A phase 3, multicentre, randomised controlled trial of very early rehabilitation after stroke (AVERT).

Protocol Version 3 – 25 April 2008

National Stroke Research Institute

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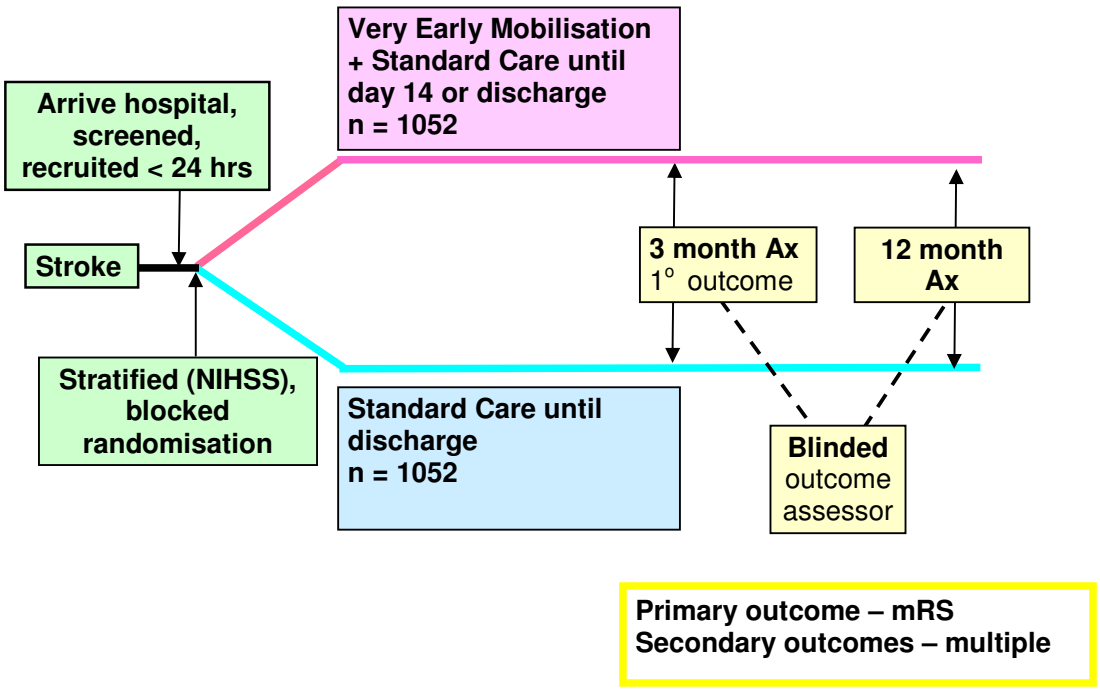
Glossary of Abbreviations

ARR	Absolute Risk Reduction
AQoL	Assessment of Quality of Life
AVERT	A Very Early Rehabilitation Trial
CI	Confidence Interval
CRF	Case Report Form
DMC	Data Safety and Monitoring Committee
IDA	Irritability, Depression and Anxiety scale
HREC	Human Research Ethics Committee
ICU	Intensive Care Unit
mRS	modified Rankin Scale
MoCA	Montreal Cognitive Assessment
NIHSS	National Institute of Health Stroke Scale
NNT	Numbers Needed to Treat
NSRI	National Stroke Research Institute
MSAS	Mobility Scale for Acute Stroke
OCSP	Oxfordshire Community Stroke Program Classification
PDA	Personal Digital Assistant
rt-PA	recombinant tissue-Plasminogen Activator
SC	Standard Care
SSS	Scandinavian Stroke Scale
VEM	Very Early Mobilisation

AVERT Pathway – Phase 3



1 Protocol Synopsis

Title	A Very Early Rehabilitation Trial (AVERT). A phase 3, multicentre, randomised controlled trial of very early rehabilitation after stroke.
Protocol	AVERT Protocol Version 3 - 25 April 2008
Sponsor	This study is financially supported by grant funding obtained from the Australian National Health and Medical Research Council (Grant Number: 386201).
Phase	Phase 3
Indication	Patients admitted within 24 hours of first or recurrent stroke.
Primary Outcome	Modified Rankin Scale score at 3 months.
Secondary Outcomes	Safety: Death rate and the rate and severity of important medical events (stroke progression, recurrent stroke, falls, angina, myocardial infarctions, deep venous thromboses, pulmonary emboli, pressure sores, chest infections, urinary tract infections) at 3 months; and all adverse events during the intervention period. Health-related quality of life: Assessment of Quality of Life and Irritability, Depression and Anxiety scale; at 3 and 12 months Cognitive function using the Montreal Cognitive Assessment (MoCA) at 3 months. Cost effectiveness and cost utility: Comprehensive questionnaire at 3 and 12 months and baseline mRS. Long term efficacy: mRS at 12 months. Activity limitations: Time to walking 50 metres; Rivermead Motor Assessment and Barthel Index at 3 and 12 months. Dose-response: Intervention dose and Modified Rankin Scale score at 3 and 12 months. Patient severity and efficacy: Mild, moderate and severe stroke (NIHSS) and mRS at 3 and 12 months Staff injury: The number, severity and type of injury to staff for AVERT patients during the intervention period.
Hypotheses	Compared to standard care (SC) alone, very early mobilisation (VEM) of stroke patients (in addition to standard care): 1. Reduces death and disability at 3 months; 2. Reduces the number and severity of complications experienced by patients at 3 months; 3. Results in better quality of life at 12 months; and 4. Is cost-effective at 12 months.
Study Design	Patients will be randomised into SC (control) or VEM (experimental intervention). Block randomisation procedures according to the patients stroke severity (mild, moderate, severe) and hospital site, with permuted blocks of various lengths. Patients and outcome assessors are blinded to intervention group.
Number of subjects	A total of 2104 patients to be recruited.
Patient & Study Duration	Patients participate in the trial for 12 months. The study will take place over 5 years with start up and recruitment over 3.5 years.
Number of Centres	Approximately 30 sites worldwide. A combination of larger metropolitan institutions and smaller regional hospitals will be involved.
Inclusion	Patients with first or recurrent stroke diagnosis, haemorrhage or infarct.

Criteria	Admitted to hospital within 24 hours of onset of symptoms for transfer (and care) in the stroke unit. Consciousness: Must at least react to verbal commands
Exclusion Criteria	Pre-stroke (retrospective) modified Rankin Scale score of 3, 4 or 5 (indicating significant previous disability). Deterioration in patient's condition in the first hour of admission resulting in direct admission to ICU, a documented clinical decision for palliative treatment (e.g. those with devastating stroke) or immediate surgery. Concurrent diagnosis of rapidly deteriorating disease (e.g. terminal cancer). Unstable coronary or other medical condition that is judged by the investigator to impose a hazard to the patient by involvement in the trial. A suspected or confirmed lower limb fracture at the time of stroke preventing the implementation of the mobilisation protocol. Patients who have received rt-PA can be recruited if the attending physician permits and if mobilisation within 24 hours of stroke is permitted. Patients cannot be concurrently recruited to drug or other intervention trials. Patients may participate in AVERT if they are also recruited to non intervention trials. Systolic blood pressure less than 110, or greater than 220mmHg. Oxygen saturation of less than 92% with supplementation. Resting heart rate of less than 40 or greater than 110 beats per minute. Temperature of greater than 38.5°C.
Intervention Groups	Control Intervention: Standard Care is usual stroke unit care. Experimental Intervention: Very Early Mobilisation (VEM). The per-protocol VEM will include patients who received an additional 3 mobilisation sessions (physiotherapy and nursing) on average per day over the intervention period. The intervention period lasts for 14 days or until the patient is discharged from stroke unit care, whichever is sooner. VEM is provided by trained physiotherapy and nursing staff according to a detailed protocol.
Randomisation Procedures	A remote, web-based, computer-generated randomisation procedure is used. Assessors have certified reliability for NIHSS and mRS.
Trial Progress	The Data Safety and Monitoring Committee will monitor compliance with the AVERT Protocol Version 3 - 25 April 2008 and make recommendations to the Steering Committee.
Safety Parameters	The Outcome Committee will confirm outcomes for serious adverse events. Serious unexpected adverse events will be reported by the Principal Investigator to the Data Safety and Monitoring Committee within 48 hours. The trial will be stopped if there is proof beyond reasonable doubt that VEM is clearly indicated or clearly contra-indicated and there is evidence that might reasonably be expected to materially influence future patient management.
Clinical Analysis	Outcomes will be reported in clinical terms of absolute risk reduction, relative risk reduction, and numbers needed to treat.
Statistical Analysis	The primary efficacy analysis will be an intention to treat, between-group comparison of mRS at 3 months analysed across the whole distribution of scores subject to the validity of shift analysis model assumptions. Should the assumptions for shift analysis not be met, then a dichotomised analysis will be conducted with mRS 0-2 (good outcome) versus mRS>2 (poor outcome). Secondary analyses include evaluations of safety, health-related quality of life, cost effectiveness and cost utility, activity limitation and staff injury.

2 AVERT Committees

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Associate Professor Julie Bernhardt (Chair)
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Dr Amanda G Thrift
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Professor Geoffrey A Donnan
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Professor Geoffrey A Donnan (Co-Chairman)
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3 What is in this Protocol?

This protocol serves to tell the main investigators and staff associated with A Very Early Rehabilitation Trial (AVERT Phase 3) why we decided to conduct this trial, who is involved in the trial and the responsibilities of members of the trial. Initial enquires regarding AVERT should be directed to the AVERT main investigator at your centre. Contact details for the Trial Manager are provided should you have any questions relating to the trial.

4 Introduction and Background Information

4.1 Early mobilisation to prevent post-stroke complications

Stroke presents a major global public health challenge, with approximately 5.5 million people dying each year from both the primary insult and secondary complications of stroke.[1] In the developed world, one in four men and one in five women can expect to suffer a stroke if they live to 85 years.[2] Stroke results in both premature death *and* disability, however, in contrast to coronary heart disease or cancer, its major burden is chronic disability rather than death.[3] Approximately one-third of stroke survivors are functionally dependent at 1 year and, in Australia, there are an estimated 63,530 disabled stroke survivors.[4] It is estimated that the total first-year costs for first-ever strokes in Australia during 1997 were A$555 million.[5, 6] The burden of stroke-related disability is likely to increase considerably over the next 20 years, as the population ages. Without effective prevention and treatment strategies, stroke-related disability and its associated costs will increase.[7] Treatments must be widely accessible, cost-effective, appropriate, safe and effective in the vast majority of patients for them to have any major impact on death or dependency. To date, the only treatments for which we have level 1 evidence are: 1) treatment in organised stroke units[8] (a component of which is rehabilitation, including mobilisation) and 2) thrombolysis[9]. While thrombolysis is currently in use in Australia, at best it is delivered to around 5% of stroke patients. We believe that further exploration of effective components of stroke unit care may improve patient outcomes and help reduce the burden of stroke.

