ambulation): Dependent walking, which requires the permanent help of others. The patient must be firmly supported by 1 or 2 people, and/or walking is possible only within a therapy session at home, or at the hospital, between parallel bars. This is the only functional level that is not independent and is therefore called non-functional.

Level 2 (household ambulation): Walking is only possible indoors, on flat, horizontal surfaces, usually within a known and controlled area, such as in the home.

Level 3 (surroundings of the house ambulation [or neighbourhood]): Patients are able to walk indoors and outdoors on uneven surfaces, and they are able to climb an occasional step or stair. Therefore, the patient is able to walk in the street, albeit within a limited and restricted walking distance.

Level 4 (independent community ambulation): Patients are able to walk on all types of irregular surfaces. They can ascend and descend steps or stairs, ramps, curbs, etc. They have a considerable, even unrestricted, walking distance, so much so that they are capable of shopping for food and accomplishing other basic chores.20 However, they are not considered normal walkers because they have aesthetic anomalies, such as an obvious limp.

Level 5 (normal ambulation): Walking is completely normal in both distance and appearance, both at home and outside and with an unlimited distance; there is no aesthetic anomaly or limp. They can tiptoe, walk on their heels, and in tandem.

Appendix P. EuroQol 5 dimensions, 5 levels (EQ-5D-5L)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

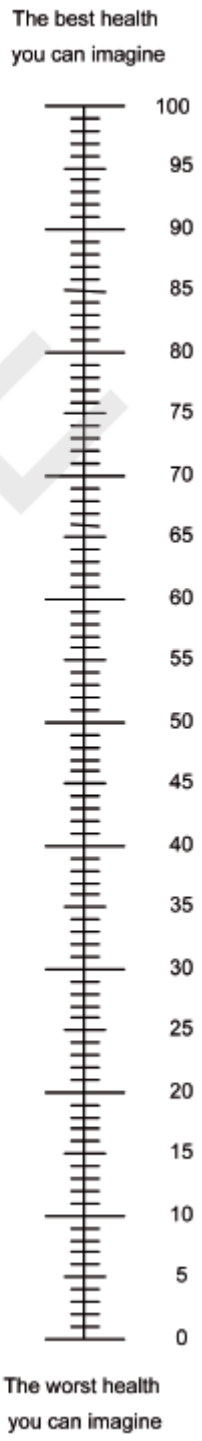
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix Q. Hospital Anxiety and Depression Scale (HADS)

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings she or he will be able to help you more. This questionnaire is designed to help your clinician know how you feel. Ignore the numbers printed on the left of the questionnaire. Read each item and underline the reply which comes closest to how you have been feeling in the past week.

Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

A **I feel tense or 'wound up':**

3 Most of the time
2 A lot of the time
1 From time to time, occasionally
0 Not at all

D **I still enjoy the things I used to enjoy:**

0 Definitely as much
1 Not quite as much
2 Only a little
3 Hardly-at all

A **I get a sort of frightened feeling as if something awful is about to happen:**

3 Very definitely and quite badly
2 Yes, but not too badly
1 A little, but it doesn't worry me
0 Not at all

D **I can laugh and see the funny side of things:**

0 As much as I always could
1 Not quite as much now
2 Definitely not so much now
3 Not at all

A **Worrying thoughts go through my mind:**

3 A great deal of the time
2 A lot of the time
1 From time to time but not too often
0 Only occasionally

D **I feel cheerful:**

3 Not at all
2 Not often
1 Sometimes
0 Most of the time

A **I can sit at ease and feel relaxed:**

0 Definitely
1 Usually
2 Not often
3 Not at all

D **I feel as if I am slowed down:**

3 Nearly all the time
2 Very often
1 Sometimes
0 Not at all

A **I get a sort of frightened feeling like 'butterflies' in the stomach:**

0 Not at all
1 Occasionally
2 Quite often
3 Very often

Appendix R. Stroke Aphasic Depression Questionnaire (SADQ-H 10)

Please indicate how many days of the last 7 the participant has shown the following behaviours:

1. Did he/she have weeping spells?

Every day this week	On 4-6 days this week	On 1- 4 days this week	Not at all this week

