HEALTH TECHNOLOGY ASSESSMENT

VOLUME 21 ISSUE 54 SEPTEMBER 2017
ISSN 1366-5278

A Very Early Rehabilitation Trial after stroke (AVERT): a Phase III, multicentre, randomised controlled trial

Peter Langhorne, Olivia Wu, Helen Rodgers, Ann Ashburn and Julie Bernhardt on behalf of the AVERT triallists' collaboration

NHS
National Institute for Health Research

DOI 10.3310/hta21540

A Very Early Rehabilitation Trial after stroke (AVERT): a Phase III, multicentre, randomised controlled trial

Peter Langhorne,[1]* Olivia Wu,[2] Helen Rodgers,[3] Ann Ashburn[4] and Julie Bernhardt[5,6] on behalf of the AVERT triallists' collaboration

[1]Academic Section of Geriatric Medicine, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
[2]Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK
[3]Institute for Ageing and Health, Medical School, Newcastle University, Newcastle upon Tyne, UK
[4]Rehabilitation Research Unit, Southampton General Hospital, Southampton, UK
[5]Stroke Division, The Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia
[6]University of Melbourne, Parkville, VIC, Australia

*Corresponding author

Declared competing interests of authors: Peter Langhorne received funding from the National Institute for Health Research; National Health Medical Research Council Australia; Chest, Heart and Stroke Scotland; the Stroke Association, UK; and Chest Heart and Stroke Association of Northern Ireland to complete this trial. Peter Langhorne is a member of Health Technology Assessment (HTA) Clinical Trials Board. Olivia Wu is a member of HTA Evidence Synthesis Board and Systematic Review Programme Advisory Group. Helen Rodgers reports grants from Newcastle University during the tenure of this grant. Julie Bernhardt reports grants from National Health and Medical Research Council Australia; NIHR; Singapore Health, Singapore; Chest, Heart and Stroke Scotland, UK; Chest Heart and Stroke Association of Northern Ireland; Stroke Association, UK, during the conduct of the study.

Published September 2017
DOI: 10.3310/hta21540

This report should be referenced as follows:

Langhorne P, Wu O, Rodgers H, Ashburn A, Bernhardt J. A Very Early Rehabilitation Trial after stroke (AVERT): a Phase III, multicentre, randomised controlled trial. *Health Technol Assess* 2017;**21**(54).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.236

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 12/01/16. The contractual start date was in August 2013. The draft report began editorial review in August 2016 and was accepted for publication in July 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Abstract

A Very Early Rehabilitation Trial after stroke (AVERT): a Phase III, multicentre, randomised controlled trial

Peter Langhorne,[1]* Olivia Wu,[2] Helen Rodgers,[3] Ann Ashburn[4] and Julie Bernhardt[5,6] on behalf of the AVERT triallists' collaboration

[1]Academic Section of Geriatric Medicine, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
[2]Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK
[3]Institute for Ageing and Health, Medical School, Newcastle University, Newcastle upon Tyne, UK
[4]Rehabilitation Research Unit, Southampton General Hospital, Southampton, UK
[5]Stroke Division, The Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia
[6]University of Melbourne, Parkville, VIC, Australia

*Corresponding author Peter.Langhorne@glasgow.ac.uk

Background: Mobilising patients early after stroke [early mobilisation (EM)] is thought to contribute to the beneficial effects of stroke unit care but it is poorly defined and lacks direct evidence of benefit.

Objectives: We assessed the effectiveness of frequent higher dose very early mobilisation (VEM) after stroke.

Design: We conducted a parallel-group, single-blind, prospective randomised controlled trial with blinded end-point assessment using a web-based computer-generated stratified randomisation.

Setting: The trial took place in 56 acute stroke units in five countries.

Participants: We included adult patients with a first or recurrent stroke who met physiological inclusion criteria.

Interventions: Patients received either usual stroke unit care (UC) or UC plus VEM commencing within 24 hours of stroke.

Main outcome measures: The primary outcome was good recovery [modified Rankin scale (mRS) score of 0–2] 3 months after stroke. Secondary outcomes at 3 months were the mRS, time to achieve walking 50 m, serious adverse events, quality of life (QoL) and costs at 12 months. Tertiary outcomes included a dose–response analysis.

Data sources: Patients, outcome assessors and investigators involved in the trial were blinded to treatment allocation.

Results: We recruited 2104 (UK, $n = 610$; Australasia, $n = 1494$) patients: 1054 allocated to VEM and 1050 to UC. Intervention protocol targets were achieved. Compared with UC, VEM patients mobilised 4.8 hours [95% confidence interval (CI) 4.1 to 5.7 hours; $p < 0.0001$] earlier, with an additional three (95% CI 3.0 to 3.5; $p < 0.0001$) mobilisation sessions per day. Fewer patients in the VEM group ($n = 480$, 46%) had a favourable outcome than in the UC group ($n = 525$, 50%) (adjusted odds ratio 0.73, 95% CI 0.59 to 0.90; $p = 0.004$). Results were consistent between Australasian and UK settings. There were no statistically significant differences in secondary outcomes at 3 months and QoL at 12 months. Dose–response analysis found a consistent pattern of an improved odds of efficacy and safety outcomes in association with increased daily frequency of out-of-bed sessions but a reduced odds with an increased amount of mobilisation (minutes per day).

Limitations: UC clinicians started mobilisation earlier each year altering the context of the trial. Other potential confounding factors included staff patient interaction.

Conclusions: Patients in the VEM group were mobilised earlier and with a higher dose of therapy than those in the UC group, which was already early. This VEM protocol was associated with reduced odds of favourable outcome at 3 months cautioning against very early high-dose mobilisation. At 12 months, health-related QoL was similar regardless of group. Shorter, more frequent mobilisation early after stroke may be associated with a more favourable outcome.

Future work: These results informed a new trial proposal [A Very Early Rehabilitation Trial – DOSE (AVERT–DOSE)] aiming to determine the optimal frequency and dose of EM.

Trial registration: The trial is registered with the Australian New Zealand Clinical Trials Registry number ACTRN12606000185561, Current Controlled Trials ISRCTN98129255 and ISRCTN98129255.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 21, No. 54. See the NIHR Journals Library website for further project information. Funding was also received from the National Health and Medical Research Council Australia, Singapore Health, Chest Heart and Stroke Scotland, Northern Ireland Chest Heart and Stroke, and the Stroke Association. In addition, National Health and Medical Research Council fellowship funding was provided to Julie Bernhardt (1058635), who also received fellowship funding from the Australia Research Council (0991086) and the National Heart Foundation (G04M1571). The Florey Institute of Neuroscience and Mental Health, which hosted the trial, acknowledges the support received from the Victorian Government via the Operational Infrastructure Support Scheme.

Contents

List of tables

List of figures

List of boxes

Glossary

AVERT intervention protocol A protocol for use by clinical staff to guide the delivery of the very early mobilisation and usual care interventions.

AVERT Online A password-protected, trial-specific web-based management system.

Contamination When the witnessing of a different intervention makes others change their usual care practice (consciously or unconsciously).

Counting mobilisations If a patient performs a mobilisation (e.g. walks to toilet with help or is sat out of bed) and then rests for 5 minutes, then their next mobilising activity (e.g. walking back from the toilet or getting back into bed) constitutes another mobilisation.

Dose A session of mobilisation given to AVERT patients.

Early mobilisation Starting out of bed, sitting, standing and walking early after stroke with no defined time from stroke onset.

Excessive fatigue When the patient reports a score of > 13 on the Borg Perceived Exertion Scale and/or AVERT staff assess that the patient is excessively fatigued (e.g. the patient's functional performance worsens significantly during the intervention).

Mobilisation The patient is assisted and encouraged in functional tasks, including activities such as sitting over the edge of the bed, standing up, sitting out of bed and walking. Upper limb movement was intended to be integrated into functional activities as appropriate. Mobilisations were performed by the AVERT nurse and/or the AVERT physiotherapist. Support staff, such as therapy assistants and students, could also be trained to provide mobilisations.

Nurse's record of mobilisation sessions The time each session started and the type of each session was recorded on AVERT Online or, if the website was not available, data were temporarily recorded on the paper nurses recording form until such time it could be entered online.

Physiotherapist's record of mobilisation session The date and time each session started, the minutes and content of each session were recorded via AVERT Online. If the online forms were unavailable, paper therapist recording forms could be used to temporarily collect the information until such time it could be entered online.

Time to first mobilisation The time from stroke onset to the time of the patient's first mobilisation out of bed (assisted or independent). This did not include the initial assessment by the AVERT physiotherapist.

Transient ischaemic attack Stroke-like symptoms that resolve completely within 24 hours.

Very early The earliest possible time after a consented patient had suffered a stroke to their first mobilisation intervention (≤ 24 hours).

Very early mobilisation The earliest possible time after a consented patient had a stroke to their first out-of-bed mobilisation.

List of abbreviations

AE	adverse event
aHR	adjusted hazard ratio
aOR	adjusted odds ratio
AQoL	assessment of quality of life
AVERT	A Very Early Rehabilitation Trial
b.p.m.	beats per minute
CART	classification and regression tree
CI	confidence interval
CRF	case report form
EM	early mobilisation
HR	hazard ratio
HRQoL	health-related quality of life
HTA	Health Technology Assessment
IDA	irritability, anxiety and depression assessment
IME	important medical event
IQR	interquartile range
IRR	incidence rate ratio
MI	main investigator
MoCA	Montreal Cognitive Assessment
mRS	modified Rankin scale
MSAS	Mobility Scale for Acute Stroke
NIHR	National Institute for Health Research
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio
QoL	quality of life
RCT	randomised controlled trial
RMAS	Rivermead Motor Assessment Scale
ROC	receiver operating characteristic
rtPA	recombinant tissue plasminogen activator
SAE	serious adverse event
TIA	transient ischaemic attack
TTFM	time to first mobilisation
UC	usual care
VEM	very early mobilisation
VERITAS	Very Early Rehabilitation on Intensive Telemetry After Stroke

Plain English summary

Despite the many recent improvements in stroke care, it is not clear which components are the most important. Early active rehabilitation (mobilisation) represents a simple treatment that could be provided for the majority of people with a stroke.

This clinical trial included people admitted to hospital with a stroke in 56 hospitals in five countries (UK, Australia, New Zealand, Malaysia and Singapore). Those who agreed to participate were assigned at random to either usual care (UC) in the stroke unit or very early mobilisation (VEM) (assisted to get out of bed within 24 hours of the first sign of stroke). This continued frequently for the first 14 days or until discharge from the stroke unit. All participants were followed up wherever they were living 3 months and 12 months later. A trained health-care worker gathered information about their ability to move about, their ability to carry out everyday activities, their mood, their quality of life and any costs associated with their care.

A total of 2104 participants took part in the trial. At 3 months, fewer participants in the VEM group were independent in everyday activities ($n = 480$, 46%) than in the UC group ($n = 525$, 50%). There were no significant differences in any of the other trial measures. Further analysis indicated that a good recovery might be best achieved with short bursts of mobilisation activity repeated regularly.

Using the information from this study, we are planning a new trial to better understand how early stroke rehabilitation can be delivered to maximise every patient's recovery.

Scientific summary

Background

The last two decades has seen a substantial change in the way that stroke patients are managed. We now have several interventions available that have good evidence of benefit for acute stroke patients. Arguably the most important of these is stroke unit care, which comprises a complex package of specialist multidisciplinary stroke care involving nurses, therapists and doctors. However, this is a complex intervention and it is difficult to provide firm advice on the key components of stroke unit care. Many descriptive studies have reported that early mobilisation (EM) (starting out of bed, sitting, standing and walking early after stroke) is believed to be an important contributor to the benefit of stroke units. However, EM is poorly described and defined. This trial focuses on very early mobilisation (VEM) commencing within 24 hours of stroke onset as a key component of stroke unit care.

Very early mobilisation comprises the commencement of sitting, standing and walking training out of bed after stroke within 24 hours of stroke onset, using a clinical protocol that tailors the activity to the severity of stroke. The biological rationale for VEM is based on the following.

1. There is good evidence that bed rest is often harmful.
2. Some of the most common and serious complications after stroke are those related to immobility.
3. Modern concepts of brain recovery after injury suggest a window of opportunity for exploiting brain plasticity and encouraging repair.

However, there are also concerns about the potential harm of VEM and, in particular, due to reduced cerebral blood flow caused by adopting an upright position too early. In view of these uncertainties, Professor Julie Bernhardt of the University of Melbourne began the A Very Early Rehabilitation Trial (AVERT) programme of work. This comprised Phase I observational studies, followed by a Phase II safety and feasibility randomised controlled trial (RCT) and, finally, the main multicentre international RCT (AVERT Phase III) that is reported here.

Objectives

The primary aim of this trial was to investigate the effectiveness of a protocol to implement VEM after stroke; with commencement of frequent out-of-bed activity within 24 hours of stroke onset, compared with usual care (UC).

The objectives of AVERT were to address four main questions.

1. Does VEM reduce death and disability at 3 months post stroke?
2. Does VEM reduce the number and severity of complications at 3 months post stroke?
3. Does VEM improve quality of life (QoL) at 12 months post stroke?
4. Is VEM cost-effective?

Methods

The AVERT was a pragmatic, prospective, parallel-group, multicentre, international, RCT with blinded assessment of outcomes and an intention to treat analysis. The National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme grant supported the UK component of the trial.

Setting
Acute stroke units in 56 hospitals in five countries: UK (England, Scotland, Northern Ireland and Wales), Australia, New Zealand, Malaysia and Singapore.

Participants
Acute stroke patients (confirmed first or recurrent stroke, cerebral infarct or intracerebral haemorrhage) who were admitted to a stroke unit within 24 hours of symptom onset. Treatment with recombinant tissue plasminogen activator (rtPA) was allowed with the agreement of the responsible clinician. Exclusion criteria included significant premorbid disability, competing care needs or acute medical instability.

Procedures
Informed consent was obtained from the patient or their nominated representative. Patients were invited to take part in a trial that was testing 'different types of rehabilitation'. Baseline data were entered on the AVERT Online electronic data capture system prior to randomisation.

Randomisation
After entry of baseline data, the online system allocated the patient to a treatment group using a 1 : 1 ratio, with computer-generated block randomisation stratified for site and severity. Patients were allocated to receive either UC alone or VEM in addition to UC. The VEM intervention commenced as soon as patients were recruited and lasted for 14 days, or until the patient was discharged from the stroke unit (whichever was sooner). Following randomisation, baseline patient data were collected on baseline demography, mobility scale for acute stroke, star cancellation test and time to first mobilisation (TTFM).

Interventions
The AVERT intervention protocol was followed for all patients randomised. Regardless of intervention group, the AVERT nurses and physiotherapists recorded information about all mobilisations via the online trial system.

Usual care was provided at the discretion of the individual sites. Trial staff documented usual stroke unit care at their site. At each site, UC was monitored to ensure that UC did not change, or changes were clarified.

The VEM intervention comprised the following key features.

- It was to begin within 24 hours of stroke onset.
- It was to focus on out-of-bed sitting, standing and walking activities.
- VEM was delivered in at least three out-of-bed sessions in addition to UC.
- Nursing and physiotherapy mobilisations were titrated according to patient functional level.

Patients allocated to VEM were managed by physiotherapy and nursing staff trained in the study procedures (AVERT nurses and physiotherapists), who followed a prescribed approach based on the baseline assessment of patient abilities from level one (fully dependent) to level four (little or no dependence). Usual risk assessments and lifting policies were applied to all mobilisations. Prior to, and during, the first mobilisation, an assessment of physiological variables was required and mobilisation was stopped if physiological variables changed beyond specified limits. VEM activities were repeated and varied as appropriate and could be reduced if associated with excessive fatigue. Nurses and therapists frequently worked together, but on Saturdays the AVERT nurse was responsible for providing and recording mobilisations.

The UC group received usual post-stroke care and the number and type of mobilisations were not prescribed but were recorded. AVERT Online was used to record therapy and nursing input to both VEM and UC groups and any deviations to the protocol were documented and reported. Care was taken not to record VEM interventions in the routine clinical records.

Blinding

Several steps were taken to maintain the integrity of the trial.

- Patients and families were not told of their allocation group.
- Treatment allocation was not written in the medical records.
- AVERT staff ensured that other staff were not aware of treatment allocation.
- The blinded outcome assessor was remote from the ward and did not have contact with any clinical care.

Outcomes

The primary outcome was survival without major disability [modified Rankin scale (mRS) score of 0–2] at 3 months after stroke. Secondary efficacy outcomes were an assumption-free ordinal shift across the range of the mRS, time (days) to walk 50 m unassisted and the proportion of patients achieving unassisted walking by 3 months. Secondary safety outcomes at 3 months were fatal and non-fatal serious adverse events (SAEs). SAEs of interest were neurological (stroke progression and recurrent stroke) and immobility related (pulmonary embolism, venous thrombosis, urinary tract infection, pressure sores and pneumonia). All fatal and non-fatal SAEs were reported according to standard definitions and independently adjudicated. At 12 months, an assessment of health-related quality of life (HRQoL) was made, using the assessment of quality of life, with costs assessed using a resources questionnaire.

Subgroup analyses were prespecified for age, stroke severity, stroke subtype (infarct or haemorrhage), treatment with rtPA and TTFM, as well as an exploratory analysis of association between treatment dose and patient outcome.

Sample size

We estimated that a sample of 2104 patients would be required to provide an 80% power to detect a significant intervention effect ($p = 0.05$) with adjustments for 5% drop-in and 10% drop-out. The trial was powered to detect an absolute risk reduction of a poor outcome (mRS score of 3–6) of at least 7.1%. The statistical and cost analysis plans were prespecified and published in advance. The primary outcome analysis used a binary logistic regression model with treatment group as an independent variable and mRS at 3 months as the dependent variable, with intention-to-treat analysis. Baseline stroke severity and age were included as treatment covariates.

A series of subgroup and exploratory analysis were prespecified to explore the range of any treatment effect and to allow analysis of association between treatment dose and patient outcome.

Results

A total of 25,237 patients were admitted within 24 hours of stroke onset, of whom 23,133 were ineligible. Main reasons for ineligibility were a lack of available recruiting staff on duty, medical instability or premorbid disability. A total of 2104 patients were recruited between July 2006 and October 2014; 1054 received VEM and 1050 received UC. A total of 34 patients were found to have a non-stroke diagnosis and 26 were never mobilised. These patients remained within the intention-to-treat analysis.

Baseline characteristics were well matched between groups. The median time to randomisation was 18 hours after stroke, 80% were experiencing a first stroke and 45% were classified as having moderate–severe stroke (National Institutes of Health Stroke Scale score of > 7). A total of 26% were aged > 80 years and 24% received rtPA.

Patients allocated to VEM began mobilisation within 24 hours of stroke and maintained earlier and higher levels of out-of-bed activity than UC patients. However, it was noted that the median TTFM in the UC group reduced during the study period. Overall, 965 (92%) VEM patients were mobilised within 24 hours compared with 623 (59%) in the UC group. There were no substantial regional differences in the delivery of the intervention.

Primary outcome

A total of 2083 (99%) patients were included in the 3-month follow-up.

At 3 months, fewer patients in the VEM group had a favourable outcome (mRS score of 0–2) than in the UC group. A total of 480 (46%) VEM patients had a favourable outcome compared with 525 (50%) in the UC group. This resulted in the significant difference between groups on the prespecified analysis [adjusted odds ratio (aOR) 0.73, 95% confidence interval (CI) 0.59 to 0.90; $p = 0.004$]. Sensitivity analysis produced similar results and unadjusted analysis of the primary outcome showed a similar (but borderline significant) direction of effect ($p = 0.068$). Subgroup analysis of the primary outcome showed a consistent pattern favouring UC across all the main subgroups. There was a suggestion of poorer outcomes with VEM in patients with severe stroke and intracerebral haemorrhage but these did not achieve statistical significance (test for interaction $p > 0.05$).

Secondary outcomes

Assumption-free ordinal analysis across the whole mRS did not show a significant difference between groups (aOR 0.94, 95% CI 0.85 to 1.03; $p = 0.193$). Similarly, there were no significant differences in walking ability (aOR 1.04, 95% CI 0.94 to 1.15; $p = 0.459$), case fatality at 3 months (aOR 1.34, 95% CI 0.93 to 1.93; $p = 0.113$) or non-fatal SAEs (incidence rate ratio 0.88, 95% CI 0.72 to 1.07; $p = 0.194$). For HRQoL, the median assessment of QoL (interquartile range) for the VEM group was 0.47 (0.07–0.81) and for the UC group was 0.49 (0.08–0.81) ($p = 0.865$).

Tertiary outcomes

Further prespecified analyses explored the relationship between treatment received and patient outcomes. These indicated that a favourable outcome (mRS score of 0–2), survival and recovery of walking at 3 months were positively associated with an increased frequency of mobilisation sessions. In contrast, a more prolonged duration of out-of-bed mobilisation activity was associated with a poorer outcome. This pattern was observed in logistic regression analysis and confirmed with a classification and regression tree analysis.

Meta-analysis of early mobilisation trials

We identified a total of nine RCTs, including AVERT, that had tested EM (within 48 hours) after stroke compared with UC. Across all trials, the median delay to starting mobilisation was 18.5 hours in the EM group and 33.3 hours in the UC group. EM showed non-significant increase in the odds of death or dependency (odds ratio 1.10, 95% CI 0.94 to 1.29).

Conclusions

This is the largest randomised trial of its kind and required strong interdisciplinary collaboration. Most patients underwent first mobilisation within 24 hours of stroke but the earlier, more frequent, higher-dose mobilisation was associated with a poorer outcome than UC. As usual stroke unit care varied from site to site and is complex in nature. It is oversimplistic to simply advise UC.

The AVERT results raise several important research questions; in particular, what are the physiological and molecular changes induced that may be harmful in some patients, who should we target for EM and how do we best describe the key characteristics of EM. These questions are being taken forward in a more detailed meta-analysis. We also propose to undertake a further dose–response trial (AVERT–DOSE) to explore the effect of frequency and dose of rehabilitation on efficacy and safety outcomes.

Trial registration

This trial is registered with the Australian New Zealand Clinical Trials Registry number ACTRN12606000185561, and Current Controlled Trials ISRCTN98129255 and ISRCTN98129255.

Funding

Funding for this study was provided by the HTA programme of the NIHR. Funding was also received from National Health and Medical Research Council Australia, Singapore Health, Chest Heart and Stroke Scotland, Northern Ireland Chest Heart and Stroke, and the Stroke Association. In addition, National Health and Medical Research Council fellowship funding was provided to Julie Bernhardt (1058635), who also received fellowship funding from the Australia Research Council (0991086) and the National Heart Foundation (G04M1571). The Florey Institute of Neuroscience and Mental Health, which hosted the trial, acknowledges the support received from the Victorian Government via the Operational Infrastructure Support Scheme.

Chapter 1 Introduction

Modern stroke unit care

The management of stroke patients has progressed greatly in the last two decades[1,2] and several interventions have provided good evidence of benefit for acute stroke patients.[1–8] These include:

1. stroke unit care[3] (a complex package of specialist multidisciplinary stroke care involving nurses, therapists and doctors)
2. aspirin for ischaemic stroke[4]
3. intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) for ischaemic stroke[5]
4. mechanical thrombectomy for major ischaemic stroke[6]
5. emergency decompressive surgery for malignant middle cerebral artery syndrome.[7]

Among these interventions, the stroke unit effect has potentially the greatest population impact as it combines both moderate effectiveness and broad applicability.[1,2] However, as it is a complex intervention it is difficult to be certain about the key components of stroke unit care.[8] Descriptive studies have reported that early mobilisation (EM) (starting out of bed, sitting, standing and walking early after stroke) is widely thought to be an important contributor to the stroke unit effect.[8–10] The other potentially important components include (1) co-ordinated multidisciplinary care, (2) skilled and specialised staff, (3) training and education of staff and (4) protocols of care covering common problems.[8,9] This trial focuses on the mobilisation component of the stroke unit rehabilitation intervention.

Rehabilitation

The term rehabilitation covers a broad philosophy and range of interventions aiming to help an individual recovering from disabling illness to minimise the impact of that illness on their level of dependence on external support.[11] The modern classification of diseases in the International Classification of Functioning, Disability and Health framework considers rehabilitation to comprise an interaction between the impact of the disease, the characteristics of the individual and the nature of their environment.[11] Rehabilitation professionals aim to act on different levels of the illness to minimise the impact on the individual.[11]

In the context of acute stroke, early rehabilitation usually covers the key impairments experienced by patients in the acute stage of the illness.[11] These include swallowing impairment, language and speech impairment, motor impairment, reduced mobility, reduced balance and reduced ability to carry out self-care activities. An early focus on mobilisation is one that is likely to be relevant to a substantial majority of acute stroke patients.