We know that stroke patients receiving organised multidisciplinary rehabilitation have reduced dependency.[8] What we don't know is the components of the rehabilitation program responsible for improved outcomes. The strongest indication for the benefit of starting mobilisation as early as possible after stroke comes from a Norwegian study in which the outcomes of stroke patients, randomised to either stroke unit or general medical ward care, were compared.[10] Patients managed in the stroke unit (and receiving very early mobilisation) were 64% (OR) less likely to be dead or disabled. Of the factors that distinguished stroke unit from general medical care, the same group found very early mobilisation to be the strongest predictor of improved outcome.[11] This analysis indicated that very early mobilisation may account for as much as 78% of the stroke unit benefit. Starting *mobilisation* (i.e. sitting out of bed, standing and walking) very early after stroke and continuing it at frequent intervals until discharge (hereafter termed "very early mobilisation or VEM") may reduce the level of disability experienced by stroke patients and reduce the number of patients requiring nursing home care.[11] Although preliminary, the evidence from these studies has prompted the inclusion of "mobilisation within 24 hours" in acute stroke care best practice guidelines both in Australia[12] and internationally.[13] *AVERT aims to determine the efficacy and cost effectiveness of very early mobilisation after stroke*.

4.2 Why might mobilisation save lives and reduce disability?

Although the true contribution of immobility to poor outcome is difficult to quantify, there is evidence that bed rest for many conditions does more harm than good.[14-16] Growing awareness of the negative impact of bed rest on muscle strength and cardiovascular fitness[15] adds weight to the argument for early mobilisation and rehabilitation. The practice of VEM aims to reduce the amount of bed rest, thereby reducing complications of immobility. Fewer complications and earlier, more frequent activity should help promote early recovery of function after stroke. The benefits of VEM still require testing in a randomised controlled trial to evaluate whether improved outcomes over current practice are possible.

4.3 A phase 2, randomised controlled trial to evaluate safety and feasibility of very early rehabilitation

4.3.1 Method

A safety and feasibility study was performed between April 2004 and February 2006 in two Melbourne metropolitan stroke units. Patients were randomly assigned to receive either standard care (SC) or very early mobilisation (VEM) in addition to standard care until discharge or 14 days (whichever was least). The primary safety outcome was the number of deaths at 3 months. Secondary safety outcomes were deterioration in physical function from admission to day 7 and admission to day 14. Other safety outcomes included the falls rate, severe falls rate, excessive fatigue and physiological stability during the intervention period. Serious adverse events were evaluated by the Data Safety and Monitoring Committee (DMC). Preliminary primary outcome was determined as the number of patients dead at 3 months.

Key feasibility issues were that VEM: (i) provided an average additional two physiotherapy mobilisation sessions per day for most VEM patients; and (iii) did not influence SC. The number of intervention sessions were recorded by AVERT physiotherapists, AVERT nurses, stroke unit physiotherapists and occupational therapists. At regular intervals during Phase 2, one-day observations of standard stroke unit care at each hospital site were conducted. Behavioural observation of patients (using the methods described by Bernhardt et al[17]) were used to determine the proportion of the day spent by patients in moderate to high levels of physical activity. By comparing Phase 2 data with baseline (Phase 1) data, we could determine whether the trial was influencing SC.

4.3.2 Results

71 patients were recruited and randomised, with no dropouts at 3 months. The median length of stroke unit stay was 6 days (range 1–51 days). The death rate for all patients was 15.5%. All patients who died were admitted with moderate to severe stroke (NIHSS 8–16, n=2; NIHSS>16, n=9). Stroke type were total anterior circulation infarct (n=16), partial anterior circulation infarct (n=23) and haemorrhage (n=9). Cause of death was stroke (n=11). Intention to treat analysis was used for the primary safety outcome. No between-group differences for death rates were found (SC: n=3/33, VEM: n=8/38; Fisher's exact test p=0.202; ARR=0.12, CI 95% -0.43–0.28). Death rates adjusted for premorbid mRS, NIHSS and age did not differ significantly between SC and VEM patients (aOR=1.80, CI 95% 0.29–11.16).

Deterioration was evaluated using the European Progressing Stroke Study definition[18] and patients were categorized as deteriorated or not deteriorated. Some patients in both groups deteriorated from admission to 7 days (SC: n=8/32, VEM: n=9/32). No statistical differences between-groups were found for the deterioration in symptoms (Fisher's exact test, *P*=0.78).

No between-group differences in falls rates were found (SC: 22.8/1000 bed days, CI 95% 0.4–45.3; VEM: 19.7/1000 bed day, CI 95% -2.1–41.4: Fisher's exact test *P*=0.81). Two severe falls at 3 months (i.e. falls leading to increased hospital stay, hospitalisation, bone fracture or head injury) were recorded for the VEM group. Excessive fatigue was defined by patient self report of physical exertion being more than 'somewhat hard work' using the Borg perceived exertion scale.[19] For patients able to report fatigue, there were similar levels of excessive fatigue reported in both groups (SC: 28.6%, VEM: 23.3%; Fisher's exact test *P*=0.75). All VEM patients were monitored for physiological stability of blood pressure, heart rate, oxygen saturation and temperature prior to mobilisation. No VEM patients were found to be physiologically unstable, or sustained a blood pressure drop of more than 30mmHg on 3 consecutive attempts to sit out of bed.[20]

Targets of an average two additional physiotherapy sessions per day were met for VEM patients. Changes to SC were examined by comparing stroke unit data obtained in 2002[17] to data obtained during the Phase 2 trial. Thirteen, one-day observation periods were completed, with 51 stroke unit patients recruited. Using multivariate binomial logistic regression, no evidence of change over time was found in moderate to high level activity (*P*=0.32, CI 95% -0.06-0.02).

4.3.3 Summary

The death rates in this trial were lower than the lower limits of the 95% confidence interval for a comparable stroke sample[21] (death rate=23.1%; CI 95% 20.8–25.4). For primary and secondary safety outcomes, no harms resulting from VEM were identified. The trial was found to be feasible, with the experimental intervention successfully provided to the majority of VEM patients and no evidence of change in standard stroke unit care.

5 Trial Objectives

Phase 3 of AVERT aims to address four main questions:

1. Does very early mobilisation reduce death and disability at 3 months post stroke?
2. Does very early mobilisation reduce the number and severity of complications at 3 months?
3. Does very early mobilisation improve quality of life at 12 months?
4. Is very early mobilisation cost effective?

5.1 Primary outcome

- Modified Rankin Scale score (mRS, Appendix A)[22-24] at 3 months.

5.2 Secondary outcomes

- Safety: Death rate and the rate and severity of important medical events (stroke progression, recurrent stroke, falls, angina, myocardial infarctions, deep venous thromboses, pulmonary emboli, pressure sores, chest infections, urinary tract infections) at 3 months; and all adverse events during the intervention period.[25]
- Health-related quality of life: Assessment of Quality of Life (AQoL, Appendix A)[26-28] and Irritability, Depression, and Anxiety scale (IDA, Appendix A)[29] at 3 and 12 months, together with cognitive function using the Montreal Cognitive Assessment (MoCA) at 3 months.
- Cost effectiveness and cost utility: Comprehensive questionnaire[5,6] at 3 and 12 months and baseline mRS.
- Long term efficacy: mRS[22-24] at 12 months.
- Activity limitations: Time (days) to walking 50 metres unassisted; Rivermead Motor Assessment (Appendix A)[30 31] and Barthel Index (Appendix A)[24 32] at 3 and 12 months.
- Dose-response: Intervention dose and mRS at 3 and 12 months.
- Patient severity and efficacy: Mild, moderate and severe stroke (NIHSS, Appendix A) and mRS at 3 and 12 months
- Staff injury: The number, severity and type of injury to staff treating AVERT patients during the intervention period.
- Success of blinding: Blinded assessor guess of group at 3 months.

6 Study Duration

The study will take place over 5 years with start up and active recruitment occurring over 3.5 years. Individual patient involvement in the trial is a maximum of twelve months.

7 Patient Population

7.1 Primary diagnosis

Patients admitted to hospital within 24 hours of a stroke. The stroke may be first or recurrent, infarct or haemorrhage (but not transient ischaemic attack).

7.2 Inclusion criteria

- Informed consent must be obtained from the patient or responsible third party
- Patients 18 years and over, with a clinical diagnosis of first or recurrent stroke, either haemorrhage or infarct
- Patient is recruited within 24 hours of onset of stroke symptoms
- Patients for admission to a stroke care unit
- Consciousness: At a minimum, patient must at least react to verbal commands.

7.3 Exclusion criteria

- Pre-stroke (retrospective) modified Rankin Scale score of 3, 4 or 5 (indicating significant previous disability)

- Deterioration in patient's condition in the first hour of admission resulting in direct admission to ICU, a documented clinical decision for palliative treatment (e.g. those with devastating stroke) or immediate surgery
- Concurrent diagnosis of rapidly deteriorating disease (e.g. terminal cancer)
- Unstable coronary or other medical condition that is judged by the investigator to impose a hazard to the patient by involvement in the trial
- A suspected or confirmed lower limb fracture at the time of stroke preventing the implementation of the mobilisation protocol
- Patients who have received rt-PA can be recruited if the attending physician permits and if mobilisation within 24 hours of stroke is permitted
- Patients cannot be concurrently recruited to drug or other intervention trials. Patients may participate in AVERT if they are also recruited to non intervention trials
- Systolic blood pressure less than 110, or greater than 220mmHg
- Oxygen saturation of less than 92% with supplementation
- Resting heart rate of less than 40 or greater than 110 beats per minute
- Temperature of greater than 38.5°C.

7.4 Randomisation criteria

Patients may be randomised to the trial if they meet the above criteria. Block randomisation procedures according to hospital site, and patients stroke severity based upon the patient's baseline National Institute of Health Stroke Scale (NIHSS).[33] Three baseline NIHSS groups will be used in this process: 'mild' (NIHSS 1-7), 'moderate' (NIHSS 8 – 16) and 'severe' (NIHSS greater than 16).[34] Permuted blocks of various lengths will be used to ensure allocation concealment.

7.5 Randomisation procedure

A remote, web-based, computer-generated randomisation procedure is used. All online submissions are secured by use of password site entry and data encryption procedures. Once patient recruitment data is submitted by the site staff via AVERT Online (https://www.avertonline.org.au), the result of randomisation to group is immediately provided back to the investigator. In the event that AVERT Online is not available, please call the Randomisation Help Line to obtain the randomisation allocation.