2. Did he/she have restless disturbed nights?

Every day this week	On 4-6 days this week	On 1- 4 days this week	Not at all this week

3. Did he/she avoid eye contact when you spoke to him/her?

Every day this week	On 4-6 days this week	On 1- 4 days this week	Not at all this week

4. Did he/she burst into tears?

Every day this week	On 4-6 days this week	On 1- 4 days this week	Not at all this week

5. Did he/she indicate suffering from aches and pains?

Every day this week	On 4-6 days this week	On 1- 4 days this week	Not at all this week

6. Did he/she get angry?

Every day this week	On 4-6 days this week	On 1- 4 days this week	Not at all this week

7. Did he/she refuse to participate in social activities?

Every day this week	On 4-6 days this week	On 1- 4 days this week	Not at all this week

8. Did he/she sit without doing anything?

Every day this week	On 4-6 days this week	On 1- 4 days this week	Not at all this week

9. Did he/she keep him/herself occupied during the day?

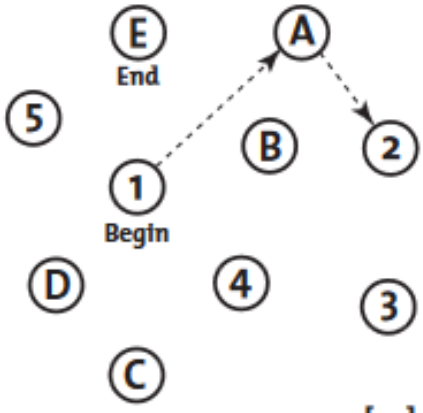
Every day this week	On 4-6 days this week	On 1- 4 days this week	Not at all this week

10. Did he/she get restless and fidgety?

Every day this week	On 4-6 days this week	On 1- 4 days this week	Not at all this week

Appendix S. Montreal Cognitive Assessment (MoCA)

VISUOSPATIAL / EXECUTIVE — POINTS



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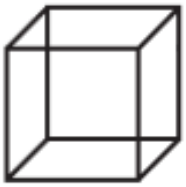


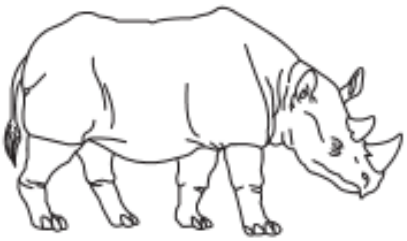
[ ] [ ]

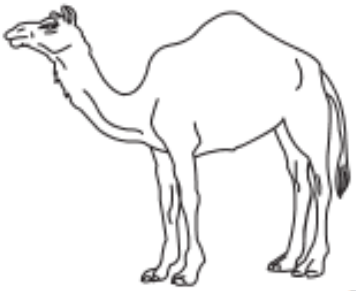
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

___/5

NAMING





[ ] [ ] [ ]

___/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

___/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

___/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

___/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

___/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

___/6

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Normal ≥ 26 / 30

TOTAL ___/30

Add 1 point if ≤ 12 yr edu

Appendix T. Fatigue Assessment Scale (FAS)

The following 10 statements refer to how you usually feel. For each statement you can choose one out of five answer categories, varying from *never* to *always*. 1 = *never*; 2 = *sometimes;* 3 = *regularly*; 4 = *often*; 5 = *always*.

	Never	Sometimes	Regularly	Often	Always
1. I am bothered by fatigue (WHOQOL)	1	2	3	4	5
2. I get tired very quickly (CIS)	1	2	3	4	5
3. I don't do much during the day (CIS)	1	2	3	4	5
4. I have enough energy for everyday life (WHOQOL)	1	2	3	4	5
5. Physically, I feel exhausted (CIS)	1	2	3	4	5
6. I have problems starting things (FS)	1	2	3	4	5
7. I have problems thinking clearly (FS)	1	2	3	4	5
8. I feel no desire to do anything (CIS)	1	2	3	4	5
9. Mentally, I feel exhausted	1	2	3	4	5
10. When I am doing something, I can concentrate quite well (CIS)	1	2	3	4	5

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Note: The abbreviations after the items indicate the scale from which the items has been abstracted. The following are the scales:
CIS - Checklist Individual Strength
WHOQOL - World Health Organization Quality of Life assessment instrument
FS - Fatigue Scale

Appendix U. Nottingham Extended ADL Scale (NEADL)

Nottingham Extended ADL Scale

The following questions are about everyday activities. Please answer by ticking ONE box for each question. Please record what you have ACTUALLY done in the last few weeks.