Early mobilisation

Early mobilisation comprises the commencement of sitting, standing and walking training out of bed early after stroke. Early descriptions of stroke units frequently refer to EM and it is thought to make an important contribution to the effectiveness of stroke unit care.[9,10] However, there are disagreements about the role of EM.[10]

Arguments around mobilisation

The biological rationale for EM is based on three principal lines of argument: (1) there is good evidence that bed rest has a harmful impact on cardiovascular, respiratory, muscular, skeletal and immune systems across many conditions[11,12] and is likely to slow recovery; (2) some of the most common and serious complications after stroke are those related to immobility[13–16] (we know that the routine day of most acute stroke patients is largely inactive;[17,18] therefore, introducing frequent training out of bed may reduce the risk of complications of immobility); and (3) current concepts of biological recovery after brain injury suggest a narrow window of opportunity for brain plasticity and repair.[19] If the brain indeed remodels itself based on experience[20] then early task-specific training may well have an important contribution to improving recovery.[21,22]

However, we must acknowledge that there are also concerns about potential harm of EM,[10,23] particularly in the first 24 hours after stroke onset. These concerns include haemodynamic considerations, such as fears that raising the patient's head early after stroke will impair cerebral blood flow and cerebral perfusion[23] or, in the case of intracerebral haemorrhage, increase the risk of inducing further bleeding.[24] As a result of these theoretical concerns, some clinicians have advocated initial bed rest for stroke patients.[23]

Given these uncertainties about the practice of EM in acute stroke patients we sought to carry out A Very Early Rehabilitation Trial (AVERT) in acute stroke patients that focused on very early (commencing within 24 hours of stroke onset), frequent out-of-bed mobilisations in the first 14 days.

AVERT programme

The AVERT programme of work that was run by Professor Julie Bernhardt of the University of Melbourne and began with Phase I observational studies. These studies demonstrated that most acute stroke patients were inactive for most of the time[17,18] but that this pattern of inactivity varied between hospitals.[17] She also demonstrated that there was considerable variation of opinion and clinical uncertainty among health-care professionals about the value of very early mobilisation (VEM).[23] These studies led to the AVERT Phase II safety and feasibility randomised controlled trial (RCT)[25,26] and the closely related Very Early Rehabilitation or Intensive Telemetry After Stroke (VERITAS) trial[27] carried out in Glasgow by Professor Peter Langhorne. These trials indicated that VEM was feasible and in the case of AVERT Phase II could be carried out within 24 hours of stroke onset. This approach was observed to be safe,[25–27] showed signals for improvements in recovery[25–28] as well as indicating that EM was probably cost-effective.[29]

Justification for the current study

The preparatory work carried out in AVERT Phases I and II led to the planning and conduct of the definitive AVERT Phase III trial.[30] This was planned as a pragmatic, international, multicentre Phase III RCT with the power to evaluate the efficacy and safety of VEM after stroke. This report outlines the AVERT Phase III international trial with some specific emphasis on the UK contribution. Much of this work has already been published by the AVERT group.[30–36] We will also refer to two related studies that were nested within the AVERT programme. These studies contribute to the understanding of AVERT, but were not specifically included in the original Health Technology Assessment (HTA) programme trial application. These comprise (1) a qualitative process evaluation[37] and (2) a study of the generalisability of the AVERT results.[38]

Chapter 2 Methods

Aims and objectives

The primary aim of this trial was to investigate the effectiveness of a protocol to implement VEM after stroke; an earlier start with frequent out-of-bed activity compared with usual care (UC), which is traditionally started later (> 24 hours).

The objectives of AVERT were designed addressed four main questions:

1. Does VEM reduce death and disability at 3 months post stroke?
2. Does VEM reduce the number and severity of complications at 3 months post stroke?
3. Does VEM improve quality of life (QoL) at 12 months post stroke?
4. Is VEM cost-effective? [Note: this aspect of the trial programme was not funded by the current National Institute for Health Research (NIHR) HTA programme grant.]

Our clinical hypotheses were as follows:

1. VEM would improve functional outcome at 3 months.
2. VEM would reduce immobility related complications.
3. VEM would accelerate walking recovery with no increase in neurological complications.
4. VEM would result in improved QoL at 12 months.
5. VEM would be cost-effective.

We aimed to carry out a large multicentre pragmatic trial recruiting a broad range of acute stroke patients including those aged > 80 years, those with intracerebral haemorrhage, those who had received rtPA and those admitted to stroke units in a range of different hospital types (small and large, urban and regional).

Trial design

We carried out a pragmatic, prospective, parallel-group, multicentre, international Phase III RCT with blinded assessment of outcomes and an intention-to-treat analysis. Full details of the trial rationale and statistical analysis plan[30] were published in advance.

Study settings

The trial was carried out in the acute stroke unit of 56 hospitals in five countries: UK (England, Scotland, Northern Ireland and Wales), Australia, New Zealand, Singapore and Malaysia. Stroke units were housed in a range of hospital settings including local and regional hospitals (see list in *Appendix 2*).

Participants

We aimed to include all eligible patients aged ≥ 18 years with a confirmed first or recurrent stroke (infarct or intracerebral haemorrhage) who were admitted to a stroke unit within 24 hours of onset. Exclusion criteria are listed below and included significant premorbid disability, acute deterioration, admission to the intensive care unit, competing care needs or physiological instability. Recruitment and informed consent could take place in the emergency room or in the acute stroke unit.

Eligibility

All patients (aged ≥ 18 years) admitted with stroke diagnosis (first or recurrent stroke, infarct or haemorrhage) were screened for suitability for inclusion into the trial. If a patient was found to be ineligible for inclusion into the trial, the reason was recorded on the stroke patient-screening log. A diagnosis of transient ischaemic attack (TIA) would not have been considered eligible and the patient would not have been recruited into the trial. However, if a patient was recruited into AVERT who, clinically, appeared to have stroke symptoms and was considered eligible but later assessment confirmed a TIA or other diagnosis, the patient remained in the trial and continued to be followed up until completion.

Inclusion criteria

- Informed consent obtained from the patient or a responsible third party.
- Patients aged ≥ 18 years with a clinical diagnosis of first or recurrent stroke, infarct or haemorrhage.
- Patients admitted to hospital within 24 hours of the onset of stroke.
- Patient for admission to the acute stroke unit.
- Patients who receive thrombolysis could be recruited if the attending physician permits and if mobilisation within 24 hours of stroke was permitted.
- Consciousness: at a minimum, the patient must at least be able to react to verbal commands.
- Patients could participate in AVERT if they were already recruited to non-intervention trials (e.g. imaging) if dual recruitment was permitted by the ethics committee.

Exclusion criteria

- Too disabled before stroke [prestroke modified Rankin scale (mRS) score of 3, 4 or 5].
- Patient diagnosed with TIA.
- Deterioration in patient's condition in the first hour of admission resulting in direct admission to intensive care unit, 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).
- A suspected or confirmed lower limb fracture at the time of stroke preventing the implementation of the mobilisation protocol.
- Patients could not be concurrently recruited to drug or other intervention trials.
- Unstable coronary or other medical condition that were judged by the investigator to impose a hazard to the patient by involvement in the trial.
- Unstable physiological variables:
    - systolic blood pressure of < 110 mmHg or > 220 mmHg
    - oxygen saturation of < 92% with supplementation
    - resting heart rate of < 40 or > 110 beats per minute (b.p.m.)
    - temperature of > 38.5°C.

Randomisation and masking

Ethics review boards approved the study at all sites. Informed consent was obtained from all patients or their nominated representative. Eligible participants were invited to participate in a trial that was testing 'different types of rehabilitation' but were not given specific information about the two approaches.[30]

After informed consent was obtained, a medical history and physical examination was performed. The following stroke assessments were carried out:

- premorbid mRS[39]
- baseline mRS[39]
- National Institutes of Health Stroke Scale (NIHSS) score[40]
- Oxfordshire Community Stroke Project[41] classification. A paper case report form (CRF) was completed by the AVERT team member (see *Appendix 3*).

Baseline NIHSS, OSCP (Oxfordshire Community Stroke Project) classification, premorbid mRS and the date of the stroke were all entered into the AVERT Online electronic data capture system prior to randomisation. AVERT Online randomly allocated the treatment group with the result immediately notified to the investigator. Participants were randomised (in a 1 : 1 ratio) through a secure remote, web-based, computer-generated block randomisation procedure with an average block size of six. Permuted blocks of various lengths were used to ensure allocation concealment.

Randomisation was stratified by:

1. study site
2. stroke severity using the NIHSS score,[40] for which mild is a NIHSS score of 1–7, moderate is a NIHSS score of 8–16 and severe is a NIHSS score of > 16.[42]

Participants were allocated to receive either usual stroke unit care alone, or usual stroke unit care in addition to the experimental intervention, VEM. VEM patients were provided the first mobilisation as soon as they were recruited and additional mobilisations according to the protocol. The intervention period lasted 14 days or until the patient was discharged from stroke unit care, whichever was sooner.

Patients were not aware of their treatment group and outcome assessors plus the investigators involved in the conduct of the trial and data management were blinded to the group assignment. To try and reduce the risk of contamination of the UC intervention, staff providing the VEM protocol were trained to conceal the mobilisation protocol and group allocation. The patient's participation would be terminated if consent had been withdrawn or if the patient's safety had been considered to be at risk.

Procedures

Following randomisation, the trial staff obtained the following patient data within 24 hours:

- demographic information
- Mobility Scale for Acute Stroke (MSAS)[43]
- Star cancellation test: a screening tool to detect the presence of unilateral spatial neglect[30]
- Time to first mobilisation (TTFM): the date, time and staff performing the first mobilisation.

The AVERT intervention protocol

The intervention protocol was not published or distributed except to trials intervention staff. AVERT staff from within the stroke unit team (i.e. site investigators, physiotherapists, nurses) were trained by clinical trial managers to deliver the AVERT intervention protocol at site initiation and investigator meetings, with refresher and new staff training provided on an ongoing basis.[35] This complex intervention required staff to work together to achieve the VEM and UC mobility targets. Trial staff agreed not to distribute or disseminate the protocol and to keep the protocol in a secure location.

To aid protocol description, the key intervention definitions are summarised in *Box 1*.

The intervention protocol was followed for all randomised patients. Information about the group to which the patient had been randomised was known only by the AVERT physiotherapist and nursing staff. The protocol for the interventions was not intended to replace any clinical decision-making of the individual therapists and nurses involved in the treatment delivery. However, the expectation was that they would adhere to the protocol whenever possible.

The protocol for VEM interventions and UC was continued until day 14 of the patient's stay in the stroke unit or until discharge from the stroke unit (whichever was sooner). If the patient was palliated then VEM was discontinued and follow-up with trial assessments continued until death or 12-month follow-up.

BOX 1 Definitions used

Dose: a session of mobilisation given to AVERT patients.

Very early: the earliest possible time after a consented patient had suffered a stroke to their first mobilisation intervention ($\leq$ 24 hours).

Mobilisation: the patient was assisted and encouraged in functional tasks, including activities such as sitting over the edge of the bed, standing up, sitting out of bed and walking. Upper limb movement would have been integrated into functional activities as appropriate. Mobilisations were performed by the AVERT nurse and/or the AVERT physiotherapist. Support staff such as therapy assistants and students could also be trained to provide mobilisations.

Counting mobilisations: when a patient performed a mobilisation (e.g. walked to the toilet with help or was sat out of bed) and rested for $\geq$ 5 minutes, then their next mobilising activity (e.g. walking back from the toilet or getting back into bed) would have constituted another mobilisation.

TTFM: this is the time from stroke onset to the time the patient is first mobilised out of bed (assisted or independent). This does not include the initial assessment by the AVERT physiotherapist.

Physiotherapist's record of mobilisation sessions: the date, time, minutes and content of each session were recorded via AVERT Online. If the online forms were unavailable, paper forms could be used to temporarily collect the information until such time as it could be entered online.

Nurse's record of mobilisation sessions: the date and time it started and the type of each mobilisation would have been recorded on AVERT Online or, if the website was not available, data were temporarily recorded on the paper nurse recording form until such time as they could be entered online.

Excessive fatigue: if the patient reported a score of > 13 on the Borg Perceived Exertion Scale and/or AVERT staff assess that the patient is excessively fatigued (e.g. the patient's functional performance worsened significantly during the intervention).

Contamination: when the witnessing of a different intervention makes others change their UC practice consciously or unconsciously.

Very early mobilisation interventions

The components of usual stroke unit care, including normal physiotherapy and nursing procedures, were provided at the discretion of the individual sites. In addition to UC, the VEM intervention included four important features.

1. It had to begin within 24 hours of stroke onset.
2. The focus had to be on sitting, standing and walking activities (i.e. out of bed).
3. VEM delivered in at least three out-of-bed sessions per day in addition to UC.
4. Nursing and physiotherapy mobilisations were titrated each day, according to patient's functional level.

The content of nursing and physiotherapy mobilisations were detailed, task-specific activities targeting the recovery of standing and walking. It was tailored to accommodate four levels of functional ability and was adjusted daily in line with participant recovery. The usual risk assessments and lifting policies were applied to all mobilisations. Even following the protocol, clinician judgement was still required when the patient's suitability to get out of bed was assessed.

Principles of very early mobilisation

The principles of the VEM intervention were developed in consultation with the early rehabilitation team in the acute stroke unit in Trondheim, Norway,[9] and used in AVERT Phase II.[25] Trained physiotherapy and nursing staff helped patients to continue task-specific out-of-bed activity that was focused on recovery of active sitting, standing and walking. The frequency and intensity (amount) was guided by the intervention protocol. This was titrated according to functional activity baseline and monitored daily and adjusted with recovery. For example, low-functioning dependent patients (level 1) had a target of active sitting with assistance with each session lasting between 10 and 30 minutes. Higher-functioning patients (level 4) would have a target of standing and walking with each session lasting 10 minutes and with no restricted maximum. The frequencies of sessions were varied according to the patient's functional level. Passive sitting was not classified as a mobilisation activity and sitting for > 50 minutes at a time was discouraged. The intervention continued for 14 days or until discharge. Physiotherapists and nurses had separate intervention targets but worked together to deliver the intervention dose. Mobilisation activities were all recorded online.

The key principles were as follows.

1. The **target dose** (the number of interventions, the type of intervention and the amount of time spent with each VEM patient) **was additional to usual stroke unit nursing and therapy** and was titrated according to the patient's level of functional ability.
2. Patients were recruited as soon as possible after stroke onset, until 24 hours (day 0). The first VEM commenced as soon as possible after recruitment and could be provided when the patient arrived on the ward, or earlier if they were in the emergency department. The VEM target TTFM was within 24 hours from stroke. When patients were routinely mobilised within 24 hours at any site, the target VEM time was 5 hours less than UC.
3. Patients should not rest in bed for long periods of the day unless they were medically unstable.
4. If medically stable (not **specifically** restricted to bed), patients were helped to perform functional (out of bed) activities **for the prescribed VEM dose according to the patient's functional level**.
5. Patients who were stable enough to **sit out of bed or sit up over the side of the bed with help** were assisted to do so **for the prescribed VEM dose according to the patient's functional level**. If, on the **first 3 days**, they required the moderate or maximum assistance of others to move themselves from chair to bed, they could not be left to sit out of bed for longer than **50 minutes** each time.
6. When sat out of bed, patients would have been comfortably seated in a supportive chair or wheelchair with the hemiplegic upper limb supported.
7. The VEM safety assessment was **strictly adhered to for the first mobilisation out of bed**. This involved measurement of vital signs and was critical to the safety of the mobilisation.
8. For patients randomised to the VEM group, the AVERT nurse and physiotherapist worked together to achieve a daily target for the frequency of sessions and minutes of physiotherapy mobilisation.

The target number of sessions and minutes of physiotherapy to be delivered each day was dictated by the level of functional ability at the start of each day

Level of functional ability

The AVERT staff assessed the patient's functional ability using the MSAS as soon as possible after recruitment and then at the start of each day. The patient was assessed as one of the four functional levels (*Table 1*). The daily assessment of level and the daily mobilisation targets were communicated to the study team. The level assigned to the patient was not changed throughout the day. If the patient's level of performance fluctuated, clinicians adjusted VEM interventions according to patient status. Usual risk assessments and lifting policies were applied to all mobilisations.

First very early mobilisation safety assessment

The first VEM mobilisation out of bed was strictly governed by a safety assessment. If the safety assessment failed then the first mobilisation did not commence until the patient achieved the safety criteria.

For the first VEM sit out-of-bed mobilisation post stroke, the following procedure was followed.

Before first mobilisation

Step 1

The following physiological variables were required:

1. systolic blood pressure of 110–220 mmHg
2. oxygen saturation of $\leq 92\%$ supplementation (see note on page 9)
3. resting heart rate of 40–110 b.p.m.
4. temperature of < 38.5 °C.

TABLE 1 Assessment of functional level

Level	Definition	Patient description
1	Equivalent to sitting from supine, MSAS	Low arousal (responded to voice but required physical prompting)
	Score = 1–4	Fully dependent. Unable to sit on the edge of the bed without the assistance of 1 or 2 people
2	Equivalent to sitting from supine, MSAS	Followed commands (verbal or non-verbal/gestures)
	Score = 5–6	Moderate to high dependence. Able to sit on the edge of the bed but would requires assistance and/or supervision. Able to stand with assistance
3	Equivalent to gait MSAS	Follows commands
	Score = 2–4	Moderate dependence. Able to walk with moderate to maximum assistance
4	Equivalent to gait MSAS	Low/no dependence
	Score = 5–6	Able to walk with minimal/no assistance

Note:

- Oxygen saturation was measured without supplemental oxygen.
- Oxygen was stopped for 1 minute. If SpO_2 was < 92%, oxygen supplementation was resumed and maintained throughout the mobilisation.
- Blood pressure was measured in the unaffected arm. Oxygen saturation was measured on the affected arm.
- If blood pressure, heart rate and oxygen saturation were within acceptable limits then the patient proceeded to the next step.

Performing the first mobilisation

Step 2

- The back of the bed was raised to > 70° of hip flexion. The measures of blood pressure, heart rate and oxygen saturation were repeated.
- If blood pressure, heart rate and oxygen saturation were within acceptable limits then the patient proceeded to the next step.
- If **blood pressure drop was > 30 mmHg** then the patient remained in bed, but was reassessed at a later time.

Step 3

- The patient was assisted to sit over the edge of the bed (feet on the floor if able). This may have required the assistance of one or two people and the patient may have required the assistance of one person to maintain sitting balance.
- The measures of blood pressure, heart rate and oxygen saturation were repeated.
- If blood pressure, heart rate and oxygen saturation were within acceptable limits then the intervention would have proceeded to the next step.
- If **blood pressure drop was > 30 mmHg** then the patient remained in bed and would have been reassessed at a later time.

Step 4

- Sitting was for 5 minutes and measures of blood pressure, heart rate and oxygen saturation were repeated.
- If blood pressure, heart rate and oxygen saturation were within acceptable limits, the intervention proceeded to the next step.
- If **blood pressure drop was > 30 mmHg** then the patient remained in bed, and reassessed at a later time.

Step 5

- An appropriate level of assistance was used (hoist or manual assistance dependent on routine assessment findings) and the patient was transferred to a comfortable chair with adjustable back to allow an angle of 90°–100° hip flexion.
- Measures of blood pressure, heart rate and oxygen saturation were repeated.
- If measures were within acceptable limits then the patient maintained sitting and was monitored for comfort.

The first out-of-bed mobilisation was interrupted and the patient returned to bed if:

- in the clinician's judgement, the patient was not tolerating the mobilisation (i.e. became less responsive, developed a headache, became nauseated or vomited or became pale or clammy)
- systolic blood pressure was < 100 mmHg or > 230 mmHg
- systolic blood pressure decrease was > 30 mmHg
- heart rate was > 120 b.p.m.
- oxygen saturation was < 90%.

Maximum sitting time for sitting out of bed was 50 minutes each time, for the first 3 days.

What if a very early mobilisation patient could not have achieved the first mobilisation?

Factors that would have affected a patient's ability to mobilise may have included (but were not limited to) (1) vital signs not within the normal listed limits, (2) an adverse event (AE) that would have led to a mobilisation restriction for a period of time (e.g. acute myocardial infarction, lower limb fracture, pneumonia, carotid endarterectomy) or (3) a deterioration which led to palliation.

In the case of a temporary interruption to mobilisation due to an event similar to those listed above, mobilisation was recommenced as soon as possible. The patient's physiological variables were reviewed every few hours (step 1). Clinical judgement was used and the first mobilisation was attempted when the patient physiological variables were within limits. When a mobilisation was planned, but not able to be performed, staff submitted a therapist or nurse recording form with the time and reason not mobilised. Whenever possible, VEM resumed at the earliest opportunity.

Usual care group

Participants who were randomised to receive UC received the usual post-stroke unit care. Prior to trial commencement, baseline UC was reported by trial staff at each site. Typical UC is described in *Table 2*. Mobilisation activity was not prescribed but all mobilisations were recorded. UC patient mobilisations at each site were monitored for change during the trial.

Recording of mobilisation sessions

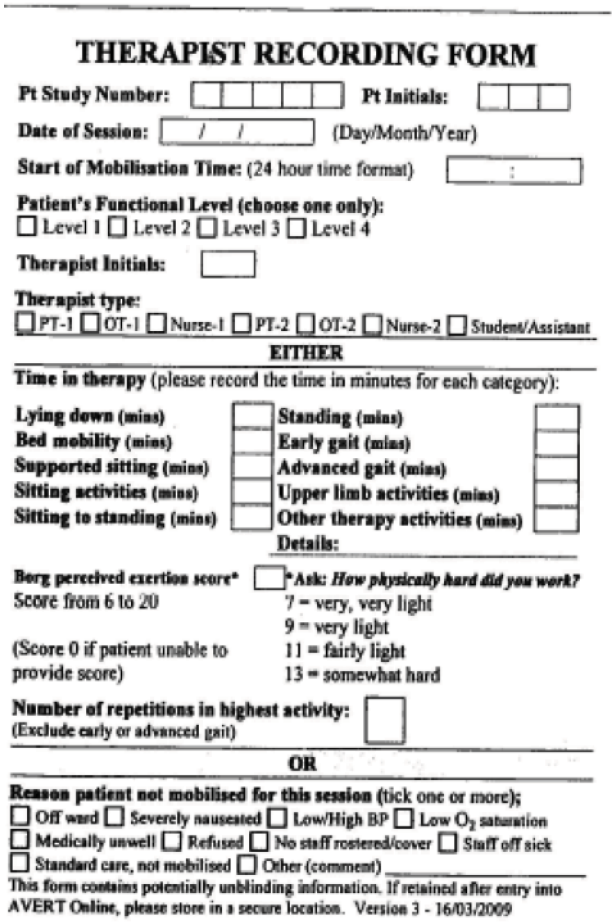
Mobilisation data for both UC and VEM patients were recorded by the AVERT physiotherapist, ward physiotherapist and occupational therapist and/or the AVERT nurse(s) using therapist and nurse recording forms, respectively, on AVERT Online. For convenience, paper therapist and nurse recording forms (*Figures 1* and *2*) were sometimes used to initially record mobilisations and then the data were transferred to AVERT Online. VEM interventions were not recorded in routine medical records.

The AVERT nurse(s) recorded all mobilisations that they were responsible for initiating that were conducted alone or with an AVERT physiotherapist, ward physiotherapist, occupational therapist or other assistant. Mobilisations in which the AVERT nurse helped either the AVERT physiotherapist or ward physiotherapist/occupational therapist for study patients (either group) were recorded by the therapist that initiated the mobilisation. The nurse involvement was acknowledged in the recording of the mobilisation. This prevented double reporting of a same mobilisation.

TABLE 2 Usual care mobilisations

Level	Patient description	Nursing activities	Physiotherapy activities
1	Low arousal Fully dependent	Approximately one mobilisation every 1 or 2 days	Approximately one treatment every 1 or 2 days
2 or 3	Moderate – high dependence	Approximately two mobilisations per day	Approximately one treatment per day, including a mobilisation
4	Low dependence	Approximately four mobilisations per day	Approximately may/may not have received treatment, would have been encouraged to have mobilised independently
		Note: this aspect varied greatly	Note: this aspect varied greatly

Note
Usual care may have differed from this description at some hospitals and UC would have continued to be provided according to routine practice.