7.6 Number of patients

Two thousand, one hundred and four (2,104) stroke patients will be recruited.

7.7 Blinding

AVERT physiotherapists and nurses cannot be blinded to the intervention because they will provide the intervention. For all other ward staff, including doctors, other nurses and therapy staff, protocols will be in place to help conceal allocation to intervention group. These measures are detailed in the AVERT Intervention Protocol. Access to the AVERT Intervention Protocol is restricted to maintain blinding and minimize contamination of standard stroke unit care.

All trial outcomes are determined by a blinded assessor. The blinded assessor will perform assessments at 3 months and 12 months at the hospital, patient's home, rehabilitation centre or place of residence. To help maintain blinding of the assessor we have applied for ethics approval to ***not tell*** participants the group to which they have been randomly allocated (approved in Phase 2). Furthermore, ***interventions provided by AVERT staff are never***

recorded in the medical record, rather it is recorded on a Personal Digital Assistant (PDA) or the Therapist/Nurse Recording Form (AVERT Online). This makes it difficult for the blinded assessor to determine the intervention group from the medical record.

It is therefore important that ***anyone*** who may know the group to which the patient has been allocated ***must not tell the patient or the assessor if they come onto the ward***. In this way, we may prevent the patient or staff from telling the blinded assessor group allocation.

8 Trial Design and Intervention Plan

8.1 Trial design

A randomised controlled trial of patients admitted to stroke units from Australian and international sites, with blinded assessment of outcomes and intention to treat analysis. Two thousand, one hundred and four stroke patients will be recruited across approximately thirty hospitals.

8.2 Interventions

Patients will be randomised to receive either standard care alone (SC), or standard care in addition to the experimental intervention, very early mobilisation (VEM). SC patients receive usual stroke unit care. VEM patients receive usual stroke unit care, and are provided additional mobilisation. VEM patients are provided mobilisation as soon as the patient is recruited. An additional three physiotherapy and nursing sessions per day are provided during the intervention period. The intervention period lasts for 14 days or until the patient is discharged from stroke unit care, whichever is sooner.

The VEM sit out of bed protocol (AVERT Intervention Protocol version 3 dated 25 April 2008) is **strictly adhered to for very early mobilisation out of bed**. Patients must be within a range of measures for blood pressure, heart rate, oxygen saturation and temperature prior to first mobilisation. Mobilisations will only proceed when the patient's blood pressure does not drop more than 30mmHg on sitting out of bed.

VEM is provided by trained physiotherapy and nursing staff according to the detailed AVERT Intervention Protocol. This document ***is not for general distribution*** and will only be provided to AVERT nurses, AVERT physiotherapists and where needed for trial evaluation (e.g. ethics committees). This is to help maintain blinding and protect against contamination of the trial.

8.3 Assessment schedule

The schedule for trial assessments is located in Appendix B.

8.3.1 Day 0 - Screening

All patients with a diagnosis of stroke will be screened for trial eligibility. Where a patient is deemed eligible and has provided informed consent, baseline data is collected.

8.3.2 Day 0 – Baseline

After consent has been obtained, the medical history and physical exam will be performed. The following stroke assessments will be performed.

- Pre morbid mRS
- Baseline mRS
- NIHSS

- OCSP

A paper CRF will be completed by the AVERT team member. Baseline NIHSS, OSCP, premorbid mRS and date of stroke must all be entered into AVERT Online (https://www.avertonline.org.au) prior to patient randomisation. If there is a problem accessing AVERT Online, the Randomisation Help Line may be called and the randomisation procedure performed manually by the AVERT Data management staff member on call.

Following randomisation, the AVERT physiotherapist will obtain the following data within the 24 hours.

- Demographic data
- Mobility Scale for Acute Stroke (MSAS)
- Star cancellation test
- Time to first mobilisation

8.3.3 Day 1 – Day 14 (or discharge)

The AVERT Intervention Protocol will be followed for all patients randomised. Information about the group to which the patient has been randomised should only be known by the AVERT physiotherapist and AVERT nursing staff.

For each mobilisation performed, AVERT nurses and physiotherapists will record information about the mobilisation via AVERT Online. In selected centres, AVERT physiotherapists, ward physiotherapists and ward occupational therapists will record mobilisation information via a PDA if available or via AVERT Online. Data from the PDA is downloaded daily ('hot synced') to a hospital computer and transferred via the internet to a central database at the AVERT office. AVERT Online will be used to record mobilisations if the PDA is not working. A paper Nurse/Therapist Recording Form may be used to record mobilisations if AVERT Online is temporarily unavailable.

During the intervention period, any adverse events are reported in the CRF. The AVERT physiotherapist will notify the blinded assessor within 24 hours of any serious adverse events.

8.3.4 Termination/Discharge

The patients participation may be terminated if consent is withdrawn, or if the patient's safety is deemed to be at risk.

The AVERT Intervention Protocol otherwise continues until Day 14 of the patients stay in the stroke unit or until discharge from the stroke unit (whichever is sooner). If the patient is palliated VEM will cease, with trial assessments continued until death or 12 month follow-up.

At discharge, the AVERT physiotherapist will complete the imaging CRF and fax to the AVERT office. In addition, if the patient ceases mobilisation for more than 24 hours, the protocol deviation CRF will be completed by the AVERT physiotherapist and faxed to the AVERT office. The blinded assessor will determine the patient's achievement of 50 metre walk with the ward physiotherapist and discharge information will be collected for the purpose of follow up assessments.

8.3.5 3 month assessment

This assessment is performed by the blinded assessor on the date scheduled by AVERT online (+/- 7 days). Where this is not possible, a protocol deviation will be documented. The blinded assessor will contact the patient/relatives and rehabilitation/accommodation units where relevant to arrange the assessment time. In the event that a patient or responsible family

member are unwilling to provide consent to continue with the assessments, the AVERT main investigator should be notified immediately.
At the assessment meeting, the following will occur:

- mRS
- IDA
- Barthel Index
- AQoL
- Rivermead Motor Assessment Scale
- 50 metre walk
- MoCA cognitive assessment
- Cost of care
- Important Medical Events
- Serious Adverse Events
- Blinded assessor group allocation guess

All ongoing adverse events including serious adverse events should be followed through to stabilisation or recovery. All assessments will be documented on CRF pages and submitted via fax to the AVERT office when complete.

8.3.6 12 month assessment

This assessment is performed by the blinded assessor. The blinded assessor will contact the patient/relatives and rehabilitation/accommodation units where relevant to arrange the assessment time. In the event that a patient or family member are unwilling to provide consent to continue with the assessments, the AVERT main investigator should be notified immediately.
At the assessment meeting, the following will occur:

- mRS
- IDA
- Barthel Index
- AQoL
- Rivermead Motor Assessment Scale
- 50 metre walk
- Cost of Care
- Serious Adverse Events

Any serious adverse events not recovered at 12 months should be followed through to stabilisation or recovery. All assessments will be documented on CRF pages and submitted to the AVERT office when complete.

8.4 Contamination and loss of blinding

Contamination will be considered to have occurred when VEM is provided to standard care patients or becomes standard care for a large number of patients. We have instituted a number of practices to ensure contamination does not occur. The VEM is provided by dedicated trial staff recruited from the ward. Measures to limit contamination (i.e., reduce the potential of the intervention practices to be adopted by staff other than the AVERT staff) are outlined in the AVERT Intervention Protocol and will help maintain the high quality of this trial. Contamination of SC will be evaluated at regular intervals throughout the trial. The AVERT Contamination Protocol has been developed and will be submitted to HRECs as a substudy of this trial at selected sites.

Whether or not unblinding has occurred will be tested at the end of the 3 month assessment. The blinded assessor will nominate the treatment group to which they think the patient was randomised. They must not try to extract this information from any source.

9 Analyses

9.1 Sample size

The study is powered to detect an absolute risk reduction (ARR) of death and disability of 7.1% or greater, based on the following rationale: (i) consensus among investigators and international advisors that an ARR of this magnitude would represent a clinically meaningful effect size (although there are no formal cost-effectiveness data to support this view); and (ii) 3 month death and institutionalisation figures from an Australian hospital (40.9%) and a very early mobilisation centre (31.8%), and estimates that very early mobilisation accounts for 78% of this 9.1% difference, giving a final absolute difference of 7.1%. A sample of 2104 patients (1052 per arm) will provide 80% power to detect a significant intervention effect (2 sided, $p = 0.05$) with adjustments for a 5% drop-in and a 10% drop out.

9.2 Populations

The efficacy and safety population will include all patients who are randomised. The per-protocol population will include: (i) VEM patients who received 3 or more mobilisation sessions (additional to SC) on average per day over the intervention period; and (ii) SC patients who receive 3 or more sessions (additional to mean SC) on average per day over the intervention period. Mobilisation sessions will be provided by physiotherapy and/or nursing. The intervention period lasts for 14 days or until the patient is discharged from stroke unit care, whichever is sooner. A per-protocol analysis will be used to explore differences in the primary outcome variable according to whether or not patients received the planned intervention dose.

9.3 Primary outcome analysis

The primary efficacy analysis will be a between-group comparison of mRS at 3 months, analysed across the whole distribution of scores subject to the validity of shift analysis model assumptions. Should the assumptions for shift analysis not be met, 3 month mRS will be dichotomised into good outcome (mRS 0 - 2) and poor outcome (mRS 3 - 6), and the groups will be compared using a binary logistic model. The primary analysis will be adjusted: with baseline NIHSS, premorbid mRS and tPA use, as covariates. Unadjusted results will also be shown. The intervention effect will be represented in terms of odds ratios. Other potential prognostic variables such as age, stroke type and side of stroke will be included in secondary efficacy analyses.

9.4 Secondary outcome analysis

9.4.1 Safety

Regression models for count data (Poisson or negative binomial regression depending on the validity of methods assumptions) will be used to compare serious adverse events between groups at 3 months. We will report risk ratios adjusted as per primary analysis with age included as a covariate.

9.4.2 Health-related quality of life

Multivariable linear regression will be used to determine the effect of intervention group on AQoL scores at 3 and 12 months post-stroke, adjusting for known confounding variables (e.g. age, sex, NIHSS, cognition and mood impairment using the IDA).