DID YOU.....	Not at all	with help	on your own with difficulty	on your own
1. Walk around outside?	☐	☐	☐	☐
2. Climb stairs?	☐	☐	☐	☐
3. Get in and out of a car?	☐	☐	☐	☐
4. Walk over uneven ground?	☐	☐	☐	☐
5. Cross roads?	☐	☐	☐	☐
6. Travel on public transport?	☐	☐	☐	☐
7. Manage to feed yourself?	☐	☐	☐	☐
8. Manage to make yourself a hot drink?	☐	☐	☐	☐
9. Take hot drinks from one room to another?	☐	☐	☐	☐
10. Do the washing up?	☐	☐	☐	☐
11. Make yourself a hot snack?	☐	☐	☐	☐

	No	With help	On your own with difficulty	On your own
12.Manage your own money when out?	☐	☐	☐	☐
13. Wash small items of clothing?	☐	☐	☐	☐
14.Do your own housework?	☐	☐	☐	☐
15.Do your own shopping?	☐	☐	☐	☐
16. Do a full clothes wash?	☐	☐	☐	☐
17.Read newspapers or books?	☐	☐	☐	☐
18.Use the telephone?	☐	☐	☐	☐
19. Write letters?	☐	☐	☐	☐
20.Go out socially?	☐	☐	☐	☐
21. Manage your own garden?	☐	☐	☐	☐
22. Drive a car?	☐	☐	☐	☐

Appendix V. Cognitive Reserve Index questionaire (CRIq)

CRI-Education

Instructions: Count 1 for each year of education. Count 0.5 for every 6-month period of vocational training courses taken.

	Years
1. Years of education (including postgraduate studies and any specialization)	.....
2. Vocational training (0.5 for every 6 months)	.....

CRI-WorkingActivity

Instruction: Indicate working years rounded off on a five-year scale (0-5-10-15-20, etc.; e.g., if a person has been working for 17 years, write down 20). The degree of intellectual involvement and personal responsibility discriminates between the 5 levels of working activity. Report on all working activities, even in the case of simultaneously held multiple jobs.

	Years
1. Low skilled manual work (farm work, gardener, housemaid, caregiver, waiter, driver, mechanic, plumber, call center operator, babysitter, etc.)	.....
2. Skilled manual work (craftsman, cook, store clerk, tailor, representative, serviceman/servicewoman, hairdresser, clerical worker, nurse, etc.)	.....
3. Skilled non manual work (business owner, white-collar employee, sales agent, priest or monk/nun, real estate agent, nursery school teacher, musician, etc.)	.....
4. Professional occupation (Managing director of a small company, lawyer, qualified freelance professional, contractor, doctor, teacher, engineer, etc.)	.....
5. Highly responsible or intellectual occupation (Managing director of a big company, senior manager, judge, university professor, surgeon, politician, etc.)	.....

CRI-LeisureTime

Instructions:

- Each item refers to activities carried out regularly throughout adult life (i.e. from 18 years onwards).
- All paid activities are excluded from this section (for paid activities, return to CRI-WorkingActivity).
- Register answers according to the frequency mentioned for each activity (e.g., weakly, monthly, annual).
- The column Years refers to the number of years in which the mentioned activity has been carried out Often/Always, overstating according to a scale of 5 to 5 years (5-10-15-20, etc.). For example, whether a person regularly reads a newspaper for 27 years, will be registered Often/Always for 30 years, even if he/she has stopped reading for many years.
- If the activity has never or seldomly been carried out (option Never/Rarely) the number of years need not be indicated.
- If over the participants lifespan the activity changed in frequency in a significant manner, only the period (in number of years) of the highest frequency is to be considered. For example, if a person drove a car every day for 40 years, but in the following 15 years he/she did so only once or twice a week, than the answer is Often/Always for 40 years.