THERAPIST RECORDING FORM

Pt Study Number: ☐☐☐☐☐ **Pt Initials:** ☐☐☐

Date of Session: ☐☐/☐☐/☐☐ (Day/Month/Year)

Start of Mobilisation Time: (24 hour time format) ☐☐:☐☐

Patient's Functional Level (choose one only):
☐ Level 1 ☐ Level 2 ☐ Level 3 ☐ Level 4

Therapist Initials: ☐☐

Therapist type:
☐ PT-1 ☐ OT-1 ☐ Nurse-1 ☐ PT-2 ☐ OT-2 ☐ Nurse-2 ☐ Student/Assistant

EITHER

Time in therapy (please record the time in minutes for each category):

Lying down (mins)	☐☐	**Standing (mins)**	☐☐
Bed mobility (mins)	☐☐	**Early gait (mins)**	☐☐
Supported sitting (mins)	☐☐	**Advanced gait (mins)**	☐☐
Sitting activities (mins)	☐☐	**Upper limb activities (mins)**	☐☐
Sitting to standing (mins)	☐☐	**Other therapy activities (mins)**	☐☐

Details:

Borg perceived exertion score* ☐☐ Score from 6 to 20
(Score 0 if patient unable to provide score)

*Ask: ***How physically hard did you work?***
7 = very, very light
9 = very light
11 = fairly light
13 = somewhat hard

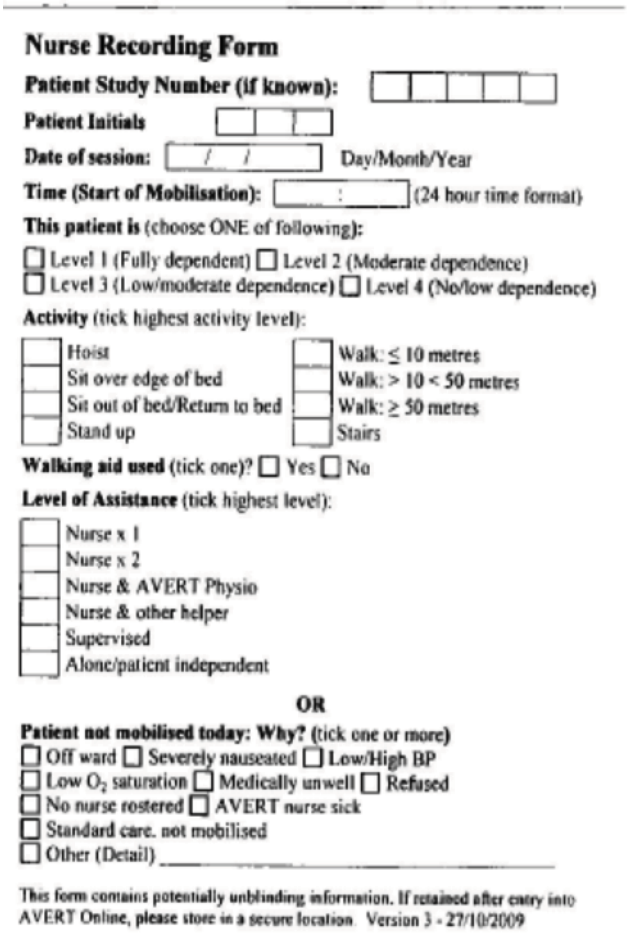
Number of repetitions in highest activity: ☐☐☐
(Exclude early or advanced gait)

OR

Reason patient not mobilised for this session (tick one or more):
☐ Off ward ☐ Severely nauseated ☐ Low/High BP ☐ Low O_2 saturation
☐ Medically unwell ☐ Refused ☐ No staff rostered/cover ☐ Staff off sick
☐ Standard care, not mobilised ☐ Other (comment) _____

This form contains potentially unblinding information. If retained after entry into AVERT Online, please store in a secure location. Version 3 - 16/03/2009

FIGURE 1 Example of the paper therapist recording form.



Nurse Recording Form

Patient Study Number (if known): ☐☐☐☐☐

Patient Initials ☐☐☐

Date of session: ☐☐/☐☐/☐☐ Day/Month/Year

Time (Start of Mobilisation): ☐☐:☐☐ (24 hour time format)

This patient is (choose ONE of following):

☐ Level 1 (Fully dependent) ☐ Level 2 (Moderate dependence)
☐ Level 3 (Low/moderate dependence) ☐ Level 4 (No/low dependence)

Activity (tick highest activity level):

☐ Hoist	☐ Walk: ≤ 10 metres
☐ Sit over edge of bed	☐ Walk: > 10 < 50 metres
☐ Sit out of bed/Return to bed	☐ Walk: ≥ 50 metres
☐ Stand up	☐ Stairs

Walking aid used (tick one)? ☐ Yes ☐ No

Level of Assistance (tick highest level):

☐ Nurse x 1
☐ Nurse x 2
☐ Nurse & AVERT Physio
☐ Nurse & other helper
☐ Supervised
☐ Alone/patient independent

OR

Patient not mobilised today: Why? (tick one or more)

☐ Off ward ☐ Severely nauseated ☐ Low/High BP
☐ Low O_2 saturation ☐ Medically unwell ☐ Refused
☐ No nurse rostered ☐ AVERT nurse sick
☐ Standard care, not mobilised
☐ Other (Detail) _____

This form contains potentially unblinding information. If retained after entry into AVERT Online, please store in a secure location. Version 3 - 27/10/2009

FIGURE 2 Example of the paper nurse recording form.

Equipment

Existing equipment (e.g. beds, standing hoists, standing frames, tilt tables, chairs, lap trays, gait aids, arm supports, safety belts, etc.) from each hospital were utilised as per usual ward policy and availability. Ward lifting policies were applied to all mobilisations for AVERT patients. The vulnerable hemiplegic shoulder was cared for with the use of lap trays when the patient was seated and the provision of slings used for transfer and walking activities.

Adherence to protocols

The online recording system allowed the intervention staff to document all mobilisations, including attempted mobilisations and reasons for when the patient was not mobilised according to protocol. Intervention staff received feedback from an external monitor about their compliance with the trial protocol. These were provided in quarterly compliance summaries and were reviewed regularly by the Data Safety and Monitoring Committee.

Contamination was a potential problem for this trial. This was because all patients in this study were situated on a single ward. This made it difficult to keep other staff on the ward from seeing the intervention

staff work with patients who had been randomised to VEM. If contamination had occurred, the results of the trial would have been diluted because intervention and UC would have become more alike.

Contamination was considered to have occurred if VEM was provided to UC patients or became UC for a large number of patients. Measures to reduce the potential of the intervention practices to be adopted by staff other than the AVERT staff included security of the intervention protocol and procedures to stop ward staff observing VEM sessions. The Data Safety and Monitoring Committee monitored contamination throughout the trial.

Data collection

Source data relating to each patient were maintained in the patient's medical record.

Source data relating to the intervention therapy given to the patient were not recorded in the patient's medical record. The therapy information was recorded in the web-based therapy/nurse forms (see *Figures 1* and *2*) on AVERT Online; data were also recorded in the individual patient's paper CRF, which would have been supported by information documented in the patient's medical record or clinical notes.

Blinding

We recognise that blinding is vital for the integrity of any RCT. As the AVERT physiotherapists and nurses were delivering the interventions, they were not blinded to the interventions but protocols were in place to conceal allocation group to all other ward staff.

The following measures were followed to maintain blinding for the AVERT study:

- A patient or their family were never told of the group to which they had been randomly allocated, even if they asked.
- The AVERT physiotherapists never wrote VEM interventions in the medical record and AVERT nurses recorded only standard information and did not refer to frequency of intervention provided.
- Anyone who did not need to know the patients group were never told, even if they asked.
- The AVERT staff ensured that other staff and AVERT patients did not become aware of the details of the VEM. VEM activities were conducted behind curtains with patients screened from other ward staff, and mobilisations performed off the ward were provided whenever this was possible.
- The blinded assessors assigned to the trial site were not on the ward when the trial took place and did not witness treatments that patients had received.
- The blinded assessor, who conducted assessments, was never told the group to which patients were allocated. The assessor had been trained in what they could and could not ask participants, therapists, nurses and other staff whom they encountered.
- The blinded assessor informed AVERT ward staff if it was necessary to visit the ward for any reason, which minimised the risk of an intervention session being witnessed. Every effort was made by AVERT staff to ensure that a session was not witnessed by the blinded assessor.

Participant assessments

Outcome assessments were done in person or by telephone by a trained assessor who was not working in the study stroke unit and was blinded to treatment allocation.

Three-month assessment

At 3 months post stroke, the assessor located the patient and conducted the assessment, which included the following.[30]

- mRS:[39] a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability.
- Irritability, anxiety and depression assessment (IDA):[44,45] following stroke.
- Barthel Index:[46] an ordinal scale used to measure performance in activities of daily living.
- assessment of quality of life (AQoL).[47]
- Rivermead Motor Assessment Scale[48] (RMAS): assesses the motor performance of patients with stroke and was developed for both clinical and research use.
- 50-metre walk:[30] assessed if the patient had not achieved walking during the 14-day intervention period.
- Montreal Cognitive Assessment (MoCA):[49] a cognitive screening test designed to assist health professionals in detecting mild cognitive impairment.
- Cost of care: the cost CRF collects resource use on acute hospital length of stay, discharge location, ambulance services, rehabilitation, stroke-related rehospitalisations, change of accommodation, aids, home modifications, community services, return to work, informal care hours and country-specific services (e.g. UK outpatient therapy; Asian maid services in the home).
- AEs, important medical events (IMEs) and serious adverse events (SAEs) (see below).

Adverse events

An AE is defined as any untoward medical occurrence in any participant involved in the study and that does not have a causal relationship to the study intervention. This included any worsening of a pre-existing event. AEs were recorded in the patient's medical record and reporting commenced from the time of informed consent. Events were recorded in the patient's CRF and included the date of onset, description, severity and duration and whether or not it was thought to be related to the study intervention.

All AEs were collected from the time of the patient's consent until the end of the intervention period and were followed until the event was resolved or had been stabilised.

Important medical events

The IMEs were prespecified events that are important outcomes measures for this study. These events included:[30]

- falls (with no soft tissue injury, with soft tissue injury, with bone fracture)
- stroke progression (defined as a worsening stroke, in the clinician's view, in the same vascular territory as the initial event occurring during the first 14 days)
- recurrent stroke (defined as a new stroke event beyond 14 days (in the clinician's view)
- pulmonary embolism
- deep-vein thrombosis
- myocardial infarction
- angina
- urinary tract infection
- pressure sores
- pneumonia
- depression (clinically diagnosed).

Serious adverse events

A SAE was an AE or IME that met any one of the following criteria:

- resulted in death
- was life-threatening

- required inpatient hospitalisation
- prolonged hospitalisation (if an event occurs while the patient is in hospital, which in itself prolongs the patient stay)
- resulted in persistent or significant disability.

Up to 3-month follow-up all IMEs, serious or not serious, were reported. After 14 days, we recorded new AEs that were classified as serious but were not IMEs. From 3–12 months, SAEs were collected.

Twelve-month assessment

At 12 months, the final assessment was conducted by the blinded assessor. The assessor made contact with the patient/relative/carer and organised the meeting.

At this visit, all 3-month assessments were repeated, except for the MoCA.

Outcomes

Primary outcome

The primary outcome was survival without major disability (mRS score of 0–2) at 3 months after stroke. A favourable outcome was defined as mRS score of 0 (no symptoms), 1 (impairment but no disability) or 2 (independent but with minor disability). A poor outcome was defined as mRS score of 3 (disability but able to walk), mRS score of 4 (disabled and unable to walk), mRS score of 5 (bed-bound and in need of full nursing care) or mRS score of 6 (death).

Secondary outcomes

Secondary outcomes included an assumption-free ordinal shift[39,40] of the mRS across the full range of the scale. This measures a change in the mRS across the whole range of the scale rather than just across one threshold. We also obtained time taken to achieve unassisted walking for 50 m and the proportion of patients achieving walking by 3 months. Death and the number of non-fatal SAEs were recorded up to 3 months.

Serious adverse events were recorded according to standard definitions and included IMEs relevant to acute stroke patient recovery (see above). Serious adverse events and deaths were independently adjudicated by an outcome committee who were blinded to treatment allocation. This included a review of the source data if necessary. The classification of complications of interest were neurological (stroke progression and recurrent stroke) and complications of immobility (deep-vein thrombosis, pulmonary embolism, pneumonia, urinary tract infection and pressure sores). At 12 months, we recorded health-related quality of life (HRQoL) and items of patient costs.

Tertiary outcomes

These are outlined in the statistical analysis plan[30] and include:

- IDA[45]
- Barthel Index[46]
- RMAS[48]
- MoCA.[49]

The tertiary outcomes are not reported in detail here.

Subgroup analyses

In view of the complex nature of the VEM intervention a number of exploratory analyses were prespecified.[30] In particular, subgroup analysis by age, stroke severity, stroke subtype (infarct or haemorrhage), treatment with thrombolysis (rtPA) and TTFM. We also prespecified an exploration of the dose of the intervention in terms of (1) TTFM, (2) frequency of mobilisation and (3) total amount of time undergoing the intervention.

Withdrawal from treatment and data collection

We anticipated that some participants would wish to withdraw from treatment. In that circumstance, the reason and date of withdrawal were documented and they were invited to allow further collection of follow-up data. Clearly, if the participant refused further follow-up then all treatment and data collection ceased at that point. We considered analyses based on last result carried forward in the event of significant loss of information.

Data retention

All study documents were confidential. Each site was issued with an investigator site file in which to store study documents. All of the study-related documents were stored in a locked area and accessible only to study staff.

At the completion of the study, all site study data and materials have been archived, at site, and have been stored in a secure area for a period of ≥ 7 years if required by hospital procedures.

Power calculation and sample size

The trial was powered to detect an absolute risk reduction of a poor outcome (mRS score of 3–6) of at least 7.1%. This threshold was based on (1) a consensus among clinicians and researchers that an absolute risk reduction of this size would be clinically meaningful and (2) observational data indicating that a hospital routinely practising EM compared with a similar Australian data set had a 9.1% better outcome on the similar variable of death or institutional care (31.8% vs. 40.9%). If EM accounted for 78% of this benefit[9] then the absolute difference would be 7.1%.

We estimated that a sample of 2104 patients would be required to provide 80% power to detect a significant intervention effect (two-sided $p = 0.05$) with adjustments for 5% drop-in and 10% drop-out. Statistical analysis was prespecified and published in advance.[30] Stata® (StataCorp LP, College Station, TX, USA)/IC (version 13) was used for all analysis. For the primary analysis we used an intention-to-treat approach with the assumption that data were missing at random. We also explored the sensitivity of our results to plausible departures from this assumption. This used both a selection model (to model the mechanism of missing data) and a pattern mixture model (modelling the differences between observed and missing data).

Statistical methods

We used standard methods for handling of missing data.[30,50] The primary efficacy analysis was carried out on an intention to treat basis with an assumption that data were missing at random.[30] We explored the sensitivity of our conclusions to plausible departures from this assumption and used both a selection model and pattern mixture model of the differences between observed and missing data. The results were plotted out over a range of assumptions.

We did the primary efficacy analysis used the binary logistic regression model, with treatment group as an independent variable and mRS outcome at 3 months as the dependent variable. This was dichotomised into scores of 0–2 as favourable outcome and scores of 3–6 as poor outcome. Baseline stroke severity (NIHSS) and age were included as treatment covariates for adjustment purposes.

The primary outcome analysis included subgroup analysis based on age (< 65 years, 65–80 years and > 80 years), stroke severity (mild NIHSS 1–7, moderate 8–16 and severe > 16), stroke type (ischaemic vs. haemorrhagic), treatment with tissue plasminogen activator, TTFM (< 12 hours, 12–24 hours and > 24 hours) and geographical region (Australia/New Zealand vs. UK, Australia/New Zealand vs. Asia), with adjustment for stroke severity and age.

We also estimated the treatment effect on the mRS using an ordinal analysis at 3 months with the assumption-free Wilcoxon Mann–Whitney *U*-test generalised odds ratio (OR) approach.[51,52] This provided a measure of effect size with confidence interval (CIs), which was stratified by age and stroke severity. Time (days) taken to achieve unassisted walking of 50 m was analysed using the Cox regression model with treatment group as the independent variable, the time to unassisted walking (censored at 3 months) as the dependent variable, and age and baseline NIHSS as covariates. The estimated effect size is presented as a hazard ratio (HR) with corresponding 95% CI. The analysis of walking status (yes or no) was analysed with a binary logistic model using treatment group as the independent variable and walking status as the dependent variable.

We used a binary logistic regression model to analyse mortality outcomes. Treatment group was the independent variable and death at 3 months was the dependent variable. Age and stroke severity were treatment covariates. We used negative binomial regression to compare the expected counts of serious complications between groups at 3 months. We report the estimated effect sizes and corresponding 95% CI as incidence rate ratios (IRRs) adjusted for age and stroke severity.

We wished to determine whether or not practice had shifted during the course of this trial. We did this by testing the association between treatment effect and trial duration by including an appropriate interaction term into the logistic regression model used in the primary analysis. We also did an exploratory analysis in which we examined the effect of time since the start of the trial on differences in dose characteristics between the two groups. We used regression models with an interaction term for treatment by time since the start of the trial; a median regression model was used for TTFM and median session frequency and a binomial regression model was used for median daily minutes per session and total treatment time over the intervention period (total minutes).

End-point analyses

Primary end point: the primary outcome was planned as 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. If the assumptions for shift analysis were not met, 3-month mRS was to be dichotomised into good outcome (mRS score of 0–2) and poor outcome (mRS score of 3–6), and the groups were compared using a binary logistic model. Although the trial was under way, new ordinal approaches to analysis were developed, tested and gained acceptance in acute stroke trial (see the statistical analysis plan). The management committee determined that an assumption-free ordinal approach to analysis should be included as a secondary outcome (statistical analysis plan). Therefore, the analysis plan was changed such that the 3-month mRS results were dichotomised into good outcome (mRS score of 0–2) and poor outcome (mRS score of 3–6), and the groups compared using a binary logistic model.[30] The primary analysis was adjusted with baseline NIHSS and premorbid mRS as covariates. Unadjusted results were also to be shown. The intervention effect was represented in terms of ORs. Other potential prognostic variables such as age, stroke type and side of stroke were included in subgroup efficacy analyses.

Secondary patient end points: regression models for count data were used to compare SAEs between groups at 3 months. Risk ratios, adjusted as per primary analysis, including age and NIHSS as covariates, were reported.

The odds of achieving unassisted walking at 3 months was analysed using binary logistic regression analyses [adjusted odds ratios (aORs) and 95% CIs]. Cox regression analysis was used to analyse the time (days) to achieve unassisted walking. This was presented as adjusted hazard ratios (aHR) with 95% CIs and was censored at 3 months.

Mortality outcomes at 3 months were analysed using binary logistic regression with death as the dependent variable (aOR with 95% CI). The dose effect on counts of SAE was analysed using binomial regression (adjusted incident rate ratio with 95% CI). Different subtypes of SAE (immobility related, neurological) were analysed separately.

Health-related QoL analysis was planned as a multivariable median regression model with a treatment group as independent variable and the AQoL score as the dependent variable. To estimate the effect of intervention group on AQoL scores at 12 months, treatment covariates for adjustment purposes would include baseline NIHSS, age and sex.

Data sharing and archiving

All deidentified trial data have been archived in secure facilities for a minimum period of 7 years. The options of data sharing arrangements were not available at the trial commencement and were not included in participant consent processes.

Economic evaluation at 12 months

The economic evaluation was not included in the NIHR HTA programme funding. However, the wider AVERT programme did include a health economic analysis;[34] therefore, we summarised the resource use data collected for an economic evaluation. We prospectively collected resource use data within the trial using standard data collection tools. The primary economic evaluation planned is a cost-effectiveness analysis comparing resource use during the 12 months of follow-up. The health outcomes of the VEM intervention were measured against a UC comparator. It was also intended to have included a cost–utility analysis.

For the cost-effectiveness analysis, the primary outcome is a mRS score of 0–2 at 12 months. It was intended that the cost–utility analysis used HRQoL expressed as quality-adjusted life-years gained over a 12-month period. This was measured using the mRS and the assessment of QoL.

Data collection tools to capture resource use were piloted in the AVERT pilot study[29] and then further adapted to accommodate local service provision in different countries. An exploratory analysis of the resource use data was planned to consider the relationship between patterns of service use in health outcomes within the trial. These health outcomes included QoL. A further objective explored economic impacts of stroke on patients, families, the broader community and the health sector.

The methods for assessing safety, effectiveness and QoL have already been published in the statistical analysis plan.[30] The economic analysis plan complements the statistical analysis plan and was finalised prior to the 12-month data collection period being completed.[34]

The economic analysis plan describes key study variables for the economic evaluation, outlines the primary cost-effectiveness analysis and describes proposed exploratory analysis. The development of the economic analysis plan was guided using recommended standards.[53] The economic analyses are under way; however, a UK-specific economic evaluation will not be undertaken as not supported with NIHR HTA programme funding.

Exploratory analyses

To further investigate the interaction between dose characteristics and patients and a favourable outcome we used (1) binary regression analysis and (2) a classification and regression tree (CART) analysis (Salford predictive modeller software suite version 7, Salford Systems, San Diego, CA, USA).

The CART is a binary partitioning statistical method that starts with the total sample. It then uses a stepwise approach to split the sample in to subsamples that are homogeneous in a defined outcome.[54] The input variable that achieves the most effective split is dichotomised by automated analysis at an optimal threshold, maximising the homogeneity within, and separation between, resulting subgroups. A 10-fold internal cross-validation is used to maximise model performance that is assessed as the area under the receiver operating characteristic (ROC) curve. The internal cross-validation divides the data randomly into 10 groups with nine used to build the model (training data set) and one used to validate the model (testing data set). CART also numerically ranks each input to build the tree by relative importance. In our analysis, we included all prespecified subgroup variables (patient age, NIHSS, stroke type, treatment with rtPA), group allocation and the three dose characteristics (TTFM, frequency and daily amount). This analysis explored the relative importance of each variable in association with achieving a favourable outcome (mRS score of 0–2). A further analysis (CART II) investigated multidimensional relationships between dose characteristics alone and favourable outcome.[55]

Both approaches to exploratory analysis examined the three main characteristics of treatment dose:

1. TTFM out of bed (hours)
2. frequency – median number of out-of-bed sessions per patient per day
3. daily amount – median minutes of out-of-bed activity per patient per day.

We also recorded total amount (total minutes of out-of-bed activity over the whole intervention period) to account for varying lengths of stay in hospital.

Nurses recorded the type of activity and the time of the day each activity began. This did not include total time in minutes as this was not routine practice. Physiotherapists recorded the type of activity, the time that the activity began and the total out-of-bed activity (minutes), as this was incorporated in normal practice. Therefore, physiotherapy data alone contributed to the variables of daily amount (minutes) and total amount (minutes) of out-of-bed activity. Both nursing and physiotherapy data contributed to TTFM and frequency of mobilisations. For the definition of frequency of mobilisation, episodes of sitting, standing or walking activity had to be separated from another episode of activity by more than 5 minutes of rest (e.g. in a chair).

In an attempt to avoid excessive collinearity between daily amount and total amount we tested two different models that were adjusted for age and baseline stroke severity for all the analysis:

1. Model 1 – TTFM, frequency (median daily number of out-of-bed sessions) and amount (median daily out-of-bed session time in 5-minute increments),
2. Model 2 – TTFM, frequency (median daily number of out-of-bed sessions) and amount (total minutes out-of-bed activity over the whole intervention period in 5-minute increments).

The primary exploratory analysis was carried out using binary logistic regression models with favourable outcome (mRS score of 0–2) at 3 months as the dependent variable.

Meta-analysis of comparable trials

We wished to set the AVERT results in the context of other similar RCTs. We updated the searches of the existing systematic review,[56] searching MEDLINE, EMBASE, CINAHL (Cumulative Index to Nursing and Allied

Health Literature), Cochrane Stroke Group trials register, several international ongoing trials registers, reference lists of articles and also performed citation searching up to 2015. Foreign language translations were sought. Two review authors assessed trial eligibility, quality and performed data extraction. We included any trial that compared EM after stroke (within 48 hours) with a more delayed mobilisation. The primary outcome was death or poor outcome (dependency or institutionalisation) at follow-up with the use of a mRS score of 3–5 as the preferred definition of poor outcome. We used a fixed-effects model to estimate ORs and 95% CIs, with the use of a random-effects model in the event of substantial heterogeneity ($I^2 > 50\%$).

Patient and public involvement

Stroke survivors in Australia contributed to the original trial development. In particular, Ms Brooke Parsons (a stroke survivor) was involved in the development of the proposal and the monitoring and progress of the trial through her role on the Trial Steering Committee. Each individual study site had varying degrees of patient and public involvement.

Role of the funding source

The various funders of the AVERT international trial had no role in study design, data collection, analysis and interpretation or in the writing of the report. The author team had full access to all data in the study.

Chapter 3 Qualitative process evaluation

Introduction

As stated in the introduction, we also refer to two related studies that were not specifically included in the original HTA programme trial application but were nested within the AVERT programme and contribute to its understanding. These are a qualitative process evaluation,[37] which is summarised here, and a study of the generalisability of AVERT,[38] which appears in the results (see *Chapter 4*).

It is particularly challenging to implement multidisciplinary stroke rehabilitation interventions when the intervention is both complex and multifaceted. This part of the trial programme aimed to better understand how the implementation of the VEM intervention was experienced by the staff involved. It has been reported that efforts to implement evidence-based recommendations in acute stroke units have had mixed success. In particular, changing clinician behaviour is particularly challenging when incorporated within pragmatic trials.[57] The qualitative process evaluation summarised here aimed to help us better understand the implementation of the VEM intervention protocol from the perspective of the health-care professionals who were responsible for its delivery. We believed that understanding the knowledge and perspectives of these staff would be important to both develop effective guidance in the future and implement the VEM intervention if it was found to be effective.

Methods

We used the standard qualitative methodological methodologies[58,59] involving AVERT trial collaborators in Scotland, Australia and New Zealand. Ethics approvals were obtained for all three countries. The Scottish component of recruitment was carried out as part of a Stroke Association-funded Doctor of Philosophy (PhD) by Ms Louise Craig, who was also our first AVERT manager in the UK. The raw Scottish data relevant to the main AVERT trial were reanalysed by colleagues in Australia using the same approach for all included study sites.