9.4.3 Cost effectiveness and cost utility

An AVERT Cost Protocol has been developed to detail the economic evaluation of the project. It addresses in detail issues briefly discussed in this section and section 9.4.2. Both cost-effectiveness (using 3 month mRS as the outcome) and cost-utility analyses (using utilities mapped from mRS scores as a proxy for AQoL at baseline)[35] will be performed. Pathway analysis (incorporating decision trees) will be used to clearly identify and cost the activity components for each arm of the trial. Standard discounting will be applied to both costs and outcomes, together with detailed sensitivity and uncertainty analysis (using the @RISK software). Costs will be analysed by intervention pathway, expenditure category and cost incidence (who bears the cost). Whilst a societal perspective will be assumed, the key focus will be on the health sector, and will include costs to the government as third party payer, costs to patients and their family and limited costs to other sectors.

Incremental cost-effectiveness ratios will be calculated for experimental intervention in comparison to standard care. To assess the incremental cost of VEM compared to SC, resource utilisation data at 3 and 12 months will be collected including: acute hospital length of stay; therapy time; aids and equipment; discharge destination; inpatient and outpatient rehabilitation input following acute hospital discharge; and any re-admissions to hospital within 3 months. Unit costs will be sourced for the 2006 reference year from the most accurate and up-to-date sources including the Medicare Benefits Schedule[36], the Pharmaceutical Benefits Schedule[37] and complemented by other sources including international sources and expert opinion. Where possible, centre-specific unit costs will be used to avoid the over-estimation of intervention costs by the application of non-representative average costs to multiple sites.

9.4.4 Efficacy

Should shift analysis be valid for primary efficacy analysis, a secondary analysis of 3 month mRS dichotomised into good outcome (mRS 0 - 2) and poor outcome (mRS 3 - 6) will be undertaken with groups compared using a binary logistic model adjusted as per primary analysis. This analysis will allow comparison with published outcomes of other acute stroke trials.

9.4.5 Activity limitation

Time for subjects to achieve unassisted walking 50 metres will be assessed using survival analysis techniques. The relationship between dichotomised Barthel Index score (0-18, poor outcome;19-20, good outcome) and intervention group will be examined using multivariable logistic regression. The relationship between Rivermead Motor Assessment and intervention will be analysed using non-parametric tests.

9.4.6 Staff injury

Information relating to injuries sustained by staff working with AVERT patients will be collected and documented on a CRF page. Information will be collected if an incident report for an AVERT patient is completed. The information collected will include the severity and type of injury.

9.4.7 Demographics

Demographic baseline characteristics of the two intervention groups will be tabulated.

9.4.8 Blinding

A two sample test of proportions will be performed to evaluate whether the blinded assessor guess of intervention group at 3 months post stroke was better than chance.

9.4.9 Post hoc analyses

The relationship between intervention dose and stroke severity to outcome and long term efficacy, are likely to be the subject of post hoc analyses given their clinical relevance.

9.5 Interim analyses

The DMC will review interim efficacy analyses for the primary outcome measure and safety analyses. The DMC will advise the chairman of the steering committee if, in their view, the randomised comparisons have provided both (i) 'proof beyond reasonable doubt' that very early mobilisation is clearly indicated or clearly contra-indicated and (ii) evidence that might reasonably be expected to materially influence future patient management.[39] Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but the DMC will work on the principle that a difference of at least 3 standard errors in an interim analysis of a major outcome event (e.g. death from all causes or falls) may be needed to justify halting, or modifying the study before the planned completed recruitment. Although formal stopping rules based upon mortality rate will not be set, given that post-stroke mortality is high, and that many factors may contribute, all deaths will be reviewed by the DMC on a case-by-case basis.

10 Safety Reporting Requirements

At 3 and 12 month evaluations, the blinded assessor will determine whether any serious adverse events (SAEs) have occurred. The blinded assessor will also be notified by the AVERT physiotherapist of any SAEs for urgent evaluation and reporting during the intervention period.

10.1 Adverse events (AEs)

An adverse event is defined as any untoward medical occurrence in any patient involved in the study and which does not necessarily have a causal relationship to the study intervention. This includes any worsening of a pre-existing event.

10.1.1 Reporting of an adverse event

Adverse events should be documented in the patients medical record or clinic notes. Adverse event reporting will begin from the time of informed consent. Events will be reported on the adverse event pages within the patients CRF and will include the date of onset, description, severity, duration, and whether or not it is thought to be related to the study intervention. If known, the medical diagnosis of an AE should be recorded in preference to listing of signs and symptoms.

10.1.2 Adverse event collection period

All adverse events will be collected from the time of the patients consent, until the end of the intervention period. Adverse events will be followed until the event is resolved, or the event has stabilized.

10.2 Important medical events (IMEs)

Definition: Listed adverse events that are important outcome measures for this trial.

- Falls - with no soft tissue injury
  - with soft tissue injury
  - with bone fracture or head injury

- Stroke Progression. Defined as a worsening stroke in the same vascular territory as the initial event occuring during the first 14 days (in the clinicians view)
- Recurrent Stroke. Defined as a new stroke event in a different vascular territory during the first 14 days, or any stroke event beyond 14 days (in the clinicians view).
- Pulmonary Embolism
- Deep Vein Thrombosis
- Myocardial Infarct
- Angina
- Urinary Tract Infection
- Pressure Sores
- Pneumonia
- Depression

10.2.1 Reporting of important medical events

Important medical event should be documented in the patients medical record or clinic notes. IMEs will be recorded from the time of informed consent. These events will be reported on important medical events pages within the patients CRF and will include the date of onset, duration, severity and whether or not it is thought to be related to the study intervention.

10.3 Serious adverse events

Definition: Any adverse event in any patient involved in the study (experimental or control group) that meets the following criteria:

- Results in death.
- Is life threatening.
- Requires inpatient hospitalisation (this does not include an emergency room visit or admission to an outpatient facility).
- Prolongation of existing hospitalisation (if an event occurs while the patient is in hospital, which in itself prolongs the patients stay).
- Results in persistent or significant disability/incapacity.

10.3.1 Reporting of a serious adverse event

Serious adverse events whether related to study intervention or not are to be reported to the blinded assessor, and the AVERT principal investigator within 24 hours of knowledge of the event. A serious adverse event CRF will be completed by the blinded assessor and faxed to the AVERT office. If there is a **serious <u>unexpected</u> adverse event** (such as suicide or other non-stroke related event) during the intervention period, the DMC will be informed by the AVERT team within 48 hours. Serious adverse events outside the intervention period should be reported to the AVERT office following 3 and 12 month assessments. SAEs will be reported by the AVERT trial team to site HRECs according to local committee protocols.

10.3.2 Assessment of severity of all adverse events

Severity can be assessed using the following definitions:

- Mild – the event causes awareness of signs or symptoms, but is easily tolerated, does not interfere with rehabilitation.
- Moderate – the event causes the patient discomfort sufficient to cause interference with current level of activity, requires more frequent monitoring or diagnostic tests.
- Severe – the event is incapacitating resulting in the patient not being able to work or do usual activity.

10.3.3 Assessment of causality of all adverse events

In order to assess the causality of an adverse event in relation to the study intervention, the following definitions will be used.

- Probably related – the event has a strong relationship to the study intervention.
- Possibly related – the event has a strong relationship to the study intervention, but could be explained by something else.
- Probably not related – the event has little relationship to the study intervention and a more likely explanation for the event exists.
- Not related – the event is due to an underlying or concurrent illness and is not related to the study intervention. There is another explanation for the event.

10.3.4 Adjudication of serious adverse events

The two medical experts of the Outcomes Committee will independently review all serious adverse events as they arise. They will provide adjudication of the type, severity and causal relationship of intervention to SAEs. Their summary report will be presented to the DMC at each scheduled meeting.

11 Patient Completion/Withdrawal

11.1 Patient completion

Patients will be deemed to have completed the study once all trial procedures and assessments have been conducted.

11.2 Patient withdrawal

The main investigator must make every reasonable effort to keep each patient in the study, except where the patient is withdrawing consent to continue, or the withdrawal is for reasons of safety. The AVERT main investigator must be notified should a withdrawal appear necessary. The reason and date of withdrawal will be documented on the Withdrawal Form (CRF) and faxed to the AVERT Office within 24 hours.

11.3 Premature termination of the study

The trial may be ceased at one or more sites. This would be due to recommendations from the DMC or the steering committee that there are staffing issues, safety concerns, low recruitment rates, poor data quality and/or insufficient dose difference between standard care and the experimental intervention. The trial may also be terminated where there are any unforeseen events that may affect the continuing ethical acceptability of the project.

12 Recording of Data

Source data relating to each patient will be maintained in the patient's medical record. Source data relating to the therapy given to the patient should not be recorded in the patient's medical record. This information is recorded in a PDA (physiotherapists and occupational therapists) and/or web based Therapy/Nurse forms (AVERT Online) provided specifically for the study. Data collected for the purpose of the trial will be entered in each patients individual CRF. Information in the CRF must be backed up by information found in the patient's medical record or clinical notes. The CRFs should be kept up to date and in order at all times.

12.1 Patient recruitment and randomisation

When a new patient is recruited, the AVERT physiotherapist, main investigator, clinical trials nurse or medical staff will submit patient details via AVERT Online (https://www.avertonline.org.au). AVERT Online provides a web based, 24 hour, secure randomisation system. If unavailable, the Day 0 CRF should be completed and the Randomisation Helpline called to obtained group randomisation.

12.2 Patient identification

All patients screened for the study will have their initials, date of birth, date of stroke, gender and estimate of stroke severity entered chronologically on the screening log. The eligible patients will be assigned a patient allocation number in sequential order. This number will be entered on all pages of the CRF. The main investigator will be responsible for retaining sufficient information about each patient (e.g. name, address, phone number and identity in the study) so that the patients may be contacted should the need arise. These records should be retained at the site and maintained in a secure and confidential manner according to local requirements.

12.3 Recording requirements

There are a number of recording requirements for the AVERT physiotherapist, AVERT nurses and hospital stroke unit staff during this trial. The AVERT physiotherapist, main investigator or medical staff will complete the patient consent documents, complete the Day 0 CRF and submit patient details via AVERT Online (https://www.avertonline.org.au). The AVERT physiotherapist completes an assessment when the patient is recruited to this study (Case Report Form (CRF) – Day 0). Day 0 CRFs should be faxed to the AVERT Office as soon as completed.

AVERT nurses and therapists are required to record the day, time, type and number of mobilisations each day for all AVERT patients (SC and VEM) on AVERT Online. Whichever AVERT staff member initiates the mobilisation, will be responsible for recording joint mobilisation sessions. If a VEM patient is unable to be mobilised during the day, this should be recorded on the nurse or therapist form. If there are technical problems with AVERT Online, then a paper Nurse or Therapist Recording Form should be used. Data should be entered on to AVERT Online as soon as AVERTOnline is operational.
In selected centres all physiotherapy mobilisation interventions delivered to all AVERT patients (SC and VEM) during the trial will be recorded using a PDA. Data recorded on the PDA by AVERT physiotherapists, stroke unit occupational therapists and stroke unit physiotherapists will be 'hot synced' and transferred via the internet to the AVERT office on a daily basis. If there are technical problems with the PDA, then the Therapist Recording Form should be used via AVERT online.