1. ACTIVITIES WITH WEEKLY FREQUENCY

	less or equal then 2 times in a week	more or equal then 3 times in a week	Years
1. Reading newspapers and magazines	☐ Never/Rarely	☐ Often/Always	.....
2. Domestic chores (cooking, washing, grocery shopping, ironing, etc.)	☐ Never/Rarely	☐ Often/Always	.....
3. Driving (not biking)	☐ Never/Rarely	☐ Often/Always	.....
4. Leisure activities (sports, hunting, dancing, chess, coin collecting, etc.)	☐ Never/Rarely	☐ Often/Always	.....
5. Using new technologies (digital cameras, computer, Internet etc.)	☐ Never/Rarely	☐ Often/Always	.....

2. ACTIVITIES WITH MONTHLY FREQUENCY

	less or equal then 2 times in a month	more or equal then 3 times in a month	Years
1. Social activities (political parties, recreational clubs, associations, etc.)	☐ Never/Rarely	☐ Often/Always	.....
2. Cinema, theater	☐ Never/Rarely	☐ Often/Always	.....
3. Gardening, DIY, small-scale operations such as knitting, etc.	☐ Never/Rarely	☐ Often/Always	.....
4. Looking after grandchildren/nieces/ nephews or elderly parents	☐ Never/Rarely	☐ Often/Always	.....
5. Voluntary work	☐ Never/Rarely	☐ Often/Always	.....
6. Artistic activities (music, singing, performance, painting, writing, etc.)	☐ Never/Rarely	☐ Often/Always	.....

3. ACTIVITIES WITH ANNUAL FREQUENCY

	less or equal then 2 times in a year	more or equal then 3 times in a year	Years
1. Exhibitions, concerts, conferences	☐ Never/Rarely	☐ Often/Always	.....
2. Journeys lasting several days	☐ Never/Rarely	☐ Often/Always	.....
3. Reading books	☐ Never/Rarely	☐ Often/Always	.....

4. ACTIVITIES WITH FIXED FREQUENCY

1. Children	☐ No	☐ Yes	number .....

			Years
2. Pet care	☐ Never/Rarely	☐ Often/Always	.....
3. Managing one's current account	☐ Never/Rarely	☐ Often/Always	.....

Questionnaire administered to: interested party ☐ family/caregiver ☐ .....

Date: ...../...../..... Interviewer: .....

Appendix W: Trail Making A and Line Bisection

Line Bisection

Participant is asked to bisect the horizontal line presented, with a vertical line at the midpoint.

Trail Making A

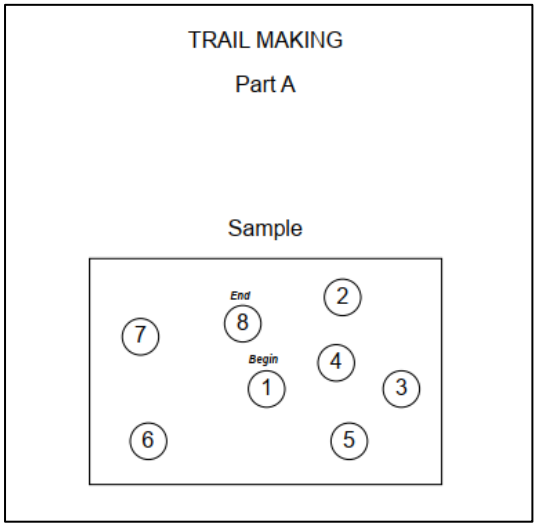
Participant is asked to connect the circles in order after practice using the sample. Time taken to complete is recorded in seconds from the point at which the patient starts.