Study sample

We used purposive sampling at participating AVERT sites. This was overseen by the trial manager in Australia and New Zealand and by Louise Craig in Scotland. Of the 72 staff who expressed interest, six did not eventually consent to take part and one moved abroad. We obtained informed consent from 33 physiotherapists, 18 nurses, one physiotherapy assistant and one speech pathologist. These staff members are based in four stroke units in Scotland, 14 in Australia and one in New Zealand.

The qualitative data were collected and analysed before the primary outcome of the trial was available. We conducted semistructured interviews facilitated by interview guides that permitted additional questions

or probes if interesting information arose.[37] The main focus of the interview was on the implementation of the VEM protocol. The Scottish interviews were conducted between 2010 and 2011 and the Australian and New Zealand interviews took place in 2014. They could be by telephone or face to face. Telephone interviews commonly ran for 30 minutes, while face-to-face interviews averaged 59 minutes. Interviews were audio-recorded, transcribed, cross-checked with participants and deidentified prior to analysis.

Analysis

We used a thematic analysis to explore the experience and perspectives of staff involved in the trial. This approach is said to be especially relevant to multimethods health research[58,59] and uses low-inference interpretation. We inductively coded the data and set about identifying themes. Each stage incorporated independent consideration by two or more researchers with subsequent discussion and consensus forming. We coded the transcripts to small sections of meaning and then through an iterative process we grouped the codes into logical and meaningful clusters in a hierarchical tree structure. This resulted in categories, descriptive themes and subthemes (*Table 3*). Emergent themes, each with subthemes, were grouped into three categories: staff experience of implementing the trial intervention, barriers to implementation of the trial intervention and strategies to overcome barriers to intervention (see *Table 3*). Stroke unit staff described the challenges of taking part in the trial and how their unit set about implementing the VEM protocol. The recent publication[37] describes the findings in detail but for the purposes of this report we have summarised the main themes as follows.

1. Staff experience of implementing the trial intervention.

    i. Extra work but rewarding: the extra work was felt to be justified by the hope that the trial might benefit stroke patient outcomes.
    ii. Team practice changes: several staff reported a positive impact on teamwork at their site. In particular, closer working of nurses and physiotherapists and some changes in their professional roles.

        – Changes to usual practice: over the duration of the trial some staff perceived a change in UC. This was not a universal perception but was noted by a substantial minority.

2. Barriers to intervention implementation.
   The main reported barriers related to the general implementation of a trial and also those specific to the VEM intervention, in particular, the frequency of the intervention.

    i. Team challenges: implementation difficulties were notable at sites that appeared to lack established interdisciplinary team working practices.
    ii. Staffing challenges: a common theme was that inadequate staffing levels made it difficult to consistently implement the VEM protocol particularly in the face of competing demands. It was recognised that experienced and trained staff were essential for successful implementation of the protocol.
    iii. Organisational or workplace barriers.

        – The acute model and culture: there was a common view that the rapid pace and focus on early discharge of acute hospitals rendered rehabilitation a low priority.
        – Barriers to acute stroke unit access: a particular problem was that significant delays were experienced while patients waited for a bed in the acute stroke unit.
        – Competing priorities: competing organisational priorities such as discharge pressure, accreditation work and transfer policies were commonly reported as being a challenge.

TABLE 3 Final coding tree used in qualitative study

Themes		Interviews[a]	Subthemes
Category 1: Staff experience of implementing the trial intervention			
1	Extra work but rewarding	27	
2	Team practice changes	24	
			Changes to UC
Category 2: Barriers to intervention implementation			
3	Team challenges	19	
4	Staffing challenges	37	
5	Organisational or workplace barriers	28	
			The acute model and culture
			Barriers to Acute Stroke Unit access
			Competing priorities
			Physical environment barriers
6	Staff attitudes and beliefs	32	
			Not 'on board'
			Beliefs about roles and capabilities
			Beliefs about consequences
7	Patients' barriers	35	
			Acuity, instability and complexity
			Severity of stroke
			Fatigue
			Family anxiety
Category 3: Overcoming implementation barriers			
8	Teamwork central to success	43	
			Communication and coordination
9	Getting staff 'on board'	35	
			Staff education and training
			Leadership for change
10	Working differently	29	
			'This is what we do here'
			Shifting control
			Staffing model changes
			Dealing with fatigue

a Number of interviews containing data supporting the theme.

iv. Physical environmental barriers: environmental barriers such as lack of equipment and chairs were reported to be barriers.
v. Staff attitudes and beliefs.

- Resistance to change of practice: resistance to changing practice was identified at some sites particularly among staff who were not experienced in clinical trials.
- Beliefs about roles and capabilities: mobilisation delays at some sites were due to nurses awaiting physiotherapists to begin mobilisation.
- Beliefs about consequences: many staff assumed a positive treatment effect from VEM, which appeared to influence their perceptions of the treatment and anecdotal outcomes.

vi. Patient barriers.

- Acuity, instability and complexity: acute health problems including unstable medical conditions and complex problems were viewed as a common barrier.
- Severity of stroke: early delivery of the VEM protocol was viewed as challenging in patients with drowsiness or reduced cognition. They would require more staff to assist mobilisation. The challenges with milder strokes were mainly due to the high frequency mandated by the VEM protocol.
- Fatigue: staff reported that fatigue was a common problem reported by patients sometimes preventing mobilisation.
- Family anxiety: on some occasions families raised concerns that the VEM intervention was preventing necessary rest.

3. Overcoming implementation barriers.
Many interviewees described strategies for implementing the VEM intervention in the face of the observed barriers. These are summarised below.

i. Teamwork is central to success: units that felt they had been successful in providing the VEM protocol frequently reported shared interdisciplinary roles with nurses, physiotherapists and others working closely together through flexible work practices and mutual trust.

- Communication and co-ordination: a component of good interdisciplinary working was effective communication and co-ordination between different members of staff.

ii. Getting staff on board: an almost universal theme was the importance of spending time and effort to get staff engaged with the new VEM practice.

- Staff education and training: this was felt to be a cornerstone of getting staff involved.
- Leadership for change: implementing the VEM protocol was seen as a whole team responsibility but required leadership.

iii. Working differently: a positive attitude to implementing the VEM protocol was seen in sites determined to work around organisational barriers and foster a culture appropriate to the trial. This included a willingness to relinquish some control of traditional roles and practices.

- Staffing model changes: some units reported using different staffing models involving nursing or allied health assistants.
- Managing patient fatigue: some units reported innovative approaches to timetabling therapy to accommodate patient fatigue.

Discussion

The interview with staff identified some common themes.[37] First, implementing the VEM protocol within AVERT was acknowledged as being a challenging task. However, despite the challenges encountered there was substantial enthusiasm about participation in the trial. This enthusiasm was largely driven by an interest in the research question and the potential benefit to future stroke patients. A strong feature of these interviews was the importance of highly effective interdisciplinary teamwork. This was widely acknowledged as being an important factor in implementation of the VEM protocol. A second key feature was the importance of effective leadership to champion and encourage the trial within their units.

A strength of the qualitative study was that information was collected and analysed prior to the main AVERT trial results becoming available. Participants were generally optimistic that the trial would be positive and this seemed to be a factor in sustaining interest over a number of years. Another study strength was that experiences were collected across three countries, and, although there were some minor intercountry differences,[37] the similarities were more striking than the differences.

Chapter 4 Statistical trial results

Screening and exploring threats to generalisability in the AVERT

In parallel with the main trial of AVERT, we also carried out a study to explore potential threats to generalisability of the main results of AVERT.[38] We wished to consider the impact of person, place, setting and practice as a framework for considering generalisability. Therefore, we used a proximal similarity model (*Figure 3*) to carry out this analysis of the first 20,000 patients screened for inclusion in AVERT, which involved 44 hospitals in five countries. Of the first 20,000 patients screened for inclusion, 1158 were recruited and randomised in AVERT.

We compared recruited patients with the target population and also explored the factors (demographic, clinical process and site factors) that were associated with participant recruitment using a proximal similarity model (see *Figure 3*) that incorporated inclusion and exclusion criteria (*Figure 4*).

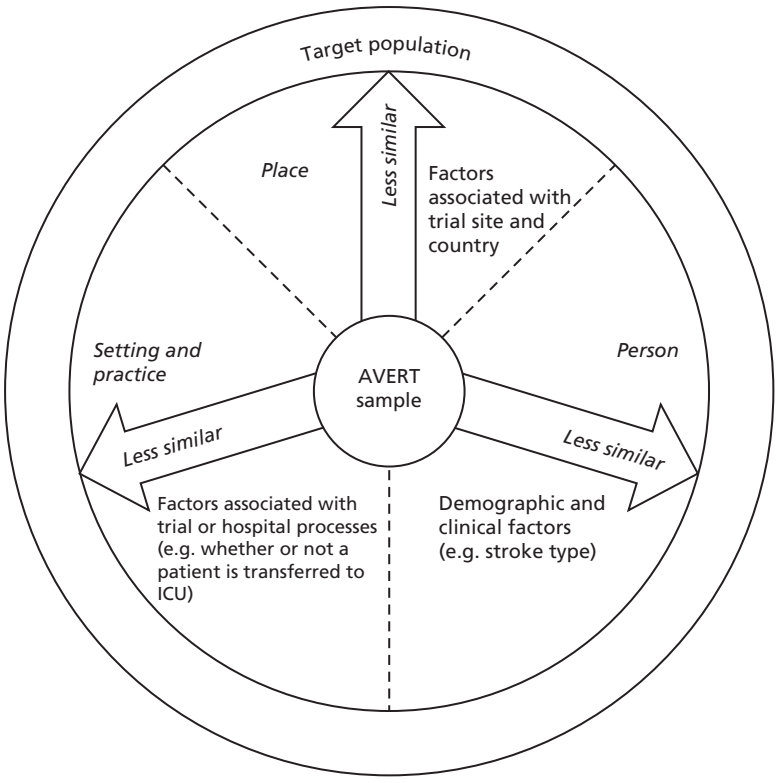


FIGURE 3 Proximal similarity framework applied to the AVERT trial: a model for conceptualising the dimensions along which the sample of patients may be similar to the target population. Each dimension (person, place, setting and practice) is affected by specific factors that may threaten external validity. ICU, intensive care unit. Reproduced with permission from Bernhardt *et al.*[38] This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

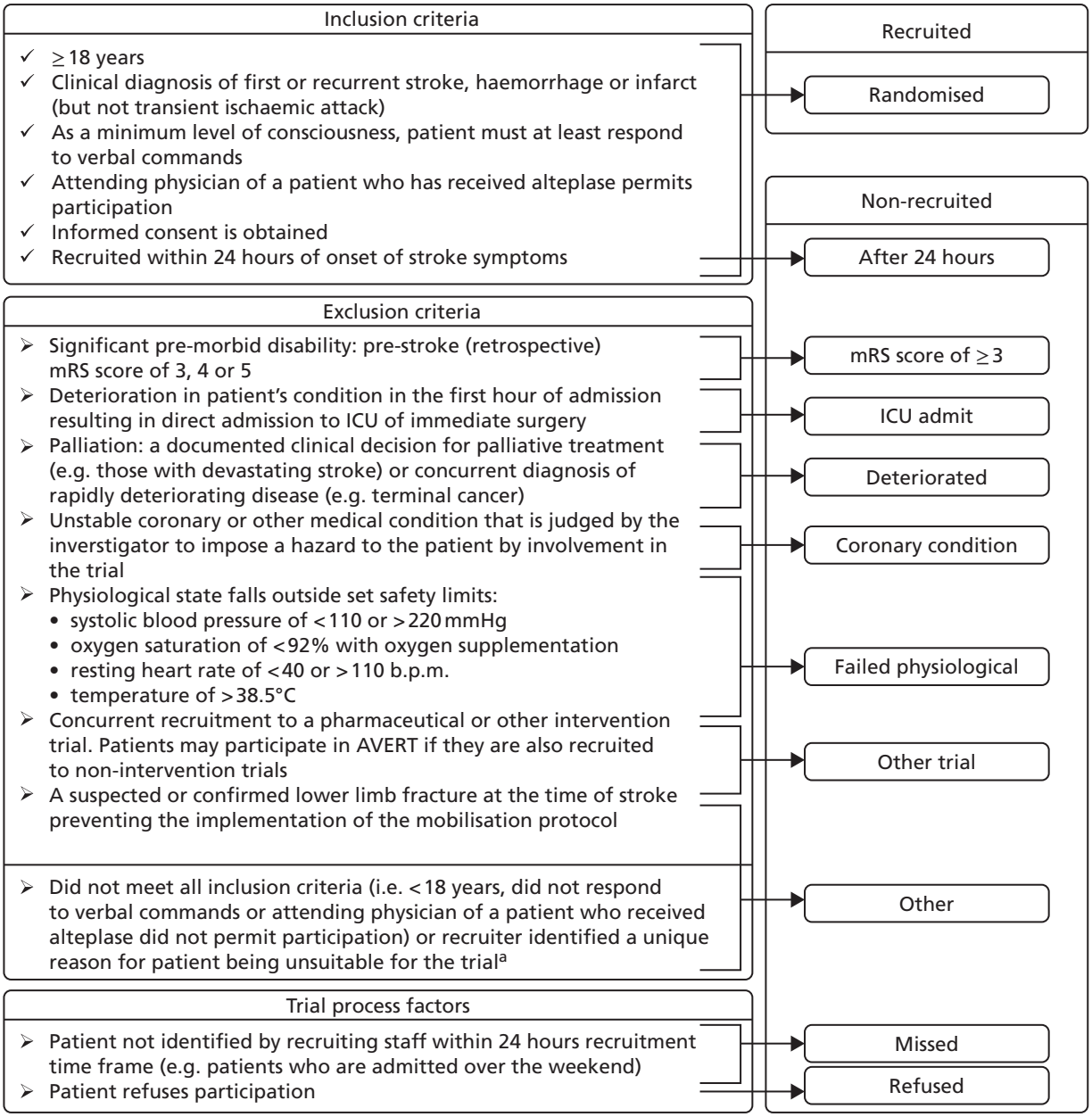


FIGURE 4 Relationship between trial inclusion/exclusion criteria and screening log categories in AVERT. a, other reasons included (but are not limited to) patients not admitted to a stroke unit, lower limb fractures and no treating therapist available. ICU, intensive care unit. Reproduced with permission from Bernhardt *et al.*[38] This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

The characteristics of participants included in the trial were broadly similar in terms of demographic and stroke characteristics with the exception that recruited participants had a greater proportion of men (*Table 4*). Late arrival to hospital (after 24 hours) was the most commonly reported reason for non-recruitment. Overall, older and female participants were less likely to be recruited to the trial. The reasons for exclusion of women rather than men applied to a range of reasons including refusal. Among severe stroke patients, the odds of exclusion because of early deterioration was particularly common (OR 10.4, 95% CI 9.3 to 11.7, $p < 0.001$).

TABLE 4 Baseline demographics of recruited vs. non-recruited patients, including significance testing for differences

Features	AVERT, non-recruited	AVERT, recruited	Difference (*p*-value) – recruited : non-recruited
n (%)	18,842 (94)	1158 (6)	
Age (years), median (IQR)	75 (64–82)	73 (63–80)	< 0.001
Range	15–102	18–100	
Female age (years), median (IQR)	78 (61–80)	76 (66–82)	
Male age (years), median (IQR)	71 (68–85)	71 (61–79)	
Female, % (95% CI)	47 (47 to 48)	37 (34 to 40)	< 0.001
NIHSS, *n* (%)			< 0.001
Mild (1–7)	10,012 (53)	619 (53)	
Moderate (8–16)	4934 (26)	358 (31)	
Severe (> 16)	3896 (21)	181 (16)	
Stroke type, *n* (%)			0.504
Ischaemic	16,328 (87)	1012 (87)	
ICH	2514 (13)	146 (13)	

ICH, intracerebral haemorrhage; IQR, interquartile range.

We found that using a screening log that captured a broad range of reasons for non-recruitment added to the collection of demographic data.[38] Similarly, the use of a model to explicitly explore generalisability was informative. However, a large screening log can only collect a limited amount of demographic and clinical information and it is quite possible that other factors may have influenced our recruitment. The proximal similarity model which explores person, place, practice and setting did provide some important information about the generalisability of this trial. Overall, the external validity appeared reasonably good.

Screening and recruitment

A summary of trial recruitment in the UK and other recruiting regions, during the period of the NIHR HTA programme grant (2012–16), is shown in *Table 5*. Recruitment from UK sites stood at 319 participants at the start of 2013 (average UK recruitment rate of seven participants per month). This compared with 19 participants per month in all other sites in Australia, New Zealand and Asia. The expansion that was possible through the NIHR HTA programme grant allowed us to recruit 291 UK participants in 2013–14 (average recruitment per month of 14 participants compared with 16 participants per month in all other sites).

The trial profile is provided in *Figure 5*. A total of 25,237 patients were admitted within 24 hours of stroke onset, of whom 23,133 were ineligible. The most common reasons were no recruiting staff available at the time of admission, medical instability, or premorbid disability. A smaller number were enrolled in other clinical trials or refused trial entry. Between 18 July 2006 and 16 October 2014, we randomly allocated 2104 patients to receive either VEM ($n = 1054$) or UC ($n = 1050$).

TABLE 5 Regional AVERT recruitment between 2011 and 2014

Country/centre	January to December 2011	January to December 2012	January to December 2013	January to October 2014	Final total
Northern Ireland total	20	12	2	2	59
Antrim	8	7	1	2	18
Belfast City	5	–	–	–	15
Craigavon	0	–	–	–	0
Daisy Hill	1	–	–	–	1
Ulster	6	5	1	–	25
Wales total	5	1	5		12
Neville Hall	5	1	5		12
Scotland total	13	26	25	30	171
Aberdeen	5	9	8	11	33
Crosshouse	–	–	–	–	3
Edinburgh	–	2	4	–	6
Forth Valley	2	12	13	20	65
Monklands	3	1			26
Western	–	–	–	–	10
Wishaw	3	2	–	–	28
England total	26	107	116	111	368
Blackpool	–	–	–	17	17
Calderdale	–	2	5		7
Harrogate	–	4	4	7	15
Hexham	2	3	–	–	5
Imperial College	9	7	8	5	29
London St George	–	–	2	5	7
North Devon	1	4		1	6
North Tyneside	1	8	7	1	17
QEQMH	–	4	9	8	21
Royal Bournemouth	–	5	18	9	32
Royal Devon	2	7	7	8	24
Royal Victoria	5	6	13	11	35
South Tyneside	2	2	3	1	8
St Mary's IoW	–	10	1	2	13
Wansbeck	3	8	4	3	18
Yeovil	1	23	24	13	61
York	–	15	11	28	54
UK total (number/month)	64 (5.3)	146 (12.2)	149 (12.4)	142 (15.8)	610
Australia/New Zealand/Asia total (number/month)	237 (19.8)	164 (13.7)	179 (14.9)	149 (15.3)	1494
Total (number/month)	301 (25.1)	309 (25.3)	322 (26.8)	271 (30.1)	2104

Note
UK had 319 participants by January 2013.

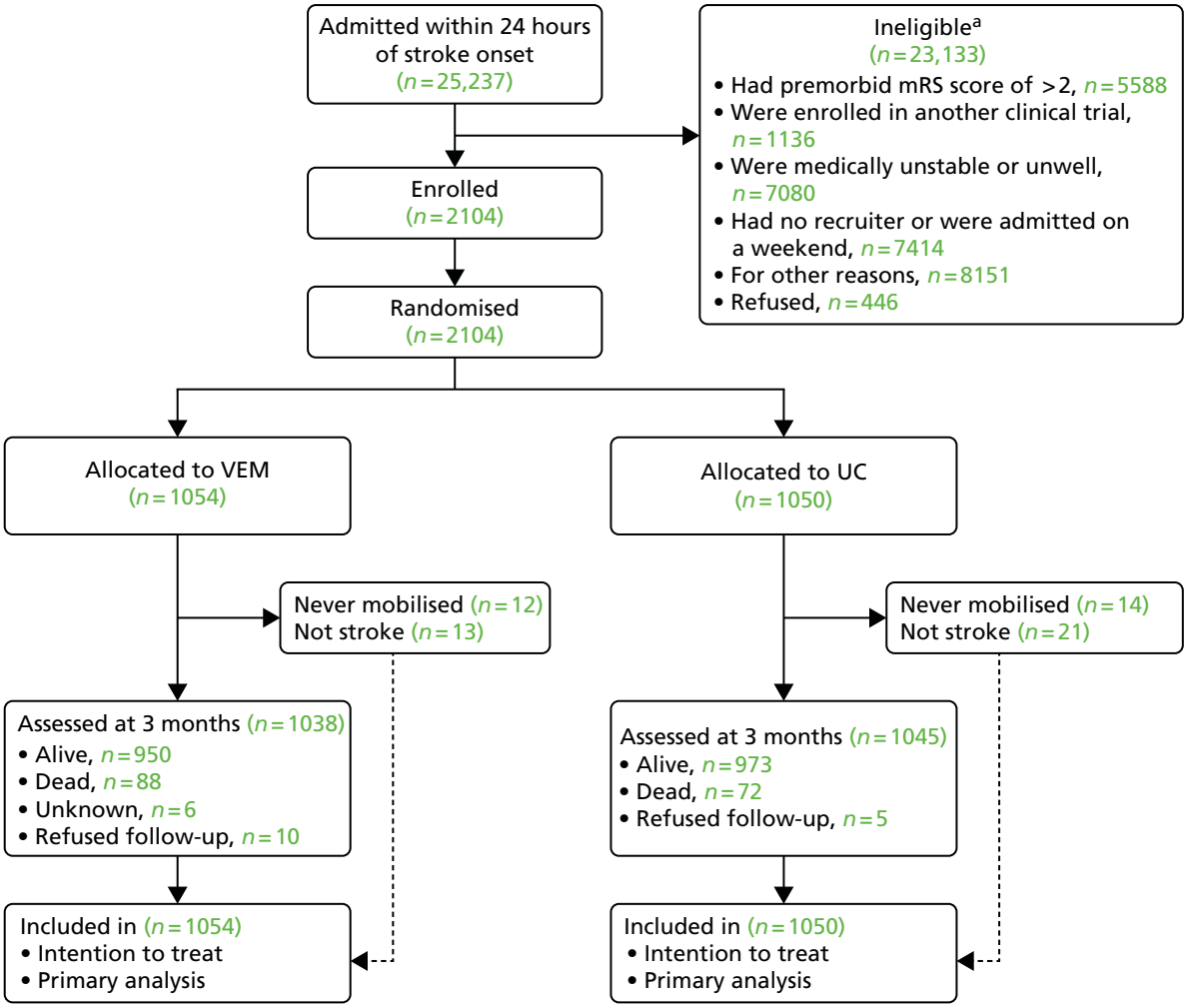


FIGURE 5 AVERT profile. a, More than one reason possible per patient. Reproduced with permission from the AVERT Trial Collaboration Group (2015).[31] This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Eligibility violations

A total of 34 patients were found to have a non-stroke diagnosis ($n = 13$ in VEM, and $n = 21$ in UC). A total of 26 were never mobilised ($n = 12$ in VEM, and $n = 14$ in UC) (see *Figure 5*). These patients remained in the trial and, if they agreed, were followed through until completion.

Participant baseline characteristics

Table 6 outlines the participant baseline characteristics that were similar between study groups. The median time to randomisation was 18 hours after stroke and was the same in both groups. The majority of patients (80%) were experiencing their first stroke and a large minority (45%) were classified as having moderate or severe stroke (NIHSS of > 7). Approximately one-quarter of patients were aged > 80 years (26%) and 24% received rtPA.