The bulk of the data required for this study will be collected by the AVERT blinded assessor. The assessor will visit the patient at 3 and 12 months post stroke. Data should be submitted via fax within one week of the patient follow-up at 3 and 12 months. All original CRF forms, including signed consent forms, will be retained on site in a locked cabinet, until such time as they are transferred to the AVERT office at the NSRI.

12.4 Data processing

TELE*form* Elite version 9® will be used for all paper assessment forms. Teleforms allow faxed data to be saved as a digital image, checked visually and transferred into an electronic database. Teleforms are faxed through to the main AVERT office, NSRI. Nursing and Therapist data is submitted to AVERT Online which is a secure website with password

access. In selected centres, therapy data is collected using electronic data forms using a Personal Digital Assistant (PDA). PDA forms are transferred via the internet to the main AVERT office, NSRI. AVERT Online (https://www.avertonline.org.au) provides the relevant staff member with feedback on when all forms are due, incomplete and completed.

12.5 Record retention

All study documents including the protocol and CRF are confidential. A study document binder will be provided to each site (Investigator file) to maintain study documents. The study documents should be maintained in a locked area, accessible to study staff only. At the completion of the study, the investigator will maintain the investigator file, copies of the CRFs and all relevant source data in accordance with the applicable regulatory requirements. Data will be maintained and secured for at least 7 years from trial completion.

12.6 Confidentiality

The investigator and the AVERT study team will preserve the confidentiality of patients taking part in this study. The patient's medical records pertaining to this study may be inspected/audited by an authorized representative of the trial, or the HREC. All records accessed will be kept strictly confidential. Consent to participate in this study includes consent to these inspections/audits.

13 Monitoring Trial Conduct

The AVERT Outcome Committee will ensure AVERT therapy staff and blinded assessors achieve certification for proficiency in the trial assessments and outcomes (NIHSS and mRS) and confirm trial outcomes for serious adverse events. The AVERT DMC will provide objective, independent monitoring of trial progress, safety and efficacy (including reviewing adverse events). Trial progress will be evaluated at regular intervals by the DMC via data on recruitment targets, group baseline characteristics and balance between intervention and control groups and compliance with the protocol.

14 Site Initiation, Staff Training and Support

AVERT staff will receive site initiation with training in protocol and procedures using a comprehensive package. An AVERT main investigator will be appointed at each site. Any new AVERT staff will be trained by the main investigator. The AVERT Trial manager will be available for the duration of the trial to provide ongoing support and training for staff members.

It is important that local AVERT staff have a clear understanding of their roles and responsibilities for trial requirements at their site. Records of the agreed roles and responsibilities of each team member will be maintained by the Trial Manager and stored both at the site and at AVERT central.

15 Consent Documentation

Informed consent is where the patient or third party is informed of the nature of the study, and is given information related to the trial aims, risks and benefits. The procedures and possible hazards will be explained by a suitably qualified person. The HREC approved patient information and consent form will be given to the patient and the patient will be given reasonable time to consider their involvement and have all questions answered before giving

consent. If the patient decides to participate they will confirm this by signing the informed consent form with the investigator, and an independent witness where required.

Written informed consent must be obtained from all patients enrolled in the trial prior to any study related procedures or assessments. The ability of a patient to provide informed consent is evaluated by medical staff. Patients for whom English is a second language will require an interpreter to assist with the consenting process.

Patients unable to give written informed consent due to reduced conscious level, cognitive or communicative problems require that their next of kin or carer complete the Third Party Information and Acknowledgement Form. In some states, consent must also be obtained from an independent third party.

The patient or carer must receive the information sheet and a photocopy of the informed consent. A photocopy of the informed consent must also be placed in the patient's hospital notes. Completed original consent forms must be filed in the site investigator file, maintained in a secure location.

If a patient or carer decides to withdraw consent, appropriate local procedures for the withdrawal of consent must be followed. The Principle Investigator, Dr Julie Bernhardt should be contacted within 24 hours of the time when a patient or carer expresses their desire to withdraw consent.

16 Ethical Approval

This study must be approved by the HREC at each participating centre prior to patient participation in the trial. The HREC should be constituted in accordance with local regulatory requirements and the approval of the protocol must be documented. Written approval of the study should clearly identify the protocol, any amendments, patient information and consent forms and any other documentation that is given to patients by title, version and date. HREC approval and ethics documents will be maintained in the study investigator folder located at each participating centre. Copies of these documents will be maintained centrally by the Trial Manager at the AVERT office.

17 Indemnity and Compensation

The hospital in which the study is conducted, warrants that the involved staff members are employees or contracted agents of the hospital, and that they are sufficiently qualified by education and training to assume responsibility for the conduct of the trial.

Public and Product Liability
The study sponsor (NSRI) will maintain levels of Public and Product Liability insurance coverage. Cover extends to the interest of any party who has entered into an agreement with the sponsor for the purpose of business. There is no cover for the negligence of the hospital, or the hospital trial staff or their subsequent liability for damage or injury. Any breach of the protocol resulting in a claim would not be covered by the sponsor.

Medical Indemnity Liability
The sponsors insurance policy includes cover for any claim for which they are held legally liable, caused by or arising from teaching or research carried out by the AVERT study team. This would include claims arising from error, omission or negligence by the AVERT study

team in the provision of health care services. Health care services include: advice, services or goods provided in respect of the physical or mental health of a patient or other person.

18 Funding

AVERT Phase 3 is supported by grant funding obtained from the National Health and Medical Research Council (Grant Number: 386201). Funding agreements between the NSRI and individual sites will be negotiated.

19 Publications

Main results from this study will be published on behalf on the AVERT trialist's collaboration with all investigators acknowledged.

20 Investigator Agreement

I have read the above protocol entitled "A phase 3, multicentre, randomised controlled trial of very early rehabilitation after stroke (AVERT)" and I agree to abide by all provisions of the protocol.

I understand that this protocol must be submitted to the Ethics/Research Committee/Board for written approval prior to initiation of this study.

Hospital Site (printed)_____

Main Investigator: Name (printed) _____

Main Investigator: Signature _____Date_____

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Appendix A: Outcome Measures

MODIFIED RANKIN SCALE

PATIENT STUDY NUMBER			·				TIME OF ASSESSMENT	
							Premorbid Day 0 ☐	Baseline ☐
							3 months ☐	12 months ☐

General Instructions

Mark the box corresponding to the patient's level of disability at the time of assessment.

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?

5 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 ☐

THE ASSESSMENT OF QUALITY OF LIFE (AQOL) INSTRUMENT:

PATIENT AND PERSON RESPONSIBLE VERSION

PATIENT STUDY NUMBER			.				TIME OF ASSESSMENT	3 months ☐ 12 months ☐

PERSON RESPONDING				ASSISTANCE FOR INTERVIEW OBTAINED FROM			
Index Case	☐	Other Relative	☐	Index Case	☐	Other Relative	☐
Spouse/Partner	☐	Friend/Associate/ Neighbour	☐	Spouse/Partner	☐	Friend/Associate/ Neighbour	☐
Sibling	☐			Sibling	☐		
Son/Daughter	☐	Carer, e.g. nurse	☐	Son/Daughter	☐	Carer, e.g. nurse	☐
Parent	☐	Other, Unspecified	☐	Parent	☐	Other, Unspecified	☐

INSTRUCTIONS

Please tick the alternative that best describes you ***during the last week***.

ILLNESS

1. Concerning my use of prescribed medicines

- I do not or rarely use any medicines at all ☐
- I use one or two medicinal drugs regularly ☐
- I need to use three or four medicinal drugs regularly ☐
- I use five or more medicinal drugs regularly ☐

2. To what extent do I rely on medicines or a medical aid? (NOT glasses or a hearing aid.). For example: walking frame, wheelchair, prosthesis etc

- I do not use any medicines and/or medical aids ☐
- I occasionally use medicines and/or medical aids ☐
- I regularly use medicines and/or medical aids ☐
- I have to constantly take medicines or use a medical aid ☐

3. Do I need regular medical treatment from a doctor or other health professional?

- I do not need regular medical treatment ☐
- Although I have some regular medical treatment, I am not dependent on this ☐
- I am dependent on having regular medical treatment ☐
- My life is dependent upon regular medical treatment ☐

INDEPENDENT LIVING

4. Do I need any help looking after myself?

- I need no help at all ☐
- Occasionally I need some help with personal care tasks ☐
- I need help with the more difficult personal care tasks ☐
- I need daily help with most or all personal care tasks ☐

5. When doing household tasks: (For example, preparing food, gardening, using the video recorder, radio, telephone or washing the car)

- I need no help at all ☐
- Occasionally I need some help with household tasks ☐
- I need help with the more difficult household tasks ☐
- I need daily help with most or all household tasks ☐

6. Thinking about how easily I can get around my home and community

- I get around my home and community by myself without any difficulty ☐
- I find it difficult to get around my home and community by myself ☐
- I cannot get around the community by myself, but I can get around my home with some difficulty ☐
- I cannot get around either the community or my home by myself ☐

SOCIAL RELATIONSHIPS

7. Because of my health, my relationships (For example: with my friends, partner or parents) are generally

- Are very close and warm ☐
- Are sometimes close and warm ☐
- Are seldom close and warm ☐
- I have no close and warm relationships ☐

8. Thinking about my relationship with other people

- I have plenty of friends, and am never lonely ☐
- Although I have friends, I am occasionally lonely ☐
- I have some friends, but am often lonely for company ☐
- I am socially isolated and feel lonely ☐

9. Thinking about my health and my relationship with my family

- My role in the family is unaffected by my health ☐
- There are some parts of my family role I cannot carry out ☐
- There are many parts of my family role I cannot carry out ☐
- I cannot carry out any part of my family role ☐

PHYSICAL SENSES

10. Thinking about my vision, including when using my glasses or contact lenses if needed

- I see normally ☐
- I have some difficulty focusing on things, or I do not see them sharply. For example: small print, a newspaper, or seeing objects in the distance ☐
- I have a lot of difficulty seeing things. My vision is blurred. For example: I can see just enough to get by with ☐
- I only see general shapes, or am blind. For example: I need a guide to move around ☐

11. Thinking about my hearing, including when using my hearing aid if needed

- I hear normally. ☐
- I have some difficulty hearing or I do not hear clearly
  For example: I ask people to speak up, or turn up the TV or radio volume. ☐
- I have difficulty hearing things clearly. For example: Often I do not understand what is said. I usually do not take part in conversations because I cannot hear what is said. ☐
- I only see general shapes, or am blind.
  For example: I need a guide to move around directly to me. ☐