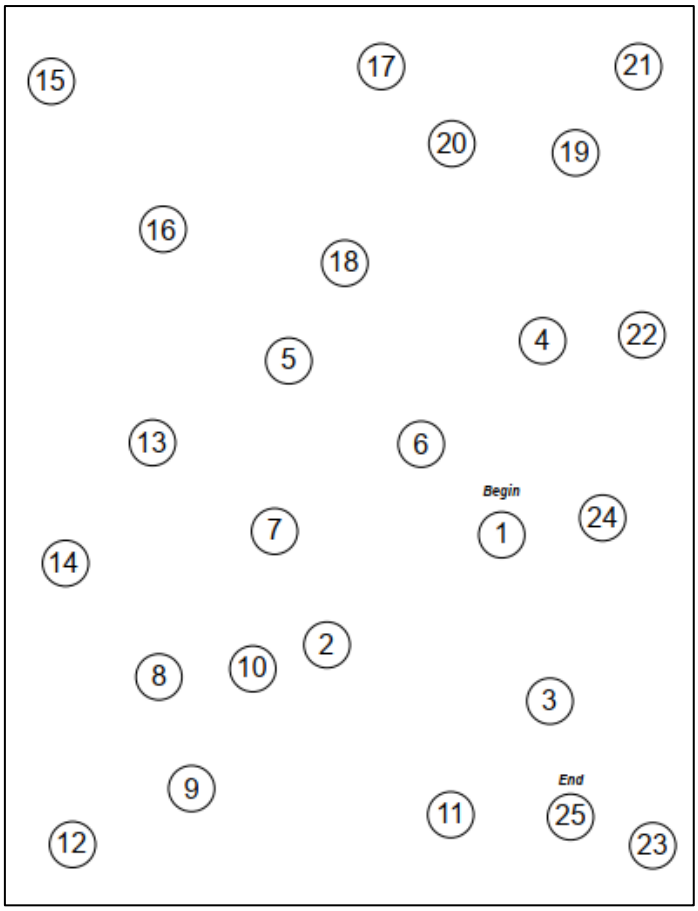
Instructions to participant.

"On this page [point] *are some numbers. Begin at number one* [point] *and draw a line from 1 to 2* [point], *2 to 3* [point], *3 to 4* [point] *and so on, in order until you reach the end [point to end circle]. Draw the lines as fast as you can and don't lift the pencil from the paper. Ready? Begin."*

- Show PART A

"On this page are the numbers 1 to 25. Do this the same way. Begin at number 1 [point] *and draw a line from 1 to 2* [point], *2 to 3* [point], *3 to 4* [point] *and so on until you reach the end* [point]. *Remember to work as fast as you can. Ready? Begin."*





Appendix X: Clinical Frailty Scale

Clinical Frailty Scale

1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

3 Managing Well – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4 Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.

5 Mildly Frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 Moderately Frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

7 Severely Frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9 Terminally Ill – Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia,** recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia,** they cannot do personal care without help.

Appendix Y: MoCA Blind

MEMORY		FACE	VELVET	CHURCH	DAISY	RED	POINTS
Read list of words, subject must repeat them. Do 2 trials even if 1st trial is successful. Do a recall after 5 minutes.	1st trial						No points
	2nd trial						

ATTENTION

Read list of digits (1 digit/sec.) Subject has to repeat them in the forward order [ ] 2 1 8 5 4 — ___/ 2

Subject has to repeat them in the backward order [ ] 7 4 2

Read list of letters. The subject must tap with his hand at each letter A. No point if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B — ___/ 1

Serial 7 subtraction starting at 100

[ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** — ___/ 3

LANGUAGE

Repeat: I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ] — ___/ 2

Fluency / Name maximum number of words in one minute that begin with the letter F.

[ ] _____ (N ≥ 11 words) — ___/ 1

ABSTRACTION

Similarity between e.g. banana - orange = fruit

[ ] train - bicycle

[ ] watch - ruler — ___/ 2

DELAYED RECALL		FACE	VELVET	CHURCH	DAISY	RED	
	Has to recall words **With no cue**	[ ]	[ ]	[ ]	[ ]	[ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

___/ 5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City — ___/ 6

© Z. Nasreddine MD **www.mocatest.org** Normal ≥ 18 / 22

TOTAL ___/ 22

Add 1 point if ≤ 12 yr edu

Administered by:_____

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