TABLE 6 Baseline patient characteristics

Features	VEM ($n = 1054$)	UC ($n = 1050$)
Recruitment region,* n *(%)		
Australia and New Zealand	617 (59)	626 (60)
Asia	126 (12)	125 (12)
UK	311 (29)	299 (28)
Age (years), mean (IQR)	***72.3 (62.3–80.3)***	***72.7 (63.4–80.4)***
< 65, *n* (%)	331 (31%)	298 (28%)
65–80, *n* (%)	448 (43%)	481 (46%)
> 80, *n* (%)	275 (26%)	271 (26%)
Sex,* n *(%)		
Female	411 (39)	407 (39)
Male	643 (61)	643 (61)
Risk factors,* n *(%)		
Hypertension	707 (67)	717 (68)
Ischaemic heart disease	235 (22)	251 (24)
Hypercholesterolaemia	421 (40)	423 (40)
Diabetes mellitus	239 (23)	228 (21)
Smoking,* n *(%)		
Never smoked	454 (43)	491 (47)
Smoker[a]	227 (22)	204 (19)
Ex-smoker[a]	352 (33)	341 (33)
Unknown	21 (2)	14 (1)
Atrial fibrillation	229 (22)	237 (23)
Premorbid history,* n *(%)		
Premorbid mRS		
0	799 (76)	786 (75)
1	145 (14)	158 (15)
2	110 (10)	106 (10)
Living arrangement at time of admission, *n* (%)		
Home alone	257 (25)	275 (26)
Home with someone	781 (74)	761 (73)
Supported accommodation	16 (1)	14 (1)
Independent walking, *n* (%)		
Without aid	908 (86)	925 (88)
With aid	146 (14)	125 (12)
Time to randomisation (hours), mean (IQR)	18.2 (12.1–21.8)	18.2 (12.5–21.8)

TABLE 6 Baseline patient characteristics (*continued*)

Features	VEM ($n = 1054$)	UC ($n = 1050$)
Stroke history*, n *(%)		
First stroke	878 (83)	843 (80)
NIHSS score, mean (IQR)	7 (4–12)	7 (4–12)
Mild (1–7)	592 (56)	578 (55)
Moderate (8–16)	315 (30)	328 (31)
Severe (> 16)	147 (14)	144 (14)
Stroke type (Oxfordshire Stroke Classification), *n* (%)		
Total anterior circulation infarct	224 (21)	232 (22)
Partial anterior circulation infarct	340 (32)	328 (31)
Posterior circulation infarct	93 (9)	106 (10)
Lacunar infarct	255 (24)	268 (26)
Intracerebral haemorrhage	142 (14)	116 (11)
rtPA treatment, *n* (%)		
Yes	247 (23)	260 (25)
Baseline walking (MSAS walking score), *n* (%)		
Independent	439 (42)	416 (40)
Supervised or assisted	522 (49)	538 (51)
Unable to walk	91 (9)	96 (9)
Unknown	2 (< 1)	0 (0)

a We defined a smoker as a current smoker or a participant who had quit smoking in the past 2 years, and an ex-smoker as a participant who had quit smoking > 2 years ago.

Participant withdrawals

A total of 2083 (99%) of patients were included in the 3-month follow-up assessment (see *Figure 5*). The main reasons for withdrawal were refusal (15 participants) and unknown (six participants). At the 12-month follow-up, 2052 (97%) completed an assessment, which showed that 24 patients were missing and 28 refused follow-up.

For UK participants ($n = 610$), 3-month follow-up assessments were complete for ≥ 98% of participants (nine withdrew). The 12-month follow-up assessments were complete for > 96% of UK participants (15 withdrew, 10 could not be contacted).

Treatment compliance

Table 7 summarises the three crucial elements of the VEM protocol. Patients allocated to VEM began mobilisation within 24 hours of stroke.

Patients in the VEM group successfully commenced mobilisation early after randomisation (median 18.5 hours after stroke). In the UC group, the median time to mobilisation was almost 5 hours later, but still within 24 hours of stroke onset. The categorisation of TTFM in the VEM and UC groups is outlined in

TABLE 7 Summary of interventions

Features	VEM ($n = 1054$)	UC ($n = 1050$)	p-value	Median shift (95% CI)
TTFM (hours)	18.5 (12.8–22.3; $n = 1042$[a])	22.4 (16.5–29.3; $n = 1036$[a])	< 0.0001	4.8 (4.1 to 5.7)
Frequency per person[b]	6.5 (4.0–9.5)	3 (2.0–4.5)	< 0.0001	3 (3 to 3.5)
Daily amount per person (minutes)[c]	31 (16.5–50.5)	10 (0–18)	< 0.0001	21.0 (20 to 22.5)
Total amount per person (minutes)[d]	201.5 (108–340)	70 (32–130)	< 0.0001	117 (107 to 128)

IQR, interquartile range.
a Twelve patients were missing from the VEM group and 14 patients were missing from the UC group. Missing patients were never mobilised, either because of an early SAE event, decision to palliate, or early death or transfer from the stroke unit. For these patients, therapy and nurse recording forms were completed throughout their stroke unit stay, with zero time and zero sessions.
b Daily sessions of out-of-bed activity.
c Minutes per day spent in out-of-bed activity.
d Total amount is over the length of stay or until 14 days after stroke (whichever took place first).
Data are median (IQR) or median (IQR; *n*), unless otherwise indicated.
Dose data for VEM includes components of both UC and VEM. Frequency is derived from nursing and therapist data. Amount (minutes) is derived from physiotherapist data only. Median estimates include days when time or number of out-of-bed sessions were zero (i.e. the patient was recorded as not getting up on that day or for that session).

Table 7. It is notable that 965 (92%) VEM patients had mobilised within 24 hours compared with 623 (59%) patients in the UC group. It was noted that the median TTFM in the UC group actually reduced during the study period. The rate of reduction was 28 minutes per year (95% CI 11.3 to 44.6 minutes; $p = 0.001$). There was no significant change in the VEM group over the same time period. As a result, there was a significant interaction between time since commencing the trial and TTFM ($p = 0.017$). In contrast, during the study period there was no significant change in the daily frequency or daily amount of out-of-bed intervention or in the total intervention time.

Content of physical therapy and nursing

Further exploration of the intervention differences between the VEM and UC groups are shown in *Figure 6*. TTFM was substantially reduced in the VEM group in all subgroups of patients except those recruited in Asia. The frequency of out-of-bed activity was increased in all VEM subgroups, especially younger patients with milder strokes. A similar pattern was seen in the amount of out-of-bed activity regardless of whether it was measured per day or over the whole intervention period.

Regional differences

Figure 6 also shows the successful delivery of VEM compared with UC regimes in the UK sites. In general, the differences were slightly less marked in the UK than other regions but, overall, UK sites delivered a 2.6-hour reduction in TTFM, with three more out-of-bed activity sessions per day. This equated to 15 minutes more out-of-bed activity per day or 90 minutes during the intervention period.

(a)

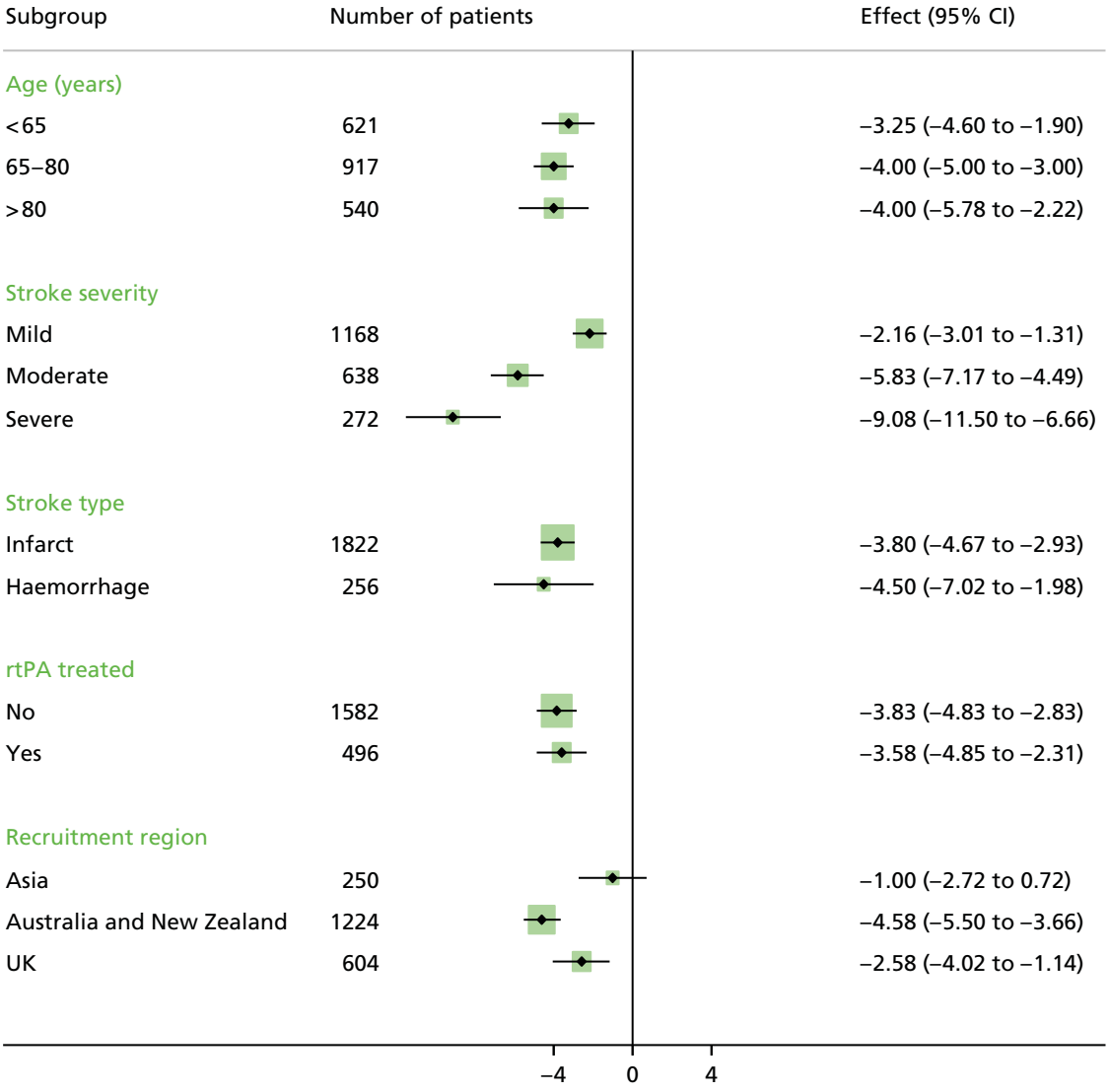


FIGURE 6 Intervention characteristics by group (VEM vs. UC) for each subgroup. (a) TTFM (hours); (b) frequency, median daily sessions of out-of-bed activity; (c) daily amount, median minutes per day in out-of-bed activity; and (d) total amount, minutes, over the intervention period. The forest plot shows the effect size and 95% CI for earlier TTFM, more frequent out-of-bed sessions, higher daily amount of out-of-bed activity and higher total dose over the intervention period in the VEM group. Titration of dose to the stroke severity is evident. Stroke severity (NIHSS): mild = 1–7, moderate = 8–16, and severe > 16. Reproduced with permission from the AVERT Trial Collaboration Group (2015).[31] This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. (*continued*)

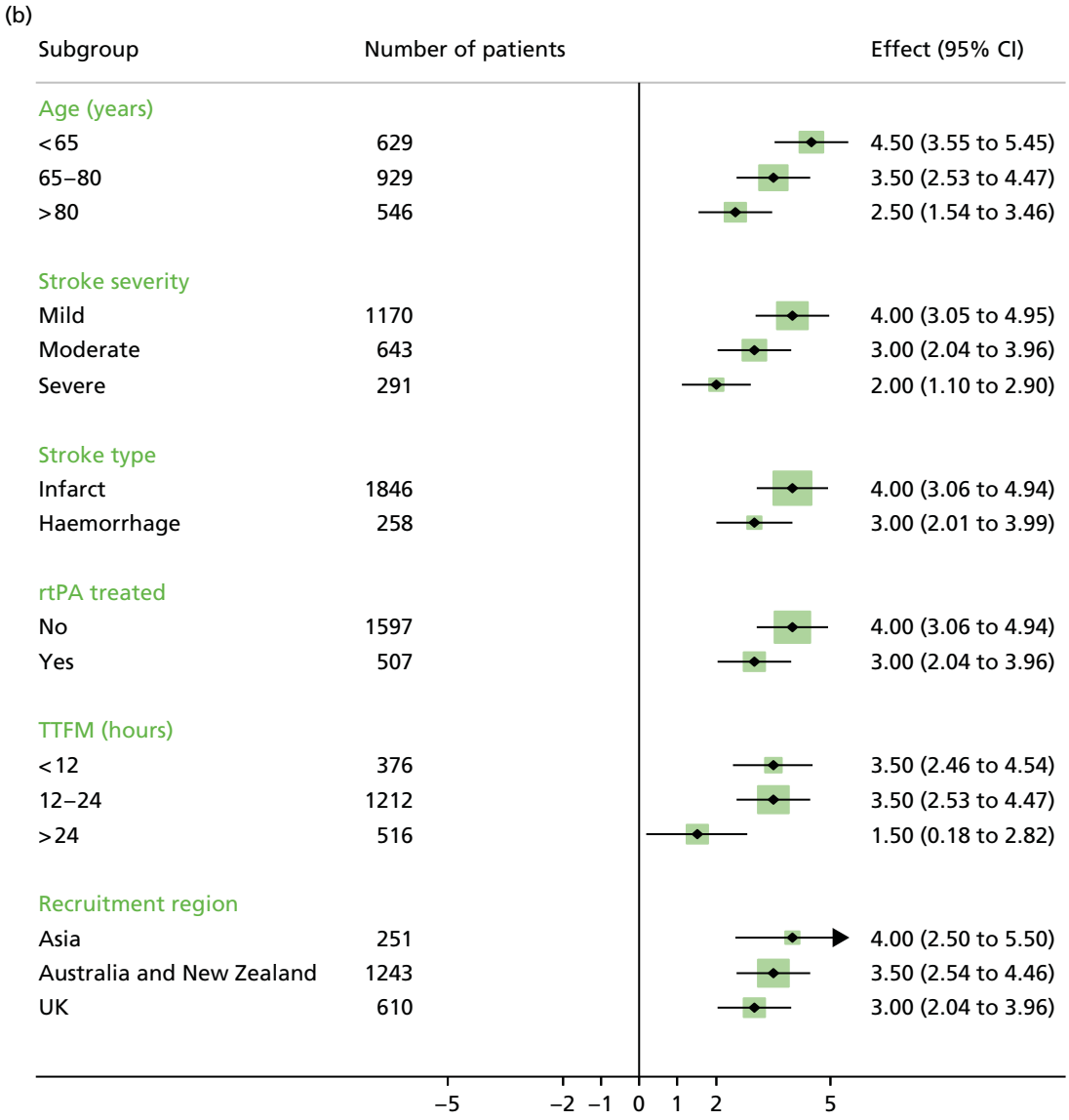


FIGURE 6 Intervention characteristics by group (VEM vs. UC) for each subgroup. (a) TTFM (hours); (b) frequency, median daily sessions of out-of-bed activity; (c) daily amount, median minutes per day in out-of-bed activity; and (d) total amount, minutes, over the intervention period. The forest plot shows the effect size and 95% CI for earlier TTFM, more frequent out-of-bed sessions, higher daily amount of out-of-bed activity and higher total dose over the intervention period in the VEM group. Titration of dose to the stroke severity is evident. Stroke severity (NIHSS): mild = 1–7, moderate = 8–16, and severe > 16. Reproduced with permission from the AVERT Trial Collaboration Group (2015).[31] This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. (*continued*)

(c)

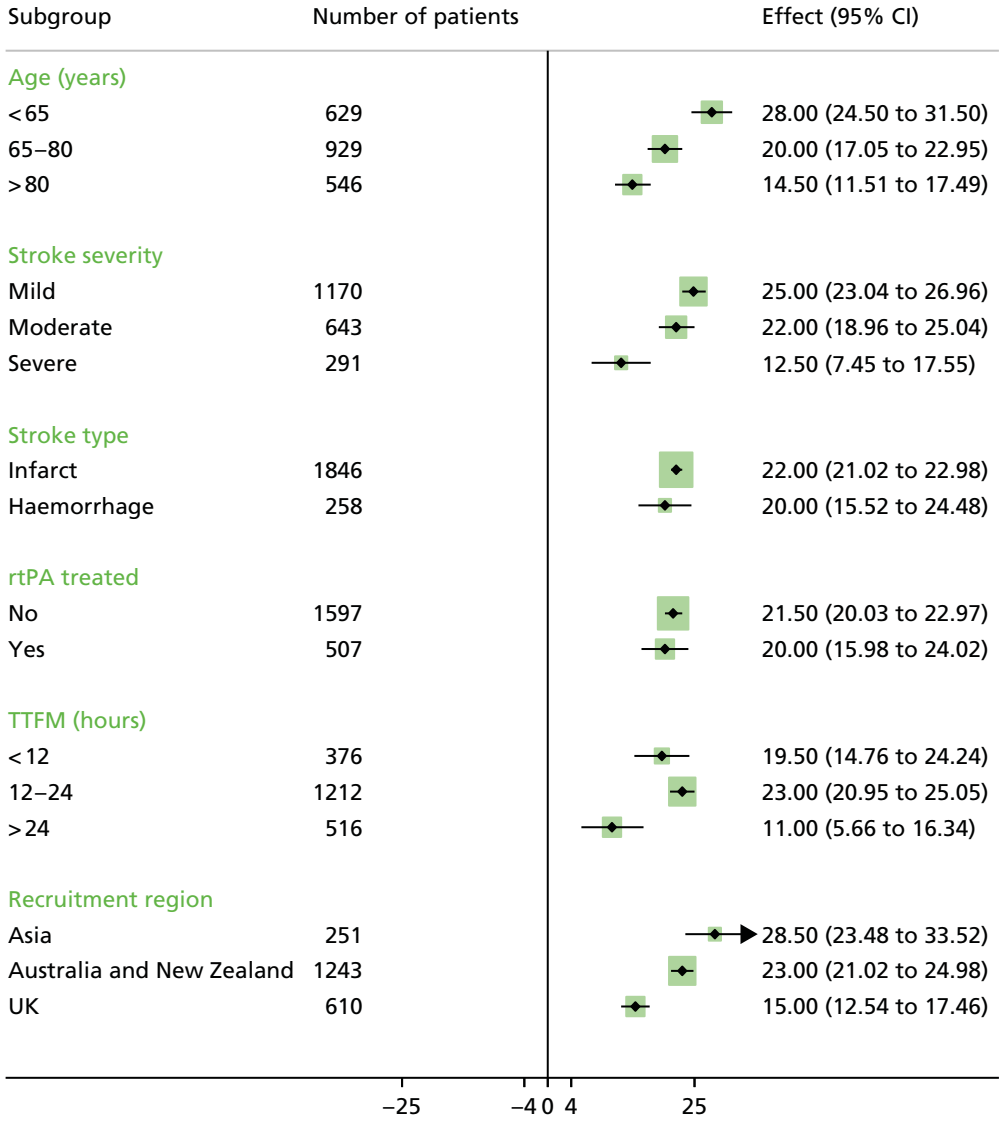


FIGURE 6 Intervention characteristics by group (VEM vs. UC) for each subgroup. (a) TTFM (hours); (b) frequency, median daily sessions of out-of-bed activity; (c) daily amount, median minutes per day in out-of-bed activity; and (d) total amount, minutes, over the intervention period. The forest plot shows the effect size and 95% CI for earlier TTFM, more frequent out-of-bed sessions, higher daily amount of out-of-bed activity and higher total dose over the intervention period in the VEM group. Titration of dose to the stroke severity is evident. Stroke severity (NIHSS): mild = 1–7, moderate = 8–16, and severe > 16. Reproduced with permission from the AVERT Trial Collaboration Group (2015).[31] This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. (*continued*)

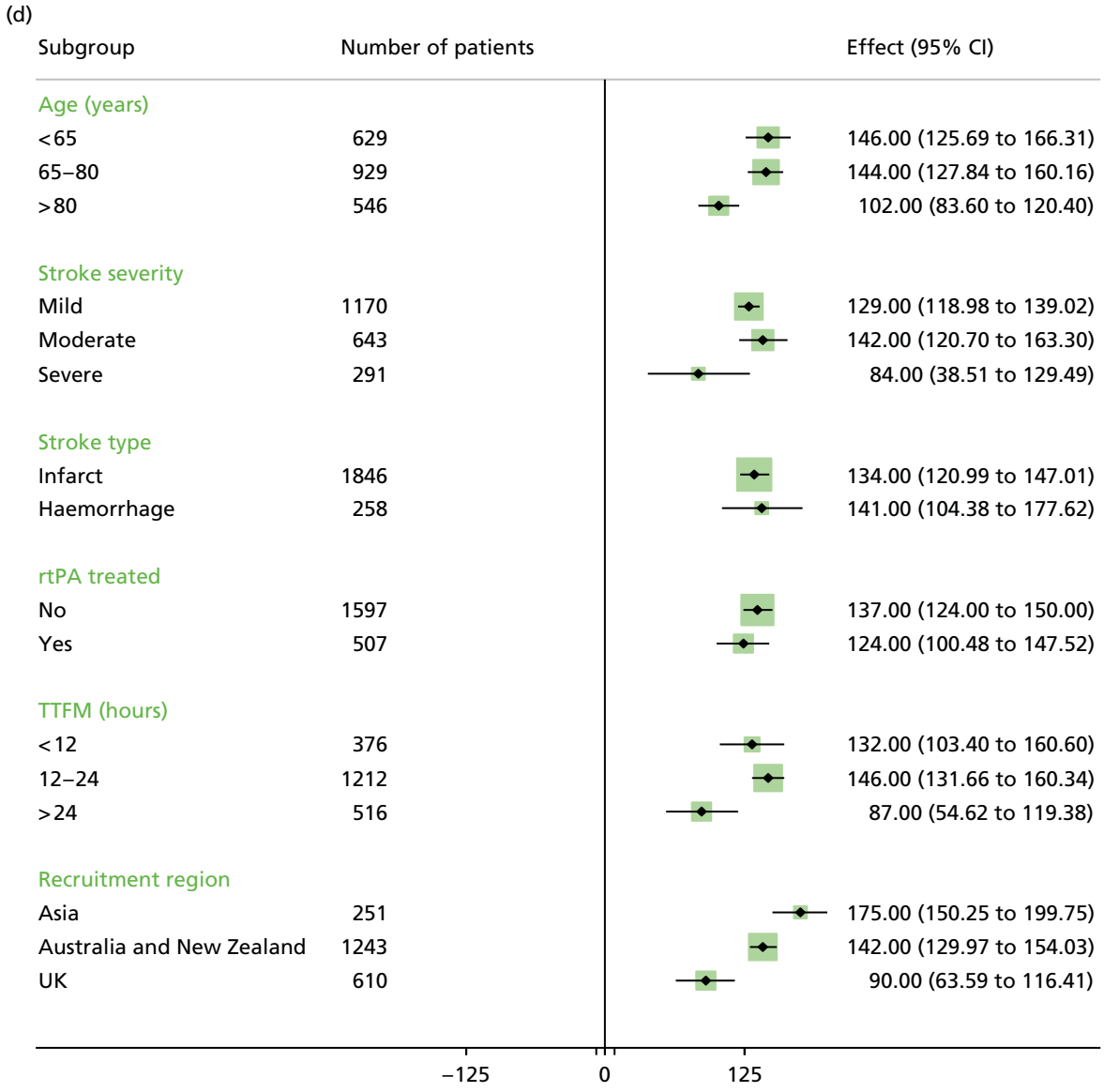


FIGURE 6 Intervention characteristics by group (VEM vs. UC) for each subgroup. (a) TTFM (hours); (b) frequency, median daily sessions of out-of-bed activity; (c) daily amount, median minutes per day in out-of-bed activity; and (d) total amount, minutes, over the intervention period. The forest plot shows the effect size and 95% CI for earlier TTFM, more frequent out-of-bed sessions, higher daily amount of out-of-bed activity and higher total dose over the intervention period in the VEM group. Titration of dose to the stroke severity is evident. Stroke severity (NIHSS): mild = 1–7, moderate = 8–16, and severe > 16. Reproduced with permission from the AVERT Trial Collaboration Group (2015).[31] This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Participant assessments

Out of the 2104 participants randomly assigned to either VEM ($n = 1054$) or UC ($n = 1050$), 2083 (99%) were available for 3-month mRS follow-up assessments (see *Figure 5*), with smaller numbers available for other outcome measures. At the 12-month follow-up, 2052 (97%) completed a mRS assessment, which showed that 24 patients were missing and 28 refused follow-up.

Primary end point: 3 months

At 3-month follow-up, fewer patients in the VEM group had a favourable outcome than the UC group (*Table 8*). This resulted in a significant difference between the groups on the prespecified analysis, which adjusted for baseline age and NIHSS (see *Table 8*): 480 (46%) in the VEM group had a favourable outcome compared with 525 (50%) in the UC group (aOR 0.73, 95% CI 0.59 to 0.90; $p = 0.004$). Sensitivity analysis produced similar results (*Figure 7*) and the treatment effect showed no interaction with time since the commencement of the trial. Unadjusted analysis of the primary outcome showed a reduction in favourable outcome that did not achieve statistical significance ($p = 0.068$).

TABLE 8 Outcomes at 3 months

Features	VEM ($n = 1038$[a])	UC ($n = 1045$[a])	Adjusted analysis		Unadjusted analysis	
			OR, generalised OR or HR[b] (95% CI)	*p*-value	OR, generalised OR or HR[b] (95% CI)	*p*-value
Primary						
Favourable outcome[c]	480 (46)	525 (50)	0.73 (0.59 to 0.90)	0.004	0.85 (0.72 to 1.0)	0.068
Secondary						
mRS category	–	–	0.94 (0.85 to 1.03)	0.193	0.94 (0.85 to 1.03)	0.202
0	90 (9)	96 (9)	–	–	–	–
1	200 (19)	204 (19)	–	–	–	–
2	190 (18)	225 (22)	–	–	–	–
3	238 (23)	218 (21)	–	–	–	–
4	140 (14)	127 (12)	–	–	–	–
5	92 (9)	103 (10)	–	–	–	–
6	88 (8)	72 (7)	–	–	–	–
Walking 50 m unassisted[d]	6 (5–7; $n = 1051$)	7 (6–8; $n = 1049$)	1.04 (0.94 to 1.15)	0.459	1.05 (0.95 to 1.16)	0.331

IQR, interquartile range.

a Sixteen patients were missing from the VEM group and five patients were missing from the UC group. These 21 patients declined follow-up or could not be found. Missing data were analysed according to our intention-to-treat strategy assuming missing at random. *Figure 7* shows results of the sensitivity analysis.

b Point estimates are ORs for the primary outcome, generalised ORs for the secondary outcome of mRS category and HRs for the secondary outcome of walking unassisted.

c mRS score of 0–2.

d Time at which 50% of participants walked. The number walking unassisted includes all patients who were recorded as having walked 50 m unassisted in the first 3 months. This number might include patients for whom we were unable to obtain 3-month mRS.