12. When I communicate with others (For example: by talking, listening, writing or signing)

- I have no trouble speaking to them or understanding what other people are saying ☐
- I have some difficulty being understood by people who do not know me.
  I have no trouble understanding what others are saying to me ☐
- I am only understood by people who know me well. I have great trouble understanding what others are saying to me ☐
- I cannot adequately communicate with others ☐

PSYCHOLOGICAL WELL-BEING

13. If I think about how I sleep

- I am able to sleep without difficulty most of the time ☐
- My sleep is interrupted some of the time, but I am usually able to go back to sleep without difficulty ☐
- My sleep is interrupted most nights, but I am usually able to go back to sleep without difficulty ☐
- I sleep in short bursts only. I am awake most of the night ☐

14. Thinking about how I generally feel

- I do not feel anxious, worried or depressed ☐
- I am slightly anxious, worried or depressed ☐
- I feel moderately anxious, worried or depressed ☐
- I am extremely anxious, worried or depressed ☐

15. How much pain or discomfort do I experience?

- None at all ☐
- I have moderate pain ☐
- I suffer from severe pain ☐
- I suffer from severe pain ☐

RIVERMEAD MOTOR ASSESSMENT – GROSS FUNCTION

PATIENT STUDY NUMBER			.				TIME OF ASSESSMENT	3 months ☐ 12 months ☐

General Instructions

Go through items in order of difficulty. Score 1 if the patient can perform the activity, score 0 if the patient cannot. Three tries are allowed; after 3 consecutive failures stop the assessment. Give no feedback of whether correct or incorrect, just general encouragement. Repeat instructions and demonstrate to patient if necessary. All exercises are to be carried out independently unless otherwise stated. If no stairs available, ask if patient can perform item. Use your clinical judgment. *Writing in brackets are instructions for the rater.*

Item	**Score**	
	0	**1**
1. Sit unsupported. (***Without holding on, on edge of bed, feet unsupported.***)	☐	☐
2. Lying to sitting on side of bed. (***Using any method.***)	☐	☐
3. Sitting to standing. ***May use hands to push up. (Must stand up in 15 seconds and stand for 15 seconds, with an aid if necessary.)***	☐	☐
4. Transfer from wheelchair to chair towards unaffected side. (***May use hands.***)	☐	☐
5. Transfer from wheelchair to chair towards affected side. (***May use hands.***)	☐	☐
6. Walk 10 metres with an aid. ***Any walking aid. (No stand-by help.)***	☐	☐
7. Climb stairs independently. (***Any method. May use banister and aid. Must be a full flight of stairs.***)	☐	☐
8. Walk 10 metres without an aid. (***No stand-by help. No caliper, splint or walking aid.***)	☐	☐
9. Walk 5 metres, pick up bean bag from floor, turn and carry back. (***Bend down any way. May use aid to walk if necessary. No stand-by help. May use either hand to pick up bean bag.***)	☐	☐
10. Walk outside 40 metres. (***May use walking aid, caliper or splint. No stand-by help.***)	☐	☐
11. Walk up and down 4 steps. (***Patient may use an aid if he would normally use one, but may not hold on to rail. This is included to test ability to negotiate kerb or stairs without a rail.***)	☐	☐
12. Run 10 metres. (***Must be symmetrical.***)	☐	☐
13. Hop on affected leg 5 times on the spot. (***Must hop on ball of foot without stooping to regain balance. No help with arms.***)	☐	☐

TOTAL SCORE			

IRRITABILITY, DEPRESSION, AND ANXIETY (IDA) SCALE

PATIENT STUDY NUMBER			.				TIME OF ASSESSMENT	3 months ☐ 12 months ☐

IMPORTANT NOTE FOR ASSESSOR

Do not complete this scale if the person is unable to communicate their answers.
Indicate if the scale was not completed. An interpreter may be used.

Independent	☐
Completed with assistance (eg read aloud)	☐
Not done/unable to be completed (communication deficit, patient refused)	☐
Unknown	☐

General Instructions

This Questionnaire is to help the researchers to know how you are feeling at present
Read each item and TICK the response that best shows how you are feeling now,
or have been feeling in the last day or two.

1. I FEEL CHEERFUL. *TICK ONE BOX ONLY*

Yes, definitely	☐
Yes, sometimes	☐
No, not much	☐
No, not at all	☐

3. MY APPETITE IS *TICK ONE BOX ONLY*

Very poor	☐
Fairly good	☐
Quite good	☐
Very Good	☐

5. I FEEL TENSE OR 'WOUND UP'. *TICK ONE BOX ONLY*

Yes, definitely	☐
Yes, sometimes	☐
No, not much	☐
No, not at all	☐

2. I CAN SIT DOWN AND RELAX QUITE EASILY. *TICK ONE BOX ONLY*

Yes, definitely	☐
Yes, sometimes	☐
No, not much	☐
No, not at all	☐

4. I LOSE MY TEMPER AND SHOUT OR SNAP AT OTHERS. *TICK ONE BOX ONLY*

Yes, definitely	☐
Yes, sometimes	☐
No, not much	☐
No, not at all	☐

6. I FEEL LIKE HARMING MYSELF. *TICK ONE BOX ONLY*

Yes, definitely	☐
Yes, sometimes	☐
No, not much	☐
No, not at all	☐

7. I HAVE KEPT UP MY OLD INTERESTS. *TICK ONE BOX ONLY*

Yes, most of them	☐
Yes, some of them	☐
No, not many of them	☐
No, none of them	☐

9. I GET SCARED OR PANICKY FOR NO VERY GOOD REASON. *TICK ONE BOX ONLY*

Yes, definitely	☐
Yes, sometimes	☐
No, not much	☐
No, not At All	☐

11. I CAN LAUGH AND FEEL AMUSED. *TICK ONE BOX ONLY*

Yes, definitely	☐
Yes, sometimes	☐
No, not much	☐
No, not At All	☐

13.I HAVE AN UNCOMFORTABLE FEELING LIKE BUTTERFLIES IN THE STOMACH. *TICK ONE BOX ONLY*

Yes, definitely	☐
Yes, sometimes	☐
No, not much	☐
No, not at all	☐

15. I'M AWAKE BEFORE I NEED TO GET UP: *TICK ONE BOX ONLY*

For 2 hours or more	☐
For about 1 hour	☐
For less than an hour	☐
Not at all, I sleep until it is time to get up	☐

17. I CAN GO OUT ON MY OWN WITHOUT FEELING ANXIOUS. *TICK ONE BOX ONLY*

Yes, always	☐
Yes, sometime	☐
No, not often	☐
No, I never can	☐

8. I AM PATIENT WITH OTHER PEOPLE. *TICK ONE BOX ONLY*

All of the time	☐
Most of the time	☐
Some of the time	☐
Hardly ever	☐

10. I GET ANGRY WITH MYSELF OR CALL MYSELF NAMES. *TICK ONE BOX ONLY*

Yes, definitely	☐
Yes, sometimes	☐
No, not much	☐
No, not at all	☐

12. I FEEL I MIGHT LOSE CONTROL AND HIT OR HURT SOMEONE. *TICK ONE BOX ONLY*

Sometimes	☐
Occasionally	☐
Rarely	☐
Never	☐

14. THE THOUGHT OF HURTING MYSELF OCCURS TO ME: *TICK ONE BOX ONLY*

Sometimes	☐
Not very often	☐
Hardly ever	☐
Not at all	☐

16. PEOPLE UPSET ME SO THAT I FEEL LIKE SLAMMING DOORS OR BANGING ABOUT *TICK ONE BOX ONLY*

Yes, often	☐
Yes, sometime	☐
Only occasionally	☐
Not at all	☐

18. LATELY I HAVE BEEN GETTING ANNOYED WITH MYSELF. *TICK ONE BOX ONLY*

Very much so	☐
Rather a lot	☐
Not much	☐
Not at all	☐

BARTHEL INDEX

PATIENT STUDY NUMBER			·				TIME OF ASSESSMENT	3 months ☐ 12 months ☐

PERSON RESPONDING				ASSISTANCE FOR INTERVIEW OBTAINED FROM			
Index Case	☐	Other Relative	☐	Index Case	☐	Other Relative	☐
Spouse/Partner	☐	Friend/Associate/	☐	Spouse/Partner	☐	Friend/Associate/	☐
Sibling	☐	Neighbour		Sibling	☐	Neighbour	
Son/Daughter	☐	Carer, e.g. nurse	☐	Son/Daughter	☐	Carer, e.g. nurse	☐
Parent	☐	Other, Unspecified	☐	Parent	☐	Other, Unspecified	☐

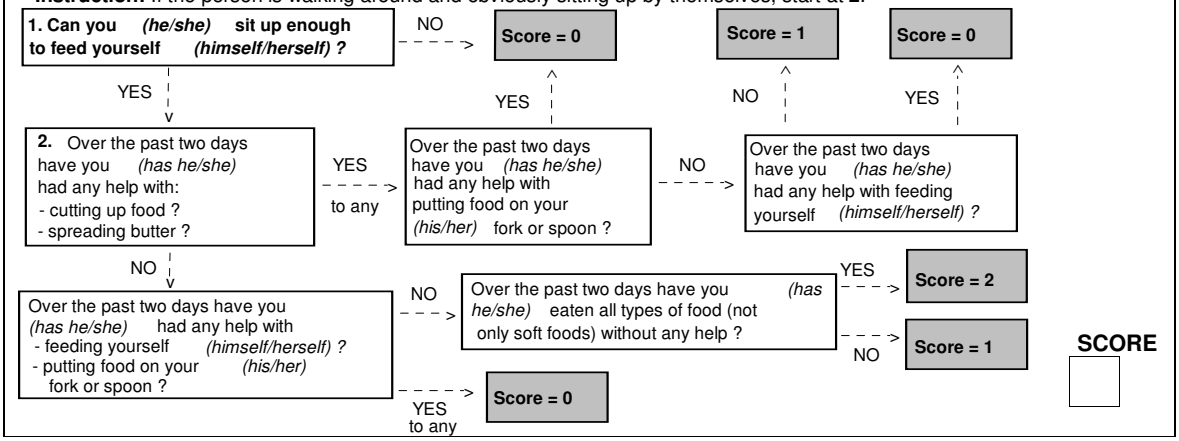
BARTHEL ACTIVITIES OF DAILY LIVING

If the participant indicates that they are not independent in any of these activities, ask "Who helps you with these tasks?", and note which person is the chief carer on the patient contact sheet.