Data are *n* (%) or median (IQR; *n*), unless otherwise indicated.

All analyses are adjusted for baseline NIHSS score and age.

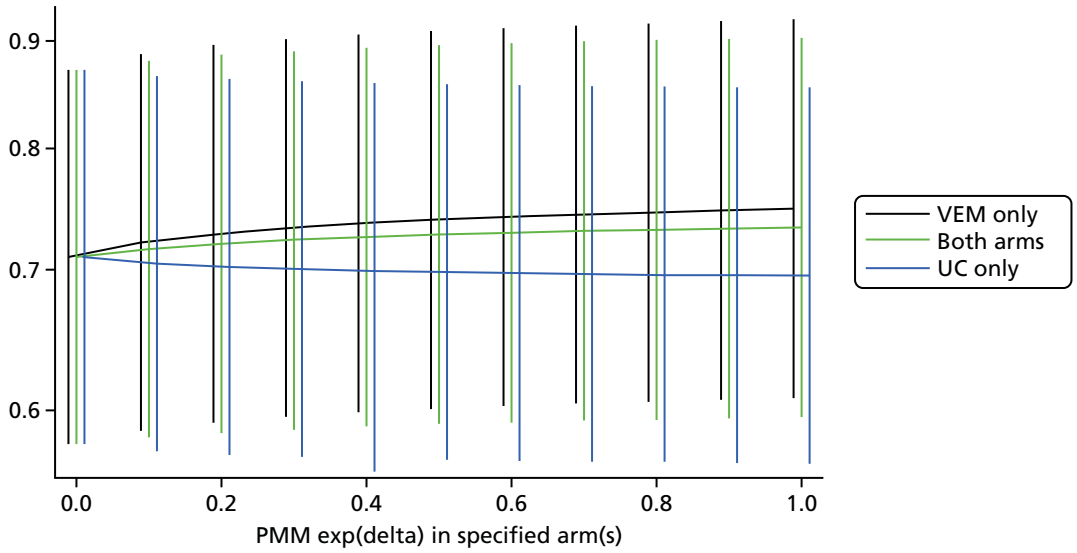


FIGURE 7 Sensitivity analysis for the primary outcome, favourable outcome (mRS score of 0–2) at 3 months. The intention-to-treat analysis assumes that data are missing at random. The sensitivity of the results to plausible departures from this assumption were explored. Assumptions about the missing data were expressed via a parameter delta [exp(delta)], which measures the degree of departure from missing at random assumption (range 0–1). The upper 95% CI is below 1 (OR 0.71, 95% CI 0.57 to 0.87; $p = 0.001$) for all the values of delta indicating that the results remain significant on the sensitivity analysis. PMM, pattern mixture model. Reproduced with permission from the AVERT Trial Collaboration Group (2015).[31] This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Secondary patient end point: 3 months

The secondary analysis included the assumption-free ordinal analysis. This did not show a significant difference between groups across the whole mRS (*Figure 8*). OR (95% CI) for an improved outcome was 0.94 (0.85 to 1.03; $p = 0.202$) for an unadjusted analysis and 0.94 (0.85 to 1.03; $p = 0.193$) for an adjusted analysis (see *Table 8*).

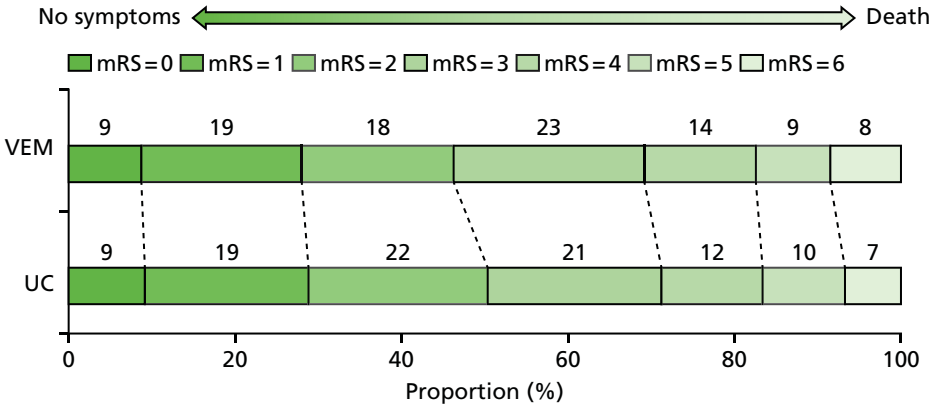


FIGURE 8 Patients achieving each mRS score at 3 months. Reproduced with permission from the AVERT Trial Collaboration Group (2015).[31] This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Walking ability

By 7 days after stroke, 50% of patients were able to walk unassisted and 784 (75%) were walking by 3 months in the VEM group. In the UC group, at 3 months, 796 (76%) were walking (aOR 0.83, 95% CI 0.64 to 1.07; $p = 0.143$). There was no significant difference in the groups in the time to walking unassisted (*Figure 9* and see *Table 8*).

Case fatality

At the 3-month follow-up, the overall case fatality was 8% (*Table 9*); 88 (8%) patients died in the VEM group and 72 (7%) in the UC group. The main causes of SAEs are outlined in *Table 9*. These accounted for two-thirds of all deaths and included stroke progression ($n = 31$ in the VEM group and $n = 19$ in the UC group), pneumonia ($n = 19$ in the VEM group and $n = 15$ in the UC group) and recurrent stroke ($n = 11$ in the VEM group and $n = 7$ in the UC group).

Length of hospital stay

For patients in the VEM group, the median length of hospital stay including acute care and rehabilitation was 16 days [interquartile range (IQR) 5–44 days]. Patients in the UC group had a hospital stay of a median of 18 days (6–43 days). The equivalent figure for acute care alone was 7 days (IQR 4–13 days) for both patients receiving VEM or UC. The rehabilitation length of stay was 28 days (15–49 days) for the VEM group and 30 days (16–51 days) for the UC group. The number of patients transferring from acute care to patient rehabilitation was 492 (46%) in the VEM group and 523 (49%) in the UC group.

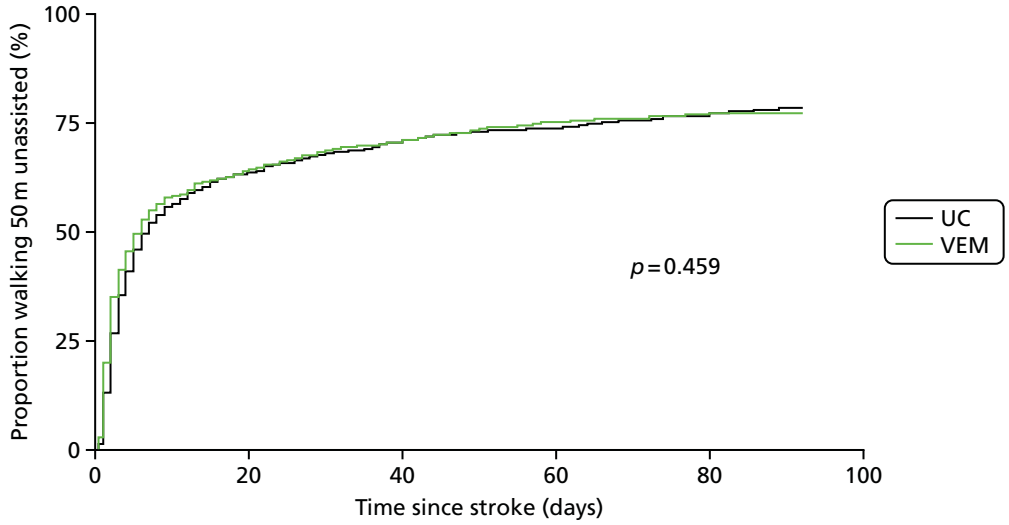
Adverse events

Serious adverse events: most patients did not have a SAE in the first 3 months of follow-up (see *Table 9*). There was no significant difference in the proportion of patients who had non-fatal SAEs (see *Table 9*). We also examined SAEs by prespecified category of complication (immobility vs. neurological). Relatively few patients in either group had a fatal or non-fatal serious complication related to immobility (see *Table 9*). The final number was 8% in each group. Serious neurological complications were recorded in < 10% of patients in either group and there were no significant differences between the groups (see *Table 9*). The most common neurological complication was stroke progression and was recorded in 72 (7%) participants in the VEM group and 56 (5%) participants in the UC group.

Staff safety: one staff injury was reported in the VEM group.

Secondary patient end point: 12 months

A total of 2052 (97.5%) participants completed the 12-month follow-up (*Figure 10*). In the VEM group, 139 participants had died, 19 refused and 16 were lost, compared with 118, nine and eight participants, respectively, in the UC group. For the UK participants ($n = 610$), assessments were complete for ≥ 96% (15 withdrew, 10 could not be contacted). Therefore, 52 (2.5%) patients did not complete mRS at 12-month follow-up (see *Figure 7*). The aOR (adjusted for age and baseline NIHSS) for a favourable outcome (mRS score of 0–2) in the VEM group was 0.84 (95% CI 0.68 to 1.03; $p = 0.089$).



Number at risk[a]

UC	1049	359	276	231	200	0
VEM	1051	342	263	215	198	0

FIGURE 9 Time taken to regain walking unassisted 50 m by 3 months. a, Number of patients who had not achieved walking. Reproduced with permission from the AVERT Trial Collaboration Group (2015).[31] This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

TABLE 9 Deaths and non-fatal serious complications at 3 months

Features	VEM ($n = 1054$)	UC ($n = 1050$)	OR or IRR[a] (95% CI)	p-value
Death	88/1048 (8)[b]	72 (7)	1.34 (0.93 to 1.93)	0.113
Non-fatal SAEs			0.88 (0.72 to 1.07)	0.194
0	853 (81)	842 (80)	–	–
1	157 (15)	146 (14)	–	–
2	32 (3)	41 (4)	–	–
3	10 (1)	16 (2)	–	–
4	2 (< 1)	4 (< 1)	–	–
5	0	1 (< 1)	–	–
Immobility SAEs[c]			0.92 (0.62 to 1.35)	0.665
0	1000 (95)	997 (95)	–	–
1	50 (5)	46 (4)	–	–
2	4 (< 1)	5 (1)	–	–
3	0	2 (< 1)	–	–
4	0	0	–	–
5	0	0	–	–
Neurological SAEs[c]			1.26 (0.95 to 1.66)	0.108
0	947 (90)	967 (92)	–	–
1	104 (10)	78 (7)	–	–
2	3 (< 1)	4 (< 1)	–	–
3	0	1 (< 1)	–	–
4	0	0	–	–

a Point estimates are OR for death and IRRS for all AEs.
b The 3-month outcome was missing (unknown) for six patients in the VEM group. Missing data were analysed according to our intention-to-treat strategy assuming missing at random. The results remain stable over the range of possible violations of this assumption.
c Immobility-related and neurological SAEs include both fatal and non-fatal complications. Immobility-related events include pulmonary embolism, deep-vein thrombosis, urinary tract infection, pressure sores and pneumonia, and neurological events include stroke progression and recurrent stroke.
Data are *n*/*N* (%) or *n* (%), unless otherwise indicated.
We did IRR analysis with event counts per person. All analyses are adjusted for age and baseline NIHSS score.

Health-related QoL: the AQoL could not be collected for 87 out of 2104 (4.1%) participants. In the VEM group, 139 had died, 36 could not be completed (refused, incomplete, not collected by assessor) and 16 could not be contacted. In the UC group, 118 had died, 27 could not be completed and eight could not be contacted. A death outcome was scored as zero and included in the analysis. A score of < 0 was classified as 'worse than death' and 0.9–1.0 was 'excellent'. Treatment covariates for adjustment are baseline NIHSS, age and sex. The per cent of proxy completions (when the patients is alive but the AQoL was completed by a family member, friend or carer) was 11.9% in the VEM group and 12.6% in the UC group. The median AQoL IQR for the VEM group was 0.47 (95% CI 0.07 to 0.81) and in the UC group was 0.49 (95% CI 0.08 to 0.81; $p = 0.865$). The adjusted median regression result was –0.0036 (95% CI –0.045 to 0.038; $p = 0.865$).

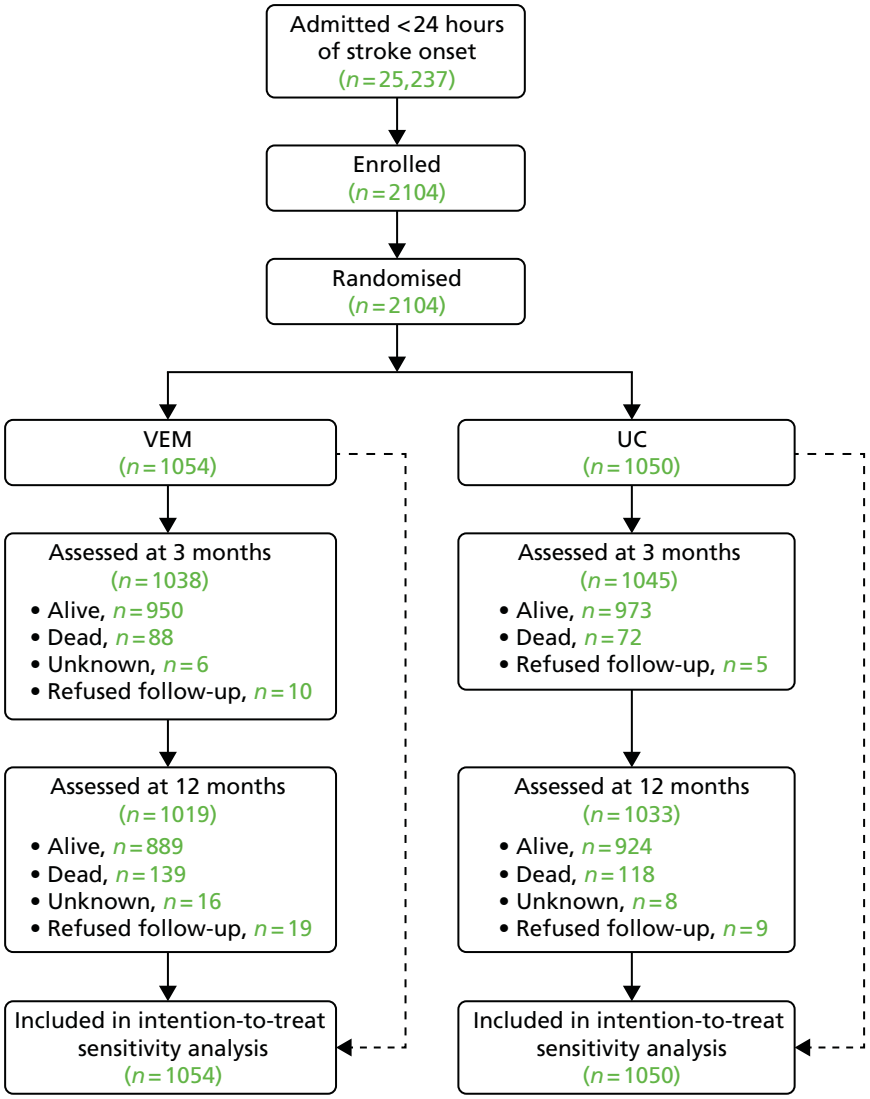


FIGURE 10 Trial profile at 12-month follow-up.

Walking ability: at 12 months, 24% (434/1836) of alive patients were not walking 50 m. The aOR between groups for walking at 12 months was 0.85 (95% CI 0.65 to 1.10; $p = 0.222$). The between-group comparison of proportion of the number of days before patients recovered walking ability was not statistically significantly different between groups (HR 1.02, 95% CI 0.94 to 1.13; $p = 0.553$).

Subgroup analyses

The prespecified subgroup analysis of the primary outcome (favourable outcome of mRS score of 0–2 at 3 months) is outlined in *Figure 11*. The pattern of results tended to favour the UC intervention across all the main subgroups. The point estimate suggested that the poorest outcomes in the VEM group were in patients with severe stroke and patients with intracerebral haemorrhage. However, within each individual subgroup analysis, no statistically significant interactions were recorded ($p > 0.05$), but the trial is underpowered to detect subgroup interactions.

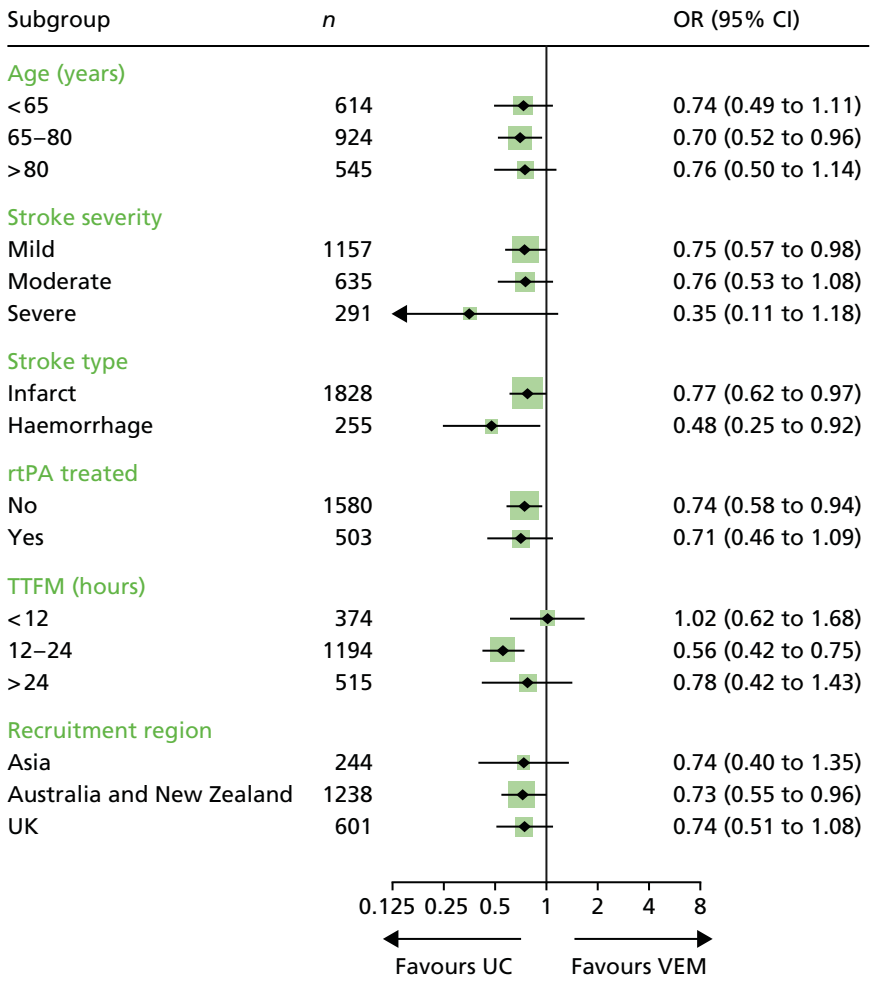


FIGURE 11 Prespecified subgroup analyses: primary outcome at 3 months. None of the individual subgroup analyses had significant treatment-by-subgroup interactions (all $p > 0.05$). Stroke severity (NIHSS): mild = 1–7, moderate = 8–16 and severe > 16. Reproduced with permission from the AVERT Trial Collaboration Group (2015).[31] This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The subgroup analysis of the secondary outcome (death at 3 months) is outlined in *Figure 12*. The pattern of results tended to favour the UC intervention across all the main subgroups. The point estimate suggesting that the poorest outcomes in the VEM group were in patients with intracerebral haemorrhage did not achieve a statistically significant level of interactions ($p > 0.05$, see *Figure 11*).

Moderator analysis

Functional outcome: further prespecified analysis explored the relationship between treatment received and patient outcomes; this analysis included all patients in a single cohort analysis and explored relationships within the group using binary logistic regression models and CART analysis. Baseline characteristics of the combined participant groups are shown in *Table 10*. It was notable that the group were representative of the stroke population: 25% were ≥ 80 years of age and 43% had a moderate or severe stroke (NIHSS score of > 7) while 12% were diagnosed with intracerebral haemorrhage.

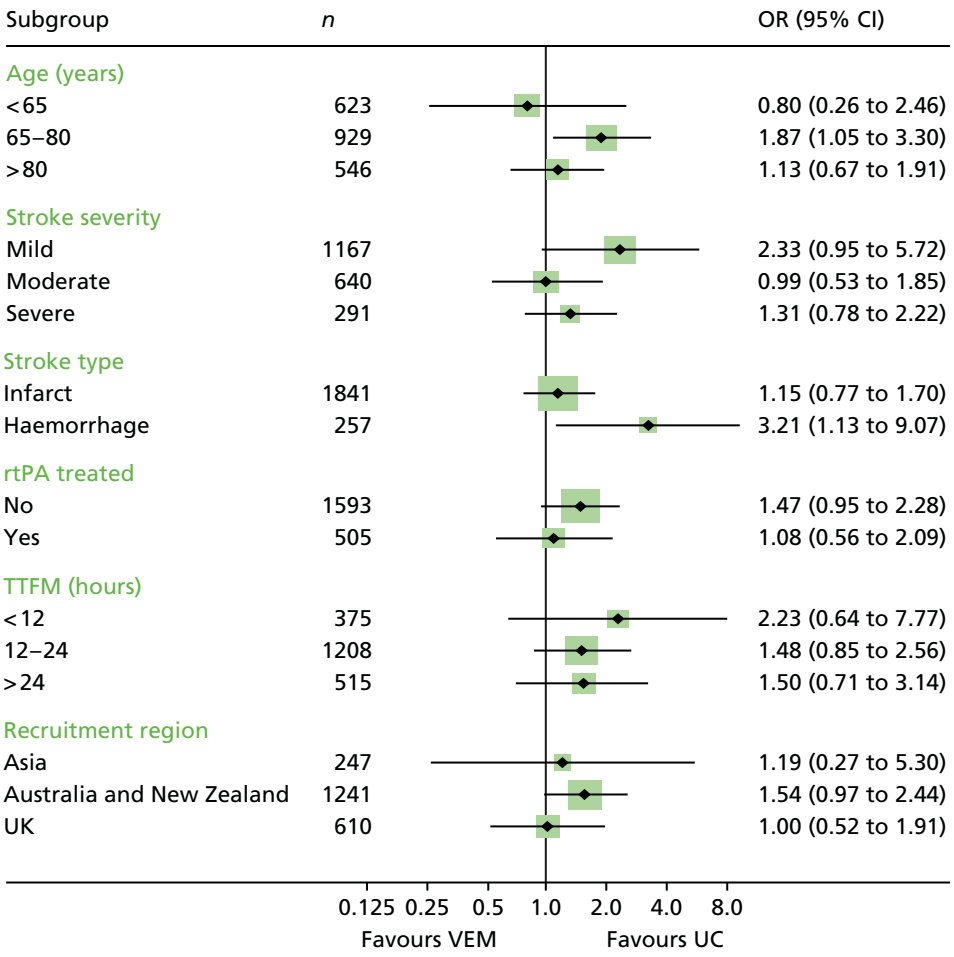


FIGURE 12 Death at 3 months by group shown for each subgroup. None of the individual subgroup analyses had significant treatment-by-subgroup interactions (all $p > 0.05$). Stroke severity (NIHSS): mild = 1–7, moderate = 8–16 and severe > 16. Reproduced with permission from the AVERT Trial Collaboration Group (2015).[31] This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The intervention characteristics for all patients are summarised in *Table 11*. The median TTFM was short [20.2 hours (IQR 14.7–23.8)] and 1588 (75%) of all participants began out-of-bed activities within 24 hours of stroke onset.

In the logistic regression analysis (*Table 12*) a longer TTFM was associated with reduced odds of favourable outcome (OR 0.99, 95% CI 0.98 to 1.00; $p = 0.036$). In the first model, the effect of timed first mobilisation was adjusted for the median daily number of sessions (frequency) and the median daily number of minutes (daily amount) as well as age and baseline severity (NIHSS). This should be interpreted as follows: for two patients with a similar age and baseline stroke severity who receive a similar frequency and daily amount of out-of-bed activity, the patient who starts mobilisation earlier has an increased odds of a favourable outcome.

We found a similar pattern of association with each of the dose characteristics for both favourable outcome (mRS score of 0–2) and walking by 3 months (see *Table 12*). All three intervention variables (timed to first mobilisation, frequency, daily amount) were significantly associated with outcome in model 1. When keeping other variables constant, every extra 5 minutes of out-of-bed activity per day was associated with reduced odds of favourable outcome. In contrast, increasing the frequency of sessions was associated with an improved odds of a favourable outcome by 13% (95% CI 9% to 18%; $p < 00.1$) and also and

TABLE 10 Baseline characteristics of all included patients (VEM and control)

Features	Patients ($N = 2104$)
Recruitment region, *n* (%)	
Australia/New Zealand	1243 (59)
Asia	251 (12)
UK	610 (29)
Patient characteristics	
Age (years), median (IQR)	73 (63–80)
Female, *n* (%)	818 (40)
Risk factors, *n* (%)	
Hypertension	1424 (68)
Ischaemic heart disease	487 (23)
Hypercholesterolaemia	929 (40)
Diabetes mellitus	467 (22)
Atrial fibrillation	466 (22)
Smoking, *n* (%)	
Never smoked	945 (45)
Smoker	431 (20)
Ex-smoker	693 (33)
Living arrangement at time of admission	
Home alone	532 (25)
Home with someone else, *n* (%)	1542 (73)
Time (hours) to randomisation, median (IQR)	18 (12–22)
First stroke, *n* (%)	1721 (82)
NIHSS score at baseline	
Median (IQR)	7 (4–12)
Mild (NIHSS 1–7), *n* (%)	1170 (56)
Moderate (NIHSS 8–16), *n* (%)	643 (31)
Severe (NIHSS score of > 16), *n* (%)	291 (14)
Stroke type (Oxfordshire Stroke Classification), *n* (%)	
Total anterior circulation infarct	456 (22)
Partial anterior circulation infarct	668 (32)
Posterior circulation infarct	199 (9)
Lacunar infarct	523 (25)
Intracerebral haemorrhage	258 (12)
Treated with rtPA	507 (24)
Baseline walking (based on MSAS), *n* (%)	
Independent	855 (41)
Supervised or assisted	1060 (50)

TABLE 11 Summary of mobilisation intervention for all patients

Characteristics	All included patients ($N = 2104$)
TTFM (hours), median (IQR)	20.2 (14.7–23.8)[a] ($n = 2078$)
Frequency per person[b] [median daily sessions of out-of-bed activity (IQR)]	5 (3–8)
Daily amount per person[c] [median minutes per day spent in out-of-bed activity (IQR)]	17.5 (6–35)
Total amount per person[c] [minutes over the intervention period[d] (median and IQR)]	120 (50–235)

a A total of 26 patients were missing data on hours to first mobilisation. These patients were never mobilised owing to an early SAE ($n = 13$), decision to palliate ($n = 5$), early death ($n = 5$), transfer from the stroke unit ($n = 1$) or drop-out ($n = 1$). For these patients, therapy and nurse recording forms were completed throughout their stroke unit stay, with zero time and zero sessions.
b Frequency of out-of-bed activity is derived from nursing and physiotherapist data.
c Amount (minutes) of out-of-bed activity is derived from physiotherapist data only.
d Total amount of out-of-bed activity over the intervention period was estimated over the total length of stay or until 14 days post stroke (whichever occurred first).
Median estimates include days when the patient was recorded as not getting up on that day (and so $n = 0$).

TABLE 12 Association of intervention characteristics with favourable outcome (mRS score of 0–2) and unassisted walking

Features	Favourable outcome (mRS score of 0–2)		Walking 50 m unassisted			
Variable	OR (95% CI)	*p*-value	Binary OR (95% CI)	*p*-value	Cox HR (95% CI)	*p*-value
Model 1						
TTFM (per extra hour of time)	0.99 (0.98 to 1.0)	0.036	1.0 (0.99 to 1.0)	0.40	0.99 (0.98 to 0.99)	< 0.001
Frequency, median daily sessions[a] (per one extra session of mobilisation)	1.13 (1.09 to 1.18)	< 0.001	1.66 (1.53 to 1.80)	< 0.001	1.10 (1.09 to 1.13)	< 0.001
Daily amount, median (per extra 5 minutes of mobilisation activity)	0.94 (0.91 to 0.97)	< 0.001	0.85 (0.81 to 0.89)	< 0.001	0.96 (0.94 to 0.97)	< 0.001
Model 2						
TTFM (per extra hour of time)	0.99 (0.98 to 1.0)	0.025	1.0 (0.99 to 1.0)	0.48	0.99 (0.98 to 0.99)	< 0.001
Frequency, median daily sessions[a] (per one extra session of mobilisation)	1.14 (1.10 to 1.18)	< 0.001	1.63 (1.51 to 1.76)	< 0.001	1.11 (1.10 to 1.13)	< 0.001
Total amount[b] (per extra 5 minutes of mobilisation activity over intervention period)	0.99 (0.98 to 0.99)	< 0.001	0.98 (0.98 to 0.99)	< 0.001	0.99 (0.99 to 0.99)	< 0.001

a Frequency of out-of-bed activity is derived from nursing and physiotherapist data.
b Amount (minutes) of out-of-bed activity is derived from physiotherapist data only.
All analyses are adjusted for age and baseline NIHSS score. Model 1 examines the association of an extra 5 minutes of out-of-bed activity per day, while model 2 includes the association of an extra 5 minutes of out-of-bed activity over the intervention period (to account for differences in length of hospital stay). The binary OR refers to walking 50 m vs. not walking 50 m at the 3-month follow-up. That is, one extra session leads to fewer days required to walking 50 m, while an extra 5 minutes daily session time is associated with more days to walking 50 m.

improved odds of walking 50 m unassisted (66%, 95% CI 53% to 80%; $p < 0.001$). The pattern was similar when the alternative model (model 2) was used.

Adverse outcomes: when exploring associations between intervention characteristics and death within 3 months, the only characteristic that reduced the odds of death was increasing session frequency (*Table 13*). Non-fatal AEs showed less consistent associations with dose characteristics. It should be noted that relatively few mobility and neurological SAEs were reported.

Classification and regression tree analysis

The CART analysis exploring the relationships with a good functional outcome (mRS score of 0–2) is outlined in *Figure 13*. This includes timed first mobilisation, intervention frequency, daily amount, patient

TABLE 13 Association of intervention characteristics with death and non-fatal SAEs

	Deaths		Non-fatal SAEs		Fatal or non-fatal neurological SAEs		Fatal or non-fatal immobility SAEs	
Features	Binary OR (95% CI)	*p*-value	IRR (95% CI)	*p*-value	IRR (95% CI)	*p*-value	IRR (95%)	*p*-value
Model 1								
TTFM (per extra hour of time)	0.99 (0.98 to 1.00)	0.07	1.0 (0.99 to 1.00)	0.71	1.0 (0.99 to 1.00)	0.45	1.00 (0.99 to 1.00)	0.59
Frequency, median daily sessions[a] (per one extra session of mobilisation)	0.78 (0.70 to 0.88)	< 0.01	0.99 (0.95 to 1.03)	0.55	0.89 (0.84 to 0.95)	< 0.01	0.94 (0.87 to 1.01)	0.11
Daily amount, median[b] (per extra 5 minutes of mobilisation activity)	0.96 (0.89 to 1.04)	0.30	0.96 (0.93 to 0.99)	0.01	1.03 (0.99 to 1.08)	0.17	0.94 (0.89 to 1.00)	0.06
Model 2								
TTFM (per extra hour of time)	0.99 (0.98 to 1.00)	0.07	0.99 (0.99 to 1.00)	0.81	1.00 (0.99 to 1.00)	0.35	1.00 (0.99 to 1.00)	0.59
Frequency, median daily sessions[a] (per one extra session of mobilisation)	0.79 (0.71 to 0.88)	< 0.01	0.96 (0.93 to 0.99)	0.02	0.93 (0.88 to 0.98)	< 0.01	0.91 (0.85 to 0.97)	< 0.01
Total amount[b] (per extra 5 minutes over intervention period of mobilisation activity)	0.99 (0.98 to 1.00)	0.06	1.00 (1.00 to 1.00)	0.49	1.00 (0.99 to 1.00)	0.32	1.0 (0.99 to 1.00)	0.41

a Frequency is derived from nursing and physiotherapist data.
b Amount (minutes) is derived from physiotherapist data only.
All analyses are adjusted for age and baseline NIHSS score. Model 1 examines the association of an extra 5 minutes of out-of-bed activity per day, while model 2 includes the association of an extra 5 minutes of out-of-bed activity over the intervention period (to account for differences in length of hospital stay). Immobility-related SAEs included deep-vein thrombosis, pulmonary embolism, pressure sores, pneumonia and urinary tract infection. Neurological SAEs include stroke progression and recurrent stroke.
Adapted with permission from Bernhardt *et al.* (2016).[33] This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

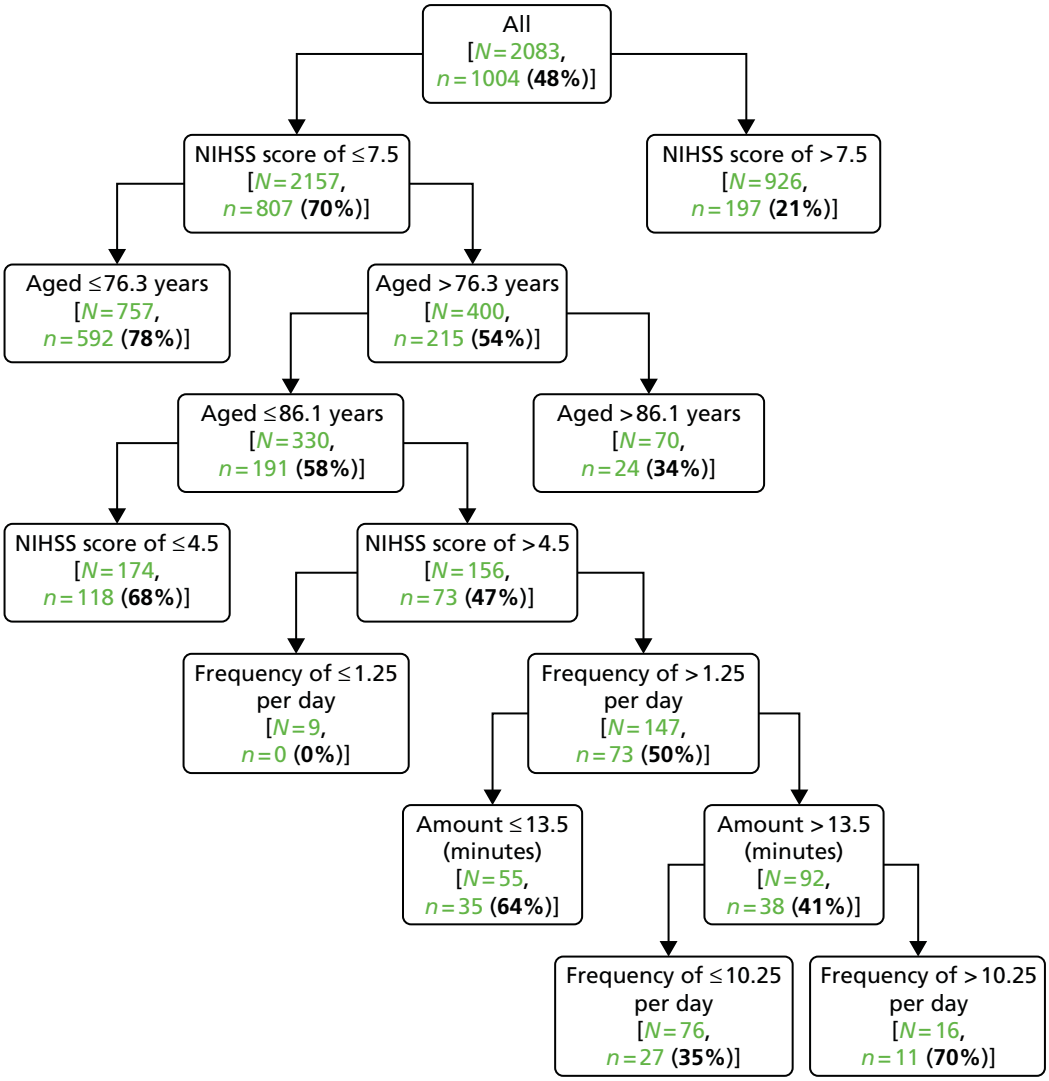


FIGURE 13 Classification and Regression Tree (CART1) advanced analysis investigating associations between dose and patient characteristics and the odds of a favourable outcome (mRS score of 0–2). Each box shows the number (*N*) with the headline characteristic plus the number of them (%, highlighted in bold) with a favourable outcome (mRS score of 0–2). Terms used include median daily number of out-of-bed sessions per day (frequency), median daily out-of-bed activity session time (amount), age (years) and stroke severity (NIHSS). Frequency is derived from nursing and physiotherapist data and amount (minutes) is derived from physiotherapist data only. Adapted with permission from Bernhardt *et al.* (2016).[33]

age, baseline NIHSS, stroke subtype, treatment with thrombolysis and randomisation group. We observed good to excellent performance with a training data set (ROC 0.78) and ROC of 0.77 in a testing data set. The relative contribution of each variable is shown on the figure. In this analysis, treatment group was not an important discriminator of patient outcome. As expected, younger patients and those with low baseline NIHSS scores had a higher probability of a favourable outcome. The association with intervention characteristics was evident further down the analysis tree. For example, at terminal node 4 (see *Figure 13*) the greater probability of favourable outcome was associated with more frequent short mobilisation sessions (no more than 13.5 minutes). Mobilisation frequency also split the tree for terminal nodes 5 and 6, suggesting that more frequent sessions to achieve a higher dose was associated with an improved odds of a good outcome. In further CART analysis (*Figures 14–16*), TTFM intervention frequency and amount plus group are all influential splitters in these models.

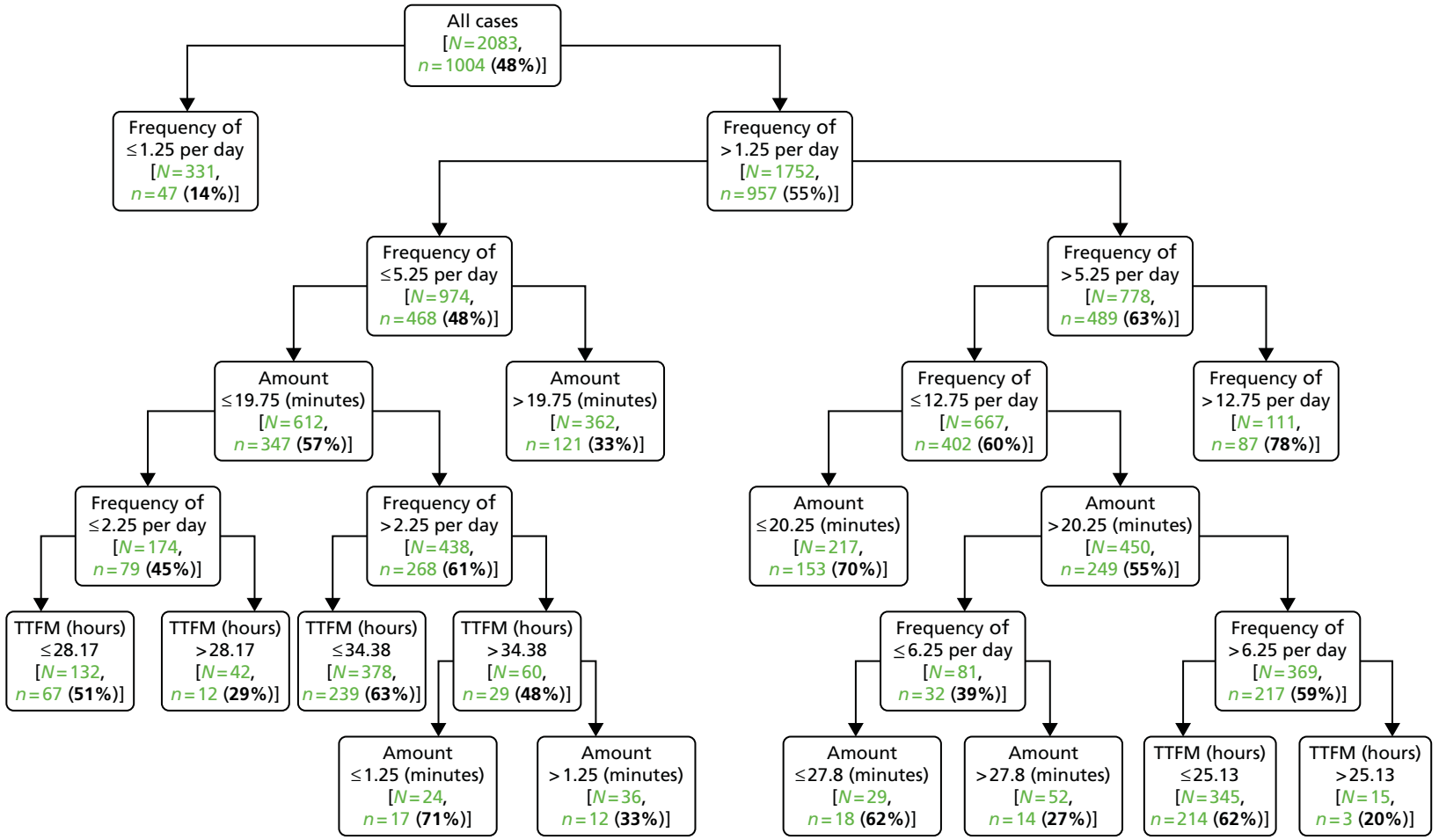


FIGURE 14 CART2. CART advanced analysis investigating associations between dose characteristics and odds of a favourable outcome (mRS score of 0–2). Each box shows the number (*N*) with the headline characteristic plus the number of them (%, highlighted in bold) with a favourable outcome (mRS score of 0–2). Terms used are TTFM, median daily number of out-of-bed sessions per day (frequency) and median daily out-of-bed activity session time (amount). Frequency is derived from nursing and therapist data and amount (minutes) is derived from physiotherapist data only. Note: the model performed well with 'training' and 'testing' and ROC results were 0.78 and 0.69, respectively. The relative importance of each characteristic was frequency (100%), daily amount (32%) and TTFM (28%). CART2 shows that frequency of out-of-bed activity is an important splitter in the model, with higher frequency and lower amounts of out-of-bed activity generally associated with better outcome. Adapted with permission from Bernhardt *et al.* (2016).[33] Copyright © 2016 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (CC BY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

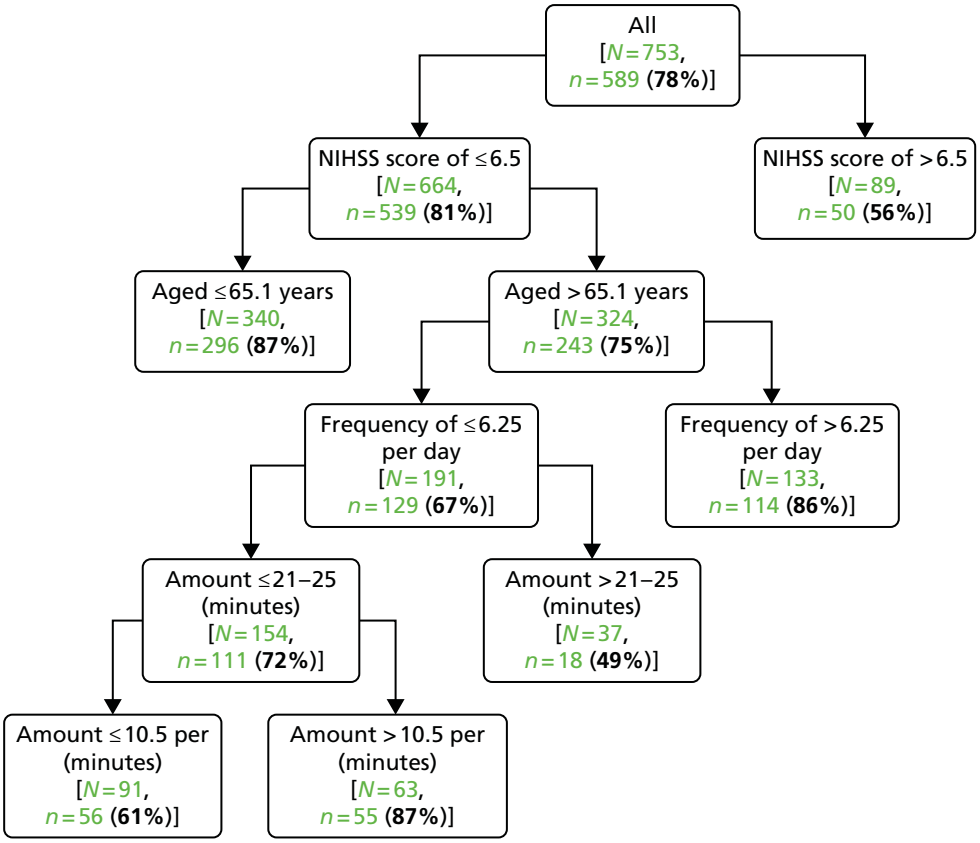


FIGURE 15 CART3. Further exploration of terminal node one from CART1 (NIHSS score of ≤ 7.5, aged ≤ 76.3 years). This CART investigates associations between dose characteristics, patient characteristics and treatment with favourable outcome (mRS score of 0–2). Each box shows the number (*N*) with the headline characteristic plus the number of them (%, highlighted in bold) with a favourable outcome (mRS score of 0–2). Variables include TTFM, median daily number of out-of-bed sessions per day (frequency) and median daily out-of-bed activity time (amount), age, baseline NIHSS, stroke type and rtPA treatment. Note: the 'training' and 'testing' ROC results were 0.68 and 0.60, respectively. Relative importance of each characteristic: frequency (100%), NIHSS score (99%), daily amount (84%), age (83%), infarct/haemorrhage (10%), TTFM (4%) and VEM group (3%). CART3 indicates that higher frequency and lower amounts are important splitters in the model. Adapted with permission from Bernhardt *et al.* (2016).[33]

Finally, we repeated the regression analysis for the UC group alone because of the potential risk of any unmeasured confounding by treatment group (additional unmeasured differences between treatment groups). This repeat analysis (*Table 14*) indicated that the same factors were important within the UC group alone.

Specific UK perspectives

Figure 6 also showed the delivery of VEM in different regions. This shows the successful delivery of VEM versus UC regimes in the UK sites. In general, the differences between VEM and UC were slightly less marked in the UK than other regions but, overall, UK sites delivered a 2.6-hour reduction in TTFM, with three more out-of-bed activity sessions per day. This equated to 15 minutes more out-of-bed activity per day or 90 minutes during the intervention period.