FEEDING

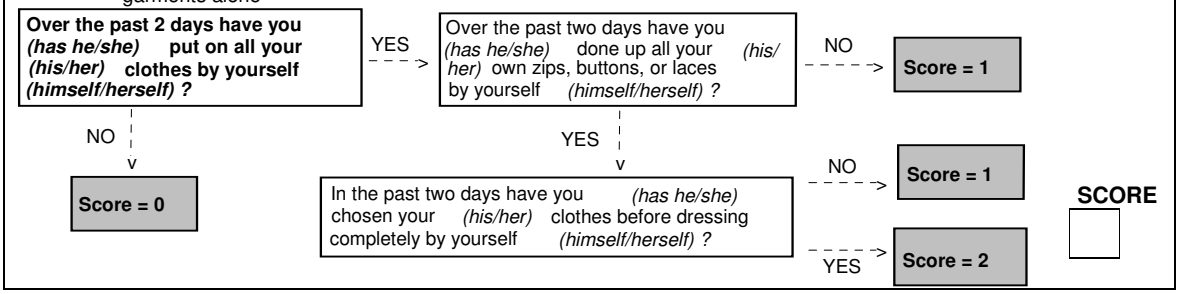
** Independent = Able to eat any normal food (not only soft food*). Food cooked and served by others (food provided in reach). But not cut up. Help = food cut up, patient feeds self*.

Instruction: If the person is walking around and obviously sitting up by themselves, start at **2**.



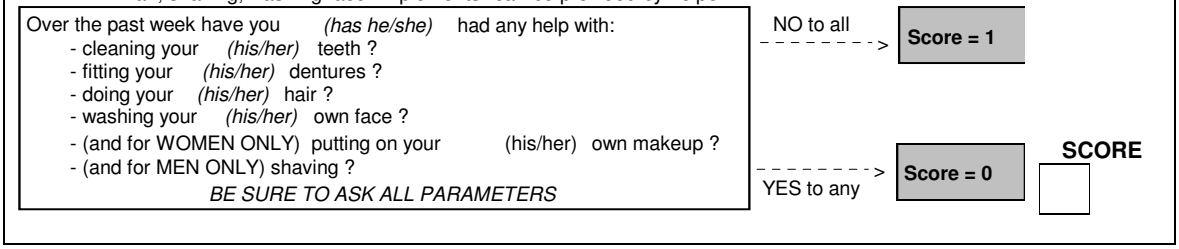
DRESSING

** Independent = Should be able to select and put on all clothes (including buttons, zips, laces etc), which may be adapted. Half = help with buttons, zips etc (CHECK!), but can put on some garments alone*



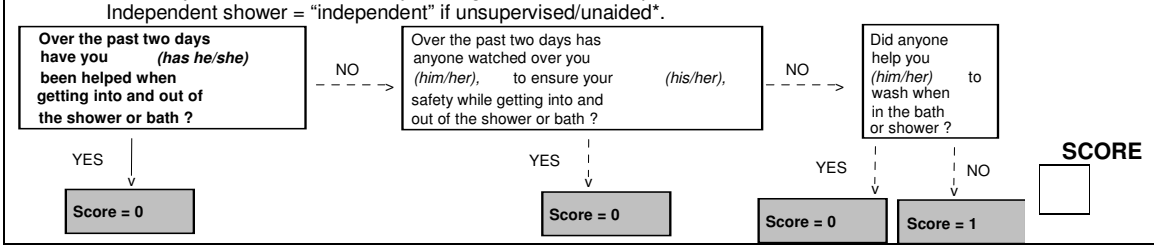
GROOMING

** Refers to preceding week. Refers to personal hygiene: doing teeth, fitting false teeth, doing hair, shaving, washing face. Implements* can be provided by helper



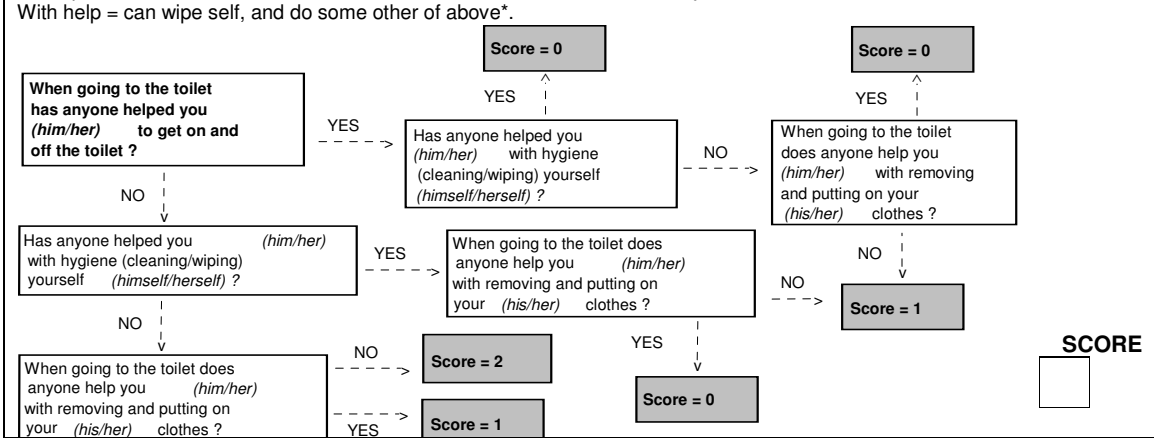
BATHING

** Usually the most difficult activity. Must get in and out unsupervised, and wash self.
Independent shower = "independent" if unsupervised/unaided*.



TOILET USE

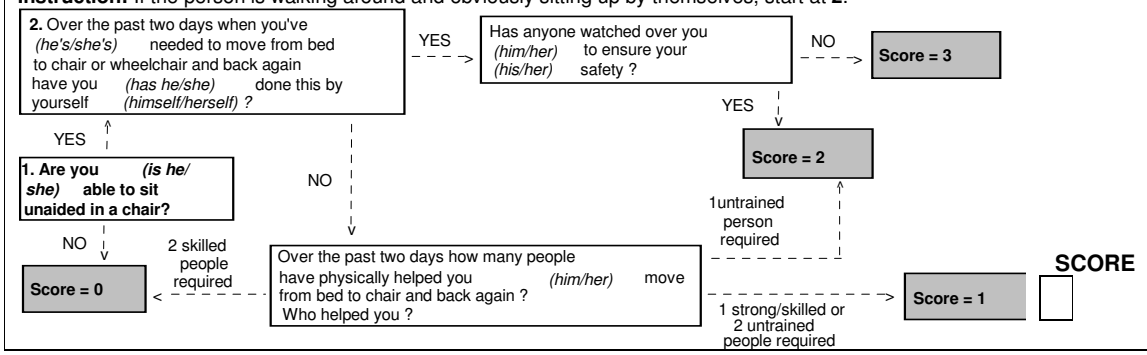
**Independent = Should be able to reach toilet/commode, undress sufficiently, clean self, dress and leave.
With help = can wipe self, and do some other of above*.



TRANSFER

** Independent = From bed to chair and back.
Dependent = no sitting balance (unable to sit); two people to lift.
Major help = one strong/skilled, or two normal people. Can sit up.
Minor help (verbal or physical) = by one, untrained person, including supervision/ moral support.

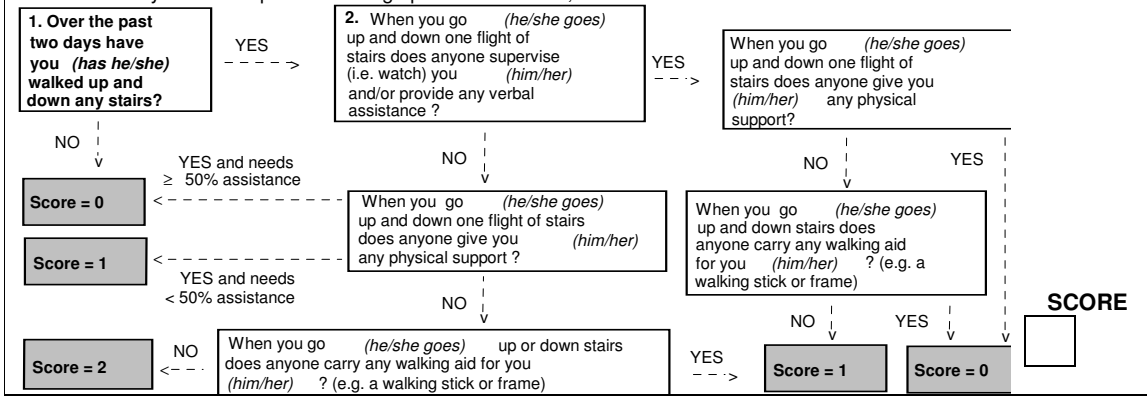
Instruction: If the person is walking around and obviously sitting up by themselves, start at **2**.



STAIRS

**Independent = Must carry any walking aid used (if used). If patient hasn't walked up or down stairs because there are no stairs at home but usually does use them while shopping, etc, score as independent (use judgment). Needs help = verbal, physical, and carrying help

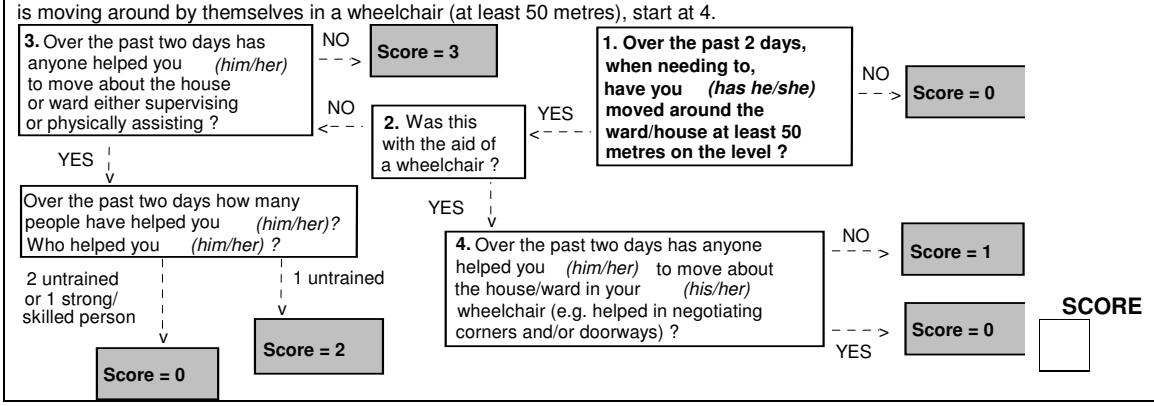
Instruction: If you see the person walking up and down stairs, start at **2**.



MOBILITY

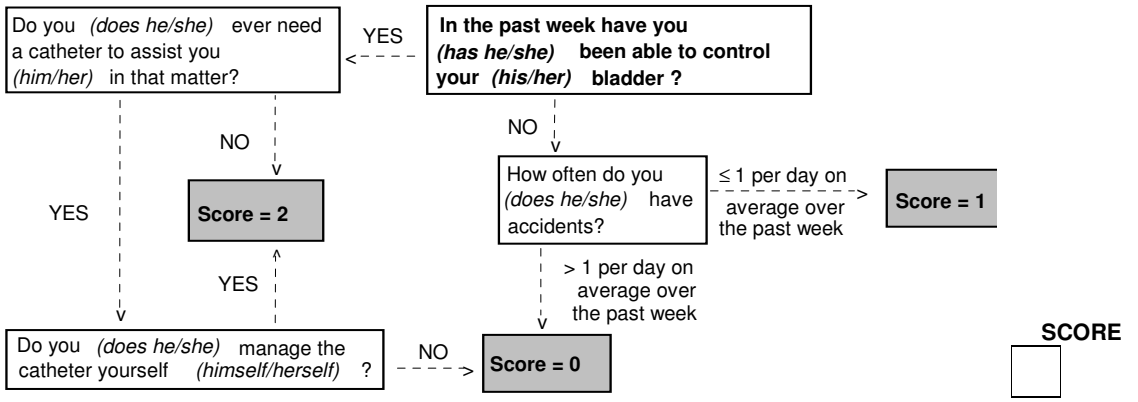
** Refers to mobility about house or ward, indoors.
Independent = May use aid (stick, frame). If in a wheelchair, must negotiate doors/corners unaided.
Help (physical/verbal) = by one, untrained person, including supervision/moral support.

Instruction: If the person is walking around by themselves (at least 50 metres), start at 3. If the person is moving around by themselves in a wheelchair (at least 50 metres), start at 4.



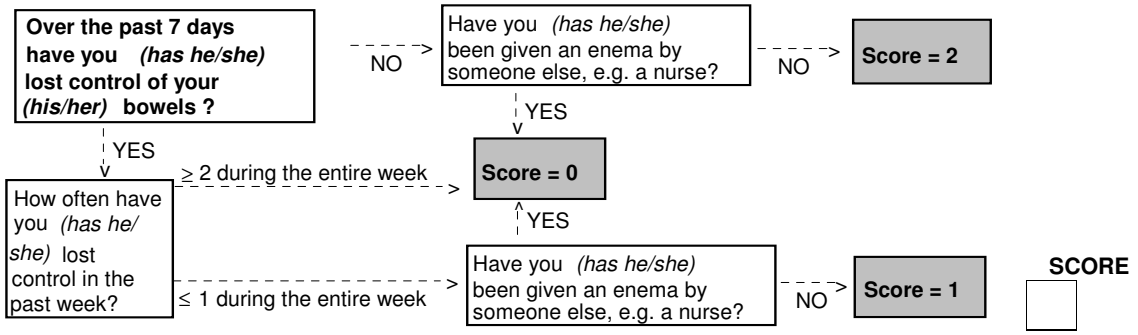
BLADDER

** Refers to preceding week. Occasional = less than once a day (max once per 24 hours).
A catheterized patient who can manage the catheter alone is registered as continent.



BOWELS

** Refers to preceding week.
If needs enema from nurse, then "incontinent". Occasional accident = once/week.



BARTHEL INDEX TOTAL		

ASSESSMENT OF STROKE SEVERITY – DAY 0
(NIH STROKE SCALE)

	PATIENT STUDY NUMBER			.				

Instructions: **Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the examination and should work quickly. Except where indicated, the patient should not be coached (ie. Repeated requests to make a special effort).**

Category	Definition	Score	NIH
Level of consciousness	Alert	☐	0
	Not alert, but arousable with minimal stimulation	☐	1
	Not alert, requires repeated stimulation to attend	☐	2
	Coma	☐	3
Ask the subject the month and their age	Answers both correctly	☐	0
	Answers one correctly	☐	1
	Both incorrect	☐	2
Ask the subject to open and close eyes and then to make a fist	Obeys both correctly	☐	0
	Obeys one correctly	☐	1
	Both incorrect	☐	2
Best gaze (only horizontal eye movement)	Normal	☐	0
	Partial gaze palsy	☐	1
	Forced deviation	☐	2
Visual field testing	No visual field loss	☐	0
	Partial hemianopia	☐	1
	Complete hemianopia	☐	2
	Bilateral hemianopia	☐	3
Facial paresis (ask subject to show teeth and raise eyebrows and close eyes tightly)	Normal symmetrical movement	☐	0
	Minor paralysis (flattened nasolabial fold, asymmetry on smiling)	☐	1
	Partial paralysis (total or near total paralysis of lower face)	☐	2
	Complete paralysis of one or both sides (absence of facial movement)	☐	3
Motor function – Right arm	Normal (extends arms 90 or 45 degrees for 10 seconds without drift)	☐	0
	Drift	☐	1
	Some effort against gravity	☐	2
	No effort against gravity	☐	3
	No movement	☐	4
	Untestable (joint fused or limb amputated)	☐	9
Motor function – Left arm	Normal (extends arms 90 or 45 degrees for 10 seconds without drift)	☐	0
	Drift	☐	1
	Some effort against gravity	☐	2
	No effort against gravity	☐	3
	No movement	☐	4
	Untestable (joint fused or limb amputated)	☐	9
Motor function – Right leg	Normal (hold leg 30 degrees position for 5 seconds)	☐	0
	Drift	☐	1
	Some effort against gravity	☐	2
	No effort against gravity	☐	3
	No movement	☐	4
	Untestable (joint fuse or limb amputated)	☐	9
Motor function – Left leg	Normal (hold leg 30 degrees position for 5 seconds)	☐	0
	Drift	☐	1
	Some effort against gravity	☐	2
	No effort against gravity	☐	3
	No movement	☐	4
	Untestable (joint fuse or limb amputated)	☐	9
Limb ataxia	No ataxia	☐	0
	Present in one limb	☐	1
	Present in two limbs	☐	2
Sensory (use pinprick to test arms, legs, trunk and face – compare sides)	Normal	☐	0
	Mild to moderate decrease in sensation	☐	1
	Severe to total sensory loss	☐	2
Best language (describe picture, name items, read sentences)	No aphasia	☐	0
	Mild to moderate aphasia	☐	1
	Severe aphasia	☐	2
	Mute	☐	3
Dysarthria (read several words)	Normal articulation	☐	0
	Mild to moderate slurring of words	☐	1
	Near unintelligible or unable to speak	☐	2
	Intubated or other physical barrier	☐	9
Extinction and inattention	Normal	☐	0
	Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities	☐	1
	Severe hemi-inattention or hemi-inattention to more than one modality	☐	2

If any item is scored "9", please give details.

(Do not include item scores of "9" in total score) **TOTAL SCORE**		

59053

Case Report Form

Cognitive Assessment, 3 Months

National Stroke Research Institute

PATIENT STUDY NUMBER

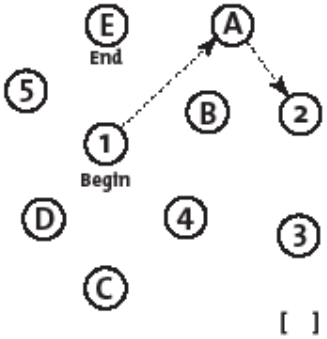
PATIENT INITIALS

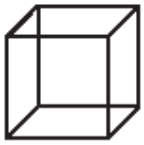
NIHSS

			POINTS
Orientation	Ask the subject the month and their age	Answers both correctly Answers one correctly Both incorrect	☐ 0 ☐ 1 ☐ 2
Language	Best language (describe picture, name items, read sentences)	No aphasia Mild to moderate aphasia Severe aphasia Mute	☐ 0 ☐ 1 ☐ 2 ☐ 3

MoCA

VISUOSPATIAL / EXECUTIVE



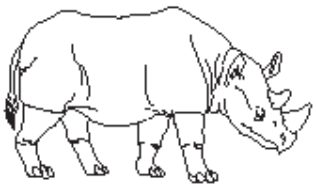
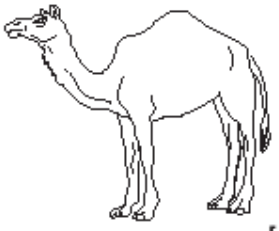


Copy cube

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	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
WITH NO CUE	[ ]	[ ]	[ ]	[ ]	[ ]	

__/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

Appendix B: Assessment Schedule, Person Responsible

Assessment	Screening	Baseline	Intervention period	Termination/ Discharge	Follow up	
Day/Month	**Day 0**	**Day 0**	**Day 0 to ≤14**	**Day ≤ 14**	**3 Months (+/- 7 days)**	**12 Months (+/- 7days)**
Eligibility	X[1, 2]		X[2]			
Informed consent	X[1, 2]	X[1, 2]				
Interpreter	X[*]	X[*]	X[*]	X[*]	X[*]	X[*]
Medical History	X[1, 2]					
Physical Exam	X[1, 2]				X[4]	X[4]
Demographic Data		X[1, 2]				
NIHSS[§]	X[1, 2]					
OCSP	X[1, 2]					
Premorbid mRS	X[1, 2]					
Baseline mRS		X[2]				
Randomisation		X[1, 2]				
MSAS		X[2]				
Star Cancellation Test		X[2]				
Time to first Mobilisation		X[2]				
Nurse Form			X[3]			
PDA entries			X[2, 6]			
Discharge mRS			X**			
End of Intervention				X[2,5]		
Discharge information			X[2,3,4,5]	X[2,3,4,5]		
mRS					X[4]	X[4]
IDA					X[4]	X[4]
Barthel Index					X[4]	X[4]
AQoL					X[4]	X[4]
RivermeadMAS					X[4]	X[4]
50 m walk			X [4, 6]	X[4]	X[4]	X[4]
MoCA					X[4]	
Cost of Care					X[4]	X[4]
Adverse Events			X[1, 2,3, 4,5]	X[1, 2, 3,4,5]		
Important Medical Events			X[1, 2,3 4,5]	X[1, 2, 3,4,5]	X[4]	
SAEs			X[1, 2,3, 4, 5]	X[1, 2, 3,4, 5]	X[4]	X[4]
Group allocation guess					X[4]	

X[1] =Neurology or Stroke Registrar
X[2]= AVERT physiotherapist
X[3] = AVERT nursing staff.
X[4] = Blinded assessor
X[5] = main investigator
X[6] = Ward physiotherapists and occupational therapists
X[*]= if required
X** = Selected sites only
[§]NIHSS and OCSP may also be performed by other trained and certified personnel