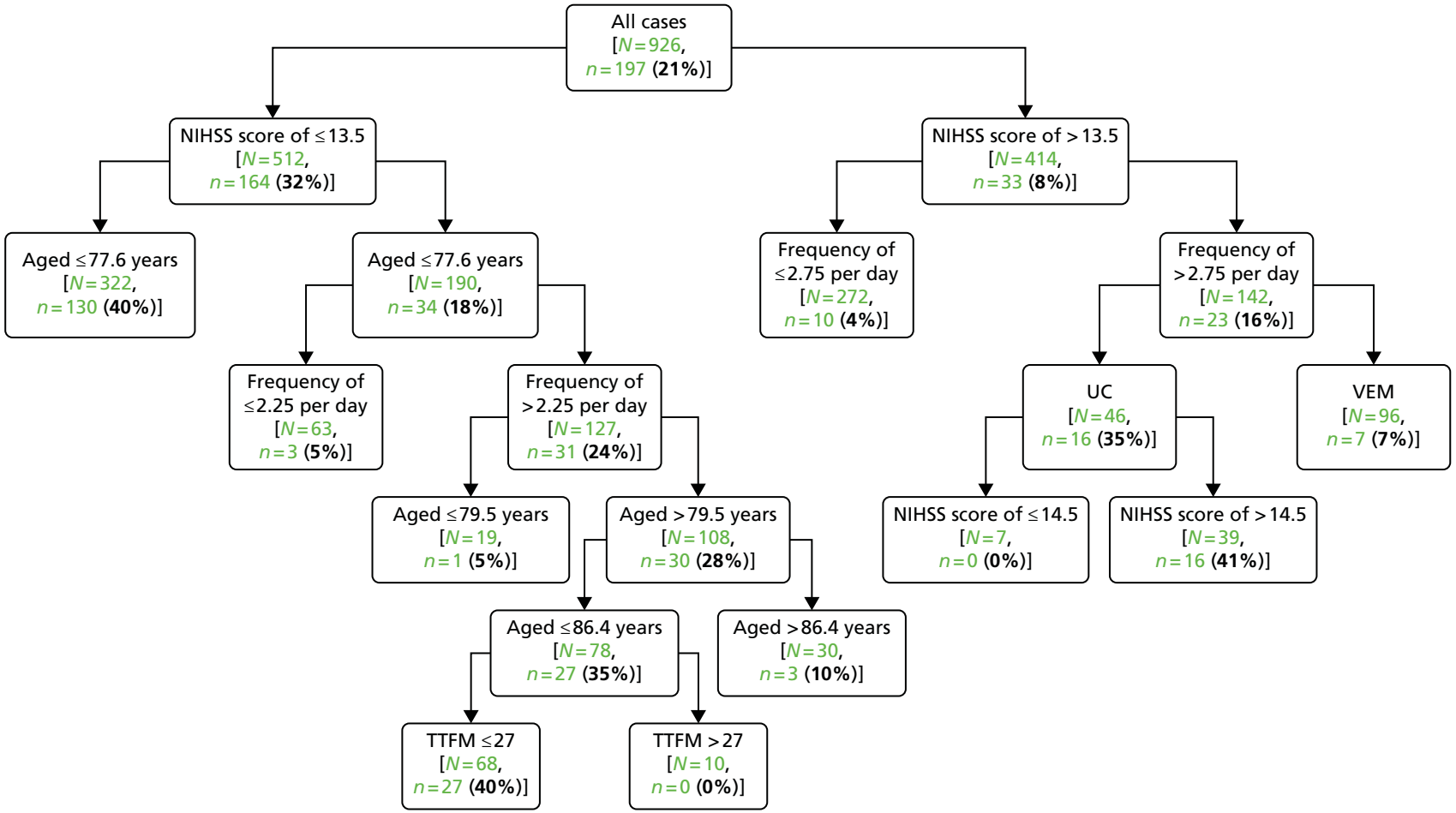


FIGURE 16 CART4. Further explanation of terminal node eight from CART1 (NIHSS score of > 7.5). This CART investigates associations between dose characteristics, patient characteristics and treatment with favourable outcome (mRS score of 0–2). Each box shows the number (*N*) with the headline characteristic plus the number of them (%, highlighted in bold) with a favourable outcome (mRS score of 0–2). Variables include TTFM, median daily number of out-of-bed sessions per day (frequency) and median daily out-of-bed activity time (amount), age, baseline NIHSS, stroke type and rtPA treatment Note: the 'training' and 'testing' ROC results were 0.81 and 0.71, respectively. Relative importance of each characteristic: NIHSS score (100%), frequency (95%), age (45%), TTFM (27%), VEM group (21%), daily amount (6%) and infarct/haemorrhage (2%). CART4 indicates that higher session frequency is associated with higher proportion of patients with a favourable outcome. Adapted with permission from Bernhardt *et al.* (2016).[33] Copyright © 2016 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (CC BY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

TABLE 14 Regression analysis for UC group only, showing an association of increased out-of-bed session frequency and reduced TTFM with the odds of a favourable outcome

Features	Favourable outcome OR (95% CI)	*p*-value
Model 1		
TTFM (per extra hour of time)	0.98 (0.97 to 0.99)	0.002
Frequency, median daily sessions (per one extra session of out-of-bed activity)	1.12 (1.04 to 1.21)	0.004
Daily amount, median (per extra 5 minutes of out-of-bed activity)	1.00 (0.93 to 1.07)	0.942
Model 2		
TTFM (per extra hour of time)	0.98 (0.97 to 0.99)	0.002
Frequency, median daily sessions (per one extra session of out-of-bed activity)	1.15 (1.06 to 1.23)	0.0001
Total amount (per extra 5 minute minutes of out-of-bed activity over intervention period)	0.98 (0.98 to 0.99)	0.001

For every 5-minute reduction in total amount spent in out-of-bed activity there was a significant increases in the odds of a favourable outcome (model 2). These findings are consistent with those reported for the whole group (see *Table 12*) and confirm the important association of frequency on achieving a favourable outcome.
All analyses are adjusted for age and baseline stroke severity (NIHSS). Favourable outcome = mRS score of 0–2.
Model 1 examines the association of TTFM, median daily session frequency and an extra 5 minutes per day with a favourable outcome.
Model 2 examines the association of an extra 5 minutes over the intervention period (up to 14 days or discharge, whichever is sooner) with the odds of a favourable outcome.
Frequency is derived from nursing and physiotherapist data and amount (minutes) is derived from physiotherapist data only.

The subgroup analyses of the primary outcome (alive and independent at 3 months) and secondary outcome (death at 3 months) are outlined in *Figures 10* and *11*. The UK results were indistinguishable from those of Asia and Australia and New Zealand, with none of the regional subgroups achieving a statistically significant level of interaction ($p > 0.05$).

Economic analysis

An economic analysis was not funded in the context of this NIHR grant. The economic analysis plan[34] had anticipated further analysis would be important in the event of the VEM intervention having a positive effect. As this was not the case, these analyses are not yet completed.

Meta-analysis of early mobilisation trials

In our systematic review of similar RCTs, we identified eight eligible trials[25,27,31,60–64] that currently have data available. Of these eight trials (2618 participants), AVERT provided the most information (2104 participants).

The median (range) delay to starting mobilisation after stroke was 18.5 (13.1–43) hours in the EM group and 33.3 (22.5–71.5) hours in the delayed group. The median difference within trials was 12.7 (4–45.6) hours. Other differences in intervention varied between trials. In at least four trials, the EM group also received more time in therapy or mobilisation activity.

Complete 3-month outcome data were available for 2542 (97%) participants (*Figure 17*). Compared with delayed mobilisation, EM showed non-significant increases in the odds of death or dependency (OR 1.10, 95% CI 0.94 to 1.29), death (OR 1.27, 95% CI 0.95 to 1.70) and a decreased odds of experiencing any complication (OR 0.89, 95% CI 0.73 to 1.08).

Repeating the analysis using a random-effects model did not alter these conclusions. There was substantial heterogeneity of intervention but the average TTFM was not significantly related to the odds of death or dependency or death alone (test for subgroup differences was $p = 0.35$ and $p = 0.19$, respectively).

Figure 17 shows the number (events) with death or poor outcome (mRS score of 3–6) at 3 months after stroke of the total number of patients (total) allocated to the EM (experimental) or delayed (control) mobilisation group. Results are presented as the OR (95% CI) of the early versus delayed mobilisation group.

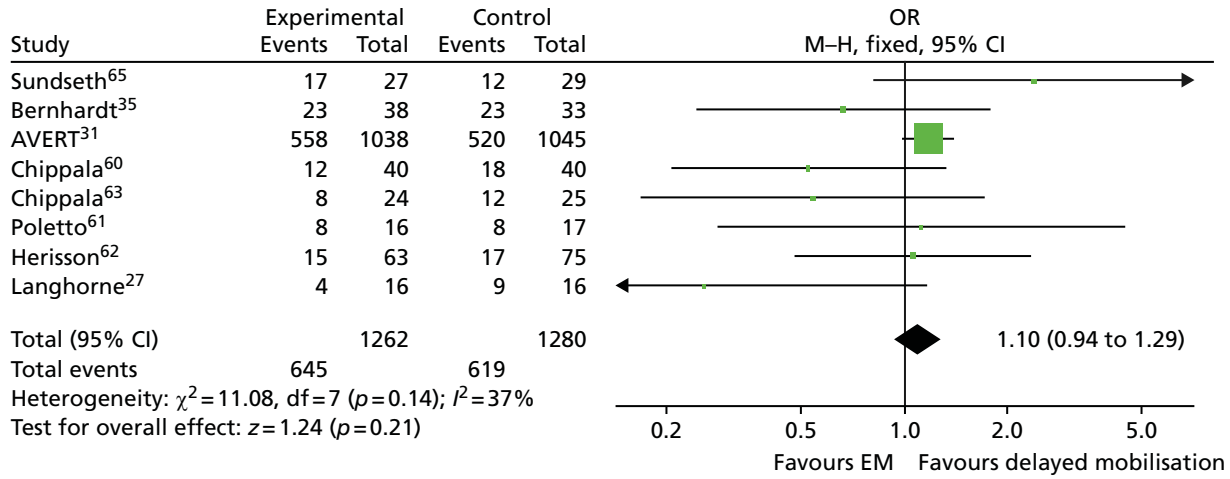


FIGURE 17 Meta-analysis of EM trials: early vs. delayed mobilisation in acute stroke patients. df, degrees of freedom; M–H, Mantel–Haenszel.

Chapter 5 Discussion

This project met its initial objectives of effectively delivering our VEM protocol with a resulting change in practice.[30] We observed earlier, more frequent and higher dose (amount of) out-of-bed mobility in terms of sitting, standing and walking activity. However, the unexpected feature was that the VEM intervention reduced the odds of a favourable outcome at 3 months after stroke compared with lower-dose UC, which started, on average, 5 hours later. It should be recognised that the outcome of this trial was observed against a background of a very high level of recovery overall. Despite having more than one-quarter of participants aged > 80 years and almost half recording a moderate or severe stroke, almost 50% had a favourable outcome in terms of independence at 3 months. Across both groups, the case fatality rate averaged only 8%. A further point to note is that HRQoL did not differ significantly between groups at the 12-month follow-up.

The prespecified subgroup analysis raised the possibility that patients with more severe stroke and those with intracerebral haemorrhage may do less well with VEM, but there was no statistically significant interaction across these subgroups. Exploration of case fatality within subgroups also suggested the possibility that intracerebral haemorrhage patients may be at higher risk of harm, but these analyses had wide CIs and were not statistically significant. Although the trial was not powered to detect differences between subgroups, these apparent differences may raise potentially important questions and warrant further investigation. In particular, there have been concerns[10,23,24,32,64] about the safety of VEM in frailer individuals (older patients and those with intracerebral haemorrhage). It is notable that patients receiving tissue plasminogen activator had outcomes that were similar to those who did not receive this treatment, hence there is no evidence that EM is particularly harmful in the context of thrombolysis.

The results of this trial are intriguing particularly because the results of smaller trials suggested that early, frequent and higher-dose VEM would result in a favourable outcome.[25–28] A favourable outcome for the VEM group was also observed in a similar pilot trial in the UK[27] and in an individual-patient meta-analysis of two small EM trials.[28] However, a non-significant increase in unfavourable outcome was reported in a more recent small Norwegian trial[65] comparing VEM (< 24 hours) versus later mobilisation (> 24 hours). It is not yet clear if the results of the current AVERT are simply providing greater precision around these smaller estimates or if there is some qualitative difference in the nature of the intervention.

We were surprised to observe the very low rates of AEs overall and, in particular, the low rates of immobility-related complications. We had anticipated that VEM would result in fewer immobility-related complications but there were no statistically significant differences between groups. One explanation could be that UC now includes a sufficiently early onset of mobilisation, which may have reduced the risk of immobility-related complications compared with historical comparisons. The modern high-quality stroke unit care in the hospitals taking part in AVERT included 75% of patients undergoing out-of-bed mobilisation within 24 hours and only 7% of patients remaining in bed for > 48 hours. It is striking that UC in the present trial (median TTFM of 22 hours) was substantially lower than in previous studies (> 30 hours). Unfortunately, we do not have access to directly comparable information from other acute stroke trials.

The AVERT is, to our knowledge, the largest acute stroke rehabilitation trial to date with a complex intervention provided by existing clinical staff. Our aim had been to undertake a trial that met the exacting quality standards of a drug or device trial but that was sufficiently inclusive to be relevant to routine practice. We achieved our aim of high intervention fidelity and complete primary end-point follow-up in > 99% of participants. We also succeeded in careful characterisation of the intervention and UC and successfully adjudicated a large number of safety outcomes. We aimed to enhance the external validity of the trial by establishing it within routine hospital care across five countries. For these reasons, we believe the results of the trial are robust and provide important new evidence. The detailed description of the dose characteristics allowed us to proceed with an exploration of the interaction between intervention and outcome.

Exploratory analysis

The prespecified exploratory analysis found a consistent association between the odds of recovery with independence (mRS score of 0–2) at 3 months and some intervention characteristics. These were irrespective of treatment group and were independently seen in the control group as well as in the combined group analysis. The odds of a favourable outcome increased with mobilisation frequency: by 13% with each additional session per day of out-of-bed activity. In contrast, an increasing amount of time spent in out-of-bed activity was associated with a reduced odds of a favourable outcome when keeping constant intervention frequency and TTFM. The same pattern of potential beneficial effect with increasing the frequency (but not the amount) of out-of-bed activity was seen consistently across most of the clinical and safety analyses.

The purpose of these prespecified analyses was to unpack the primary results of the VEM intervention, which was essentially complex in nature.[66] The VEM intervention was defined in terms of TTFM but also included more frequent and higher-dose out-of-bed activity. The dose–response analysis suggests that increasing the frequency of mobilisation may help reduce disability and immobility while, in contrast, increasing the total time of out-of-bed activity in the early phase after stroke was associated with poorer outcomes. In summary, the exploratory analyses indicate that short, frequent sessions may be preferable for many stroke patients early after stroke.

The potential impact of TTFM was less clear probably because of a relatively compact distribution of this variable; therefore, the optimal time to commence out-of-bed activity is still uncertain. Animal studies have suggested that very high-dose training in the early post-stroke phase may increase brain lesion volume,[67] but were not associated with the behavioural outcomes that are analogous to disability measures. However, conflicting results have also been reported in which moderate exercise reduced lesion volume and protected ischaemic tissue against secondary damage.[68–70]

The conventional multivariable analysis was supplemented with the CART analysis. This was to provide an independent exploration using methodology based on different assumptions. Even when we included patient characteristics that strongly predict outcome after stroke, such as age and stroke severity, the intervention characteristics had an important role in defining patient groups. In particular, in patients with more severe stroke (NIHSS score of > 13), more frequent mobilisation sessions were associated with a more favourable outcome.

Particular strengths of this exploratory study are that the dose–response analysis was prespecified in the expectation that we would need to explore the intervention in greater detail. One potential criticism of the exploratory analysis is the possibility that the intervention protocol could have influenced our findings because the intervention dose was titrated to stroke severity and patients with less severe stroke would get a higher intervention dose. However, to exclude this possibility we repeated the analysis within the UC group alone and found the same relationship between TTFM, mobilisation frequency and the amount of time in mobilisation. In particular, when you maintain mobilisation time and the median minutes of out-of-bed activity is constant, more frequent sessions in the control group were associated with an improved odds of a good outcome of 1.12 (95% CI 1.04 to 1.21; $p = 0.004$). *Table 12* outlines the association between TTFM and a marginally improved outcome and the lack of association between total amount of out-of-bed activity and outcome. Although the intervention protocol may have provided some confounding of the observed associations, it cannot explain all the findings observed. The key observations from the exploratory analysis are as follows:

1. Mobility interventions embedded within routine care and delivered in the acute phase can influence a patient's long-term outcomes. It is very important that triallists carefully define and measure these aspects of care.
2. The generally accepted philosophy that more practice is always better requires reconsideration particularly early after stroke.
3. The frequency of mobility may be more important than other aspects of delivery. This requires further investigation.

Strengths and limitations

We found that using a screening log that captured a broad range of reasons for non-recruitment added to the collection of demographic data.[38] Similarly, the use of a model to explicitly explore generalisability was informative. However, a large screening log can collect only a limited amount of demographic and clinical information and it is quite possible that other factors influenced our recruitment.

The AVERT is largest acute stroke rehabilitation trial with a complex intervention provided by existing clinical staff. We achieved our aim of undertaking a trial that met the exacting quality standards of a drug or device trial but that was relevant to routine practice. It was established within routine hospital care across five countries. We achieved complete primary end-point follow-up in > 99% of participants and successfully adjudicated a large number of safety outcomes. For these reasons, we believe that the results of the trial are robust and provide important new evidence.

We believe that we achieved our aim of high intervention fidelity (the extent to which staff adheres to treatment protocols). This is a challenging part of trials of a complex intervention.[66] Within AVERT, sites were monitored on their delivery of VEM and UC and successful delivered differences in the intervention.[36] We provided trial protocols to treating staff who were trained in protocol intervention. Site initiation sessions were used to discuss and resolve local barriers and we provided reminders, decision tools and ongoing support for queries. The use of site champions and arrangements such as coleadership from a nurse and a physiotherapist were seen to be positive factors. It seems advisable that trial protocols for complex interventions include an implementation plan with the approach that would be used to achieve, measure and monitor acceptable fidelity standards. We also succeeded in careful characterisation of the VEM intervention and UC. Establishing fidelity provides confidence that the intervention was properly tested and that the outcome results can be correctly attributed to the intervention.

Despite these efforts, it is notable that UC TTFM had changed over time (but not the other aspects of mobilisation, frequency and total time of out-of-bed activities). Although UC was not standardised, careful trial monitoring allowed tracking of UC over time and provided reassurance that time to start mobilisation differences between groups were maintained. Mobilisation dose did not change over time. Although the reasons for earlier UC TTFM over time are unclear, it remains possible that many staff assumed that commencing earlier was safe and/or effective, and this unconsciously influenced their delivery of UC over time. External influences include more recent recommendations in clinical practice guidelines to mobilise early and intensively.

The AVERT has several limitations which are largely due to the large study size. In a large international trial it is difficult to collect more than a small amount of information about potential modifying or confounding factors such as physiological variations. It was also difficult to collect detailed information about staff–patient interactions. As AVERT was a pragmatic trial, we were not prescriptive about UC and it is interesting to note that TTFM appeared to change substantially during the period of the trial. This occurred despite independent monitoring, reporting and feedback to the study sites about the nature of their UC and VEM. As a result of the changes in standard mobilisation practice, by the end of the trial approximately two-thirds of patients receiving UC had started out-of-bed activity within 24 hours of stroke onset. It is uncertain if this change is a consequence of contamination from the trial protocol or the result of changing attitudes to EM over time, as was reflected in some recent clinical guidelines.

Comparison with other trials

Our systematic review was dominated by AVERT but confirmed that EM (within 48 hours) was not associated with improved outcomes compared with delayed mobilisation. However, it should be noted that in the majority of trials included in the review, mobilisation commenced within 48 hours of stroke onset rather than 24 hours. Furthermore, it is important to recognise that despite public education efforts to

improve identification of stroke and seek early medical attention, patients are often delayed in reaching hospital. Generally, discussion of the timing of commencement of mobilisation is relative to time of admission which may be significantly later than time of stroke onset. All AVERT data are relative to time of stroke onset. In view of the complexity of the intervention and the uncertainty around the effect estimates, more detailed analyses are warranted.

Implications for practice

Delivery of AVERT required commitment to delivering a VEM intervention that needed strong interdisciplinary collaboration between nurses and physiotherapists and some modification of current care models. The qualitative analysis contributed some unique insights into what factors may be important to successful teams aiming to deliver a complex multidisciplinary intervention.

The results of AVERT should influence clinical practice. Most clinical practice guidelines had recommended EM[10] but there was little specific advice provided. We would conclude that our high-dose frequent mobilisation protocol within 24 hours of stroke onset was less effective than UC and should not be routinely applied. However, because the UC protocol is also complex in nature, and increasingly featured a shift to early onset mobilisation, then it is over-simplistic to simply advise UC. When mobilisations are attempted early after stroke, short, frequent mobilisations are associated with better outcomes. Further exploration of this data set is essential and, as outlined in our published statistical analysis plan, we propose further dose–response analyses to explore the effect of dose rehabilitation on clinical and safety outcomes.

Implications for research

The AVERT results challenge several previous assumptions and raise several important research questions that can be listed as follows:

1. What should mobilisation entail: are there aspects that can safely be implemented?
2. Who should we target for early intervention? In particular, are there patient groups for whom EM is safe or unsafe?
3. Are important physiological and molecular changes induced by early physical activity in ischaemic tissue? In particular, does early active mobilisation induce early neurological changes that are detrimental to recovery?
4. How do we best describe the characteristics of EM? We still lack a clear and widely accepted descriptive framework for EM activities.

The AVERT group are planning a new trial to unpack the combined influences of mobilisation frequency and dose (duration).

A more detailed meta-analysis of existing trials is also needed to explore the limitations of the AVERT results in the context of other similar trials.

Acknowledgements

Contributions of authors

Professor Peter Langhorne was the chief investigator for the UK, was the lead grant holder and compiled, drafted and revised the manuscript.

Professor Olivia Wu, **Professor Helen Rodgers**, and **Professor Ann Ashburn** were grant holders and revised the manuscript.

Professor Julie Bernhardt was principal investigator for the international trial, was a grant holder and revised the manuscript.

Other contributions

We particularly want to thank the participants in this trial, and their families, who have supported this study. We are very grateful to all the AVERT collaboration investigators for their hard work and dedication and the many individuals not specifically mentioned in the report.

We specifically want to thank Sheila Lennon and Michael Power for their role in developing the Northern Ireland phase of the trial. We also received exceptional support from Jan Chamberlain (Florey Institute) and the office staff at the University of Glasgow (Beverly Armstrong, Louise Craig, Fiona Graham, Lynn Legg, Rosemary Morrison, Heather Moorhead, Lorraine O'Donohue, Susan Rogers and Myra Smith).

Patient and public involvement

Stroke survivors formed part of the original trial development team in Australia. The AVERT protocol was developed in consultation with service users and a stroke survivor (Ms Brooke Parsons) who took part in monthly management committee meetings. Ms Parsons sat on both the Management and Trial Steering Committee for the AVERT project and was a regular attendee at meetings. Ms Parsons also attended the AVERT triallists' meeting held in Glasgow on 16 April 2015 to precede the presentation of the 3-month outcome results at the inaugural European Stroke Organisation conference in Glasgow on 17–19 April 2015.

Information newsletters with trial updates and stroke survivor stories were provided to all interested trial participants twice a year. These were posted, e-mailed or delivered to people involved in the trial by the blinded assessors. In addition, there was a website that could be accessed at any time to obtain more up-to-date information about news of the trial (www.florey.edu.au/very-early-rehabilitation-trial-avert).

Data sharing statement

A considerable number of analyses are currently under way for this trial data set. As these analyses are completed we anticipate that data will become available to the scientific community with as few restrictions as feasible. All deidentified trial data in *Chapter 2* have been archived in secure facilities for a minimum period of 7 years. The options of data sharing arrangements were not available at the trial commencement and were not included in participant consent processes.

AVERT collaboration group

Management Committee

Julie Bernhardt (chairperson), Leonid Churilov, Janice Collier, Helen Dewey, Geoffrey Donnan, Fiona Ellery, Peter Langhorne, Richard Lindley, Marjory Moodie, Brooke Parsons (consumer representative) and Amanda Thrift.

Trial Steering Committee

Geoffrey Donnan (cochairperson), Helen Dewey (cochairperson), Julie Bernhardt, Peter Langhorne, Richard Lindley, Amanda Thrift, Marjory Moodie, Brooke Parsons (consumer representative) and main investigators (MIs) from all participating hospitals.

International advisors

Bent Indredavik, Anne Loege and Torunn Askim.

Data Monitoring Committee

Phillip Bath (University of Nottingham, Nottingham, UK; chairperson), Christopher Bladin (Box Hill Hospital, Melbourne, VA, Australia), Christopher Reid (Monash University, Melbourne, VA, Australia), Stephen Read (Royal Brisbane and Women's Hospital, Melbourne, VA, Australia) and Cathy Said (Austin Health, Melbourne, VA, Australia).

Outcomes Committee

Sandy Middleton (Australian Catholic University, Sydney, NSW, Australia; chairperson), Judith Frayne (Alfred Hospital, Melbourne, VA, Australia) and Velandai Srikanth (Monash Health, Melbourne, VA, Australia).

Country leaders and grant holders

Australia: Julie Bernhardt (National Health and Medical Research Council: Helen Dewey, Julie Bernhardt, Geoffrey Donnan, Amanda Thrift, Robert Carter and Richard Lindley), (National Health and Medical Research Council: Julie Bernhardt, Geoff Donnan, Richard Lindley, Amanda Thrift, Peter Langhorne, Marjory Moodie, Helen Dewey and Leonid Churilov).

UK: Peter Langhorne (Chest Heart and Stroke Scotland: Peter Langhorne, Olivia Wu, Julie Bernhardt, Matthew Walters Claire Ritchie and Lorraine Smith), (The Stroke Association: Peter Langhorne, Olivia Wu, Anne Ashburn, Helen Rodgers and Julie Bernhardt), (HTA: Peter Langhorne, Anne Ashburn, Julie Bernhardt, Helen Rogers and Olivia Wu).

Northern Ireland: Sheila Lennon (Northern Ireland Chest Heart and Stroke: Sheila Lennon, Michael Power and Julie Bernhardt).

Singapore: Shahul Hameed (Singhealth: Shahul Hameed, Ratnagopal Pavanni, Peter Lim, Julie Bernhardt and Dawn Tan).

Statistics and data management

Leonid Churilov, Tim Brewer, Janice Collier, Nick Haritos, Edwin Leong, Cecilia Li, Caesar NayWin, Marcus Nicol, Liudmyla Olenka and Li Chun Quang.

Health economics

Marjory Moodie, Robert Carter, Silvia Hope, Lauren Sheppard, Kiusiang Tay-Teo and Olivia Wu.

Cognition

Toby Cumming and Thomas Linden.

Trial Coordinating Centres

The Florey Institute of Neuroscience and Mental Health, Melbourne, VA, Australia. Karen Borschmann, Jan Chamberlain, Janice Collier, Toby Cumming, Fiona Ellery, Teresa Occhiodoro, Helen Palfreeman, Tara Purvis, Bernadette Sirgo, Nick Tiliacos, John Van Holsteyn and Henry Zhao.

University of Glasgow, Glasgow, UK. Beverly Armstrong, Louise Craig, Fiona Graham, Lynn Legg, Rosemary Morrison, Heather Moorhead, Lorraine O'Donohue, Susan Rogers and Myra Smith.

University of Central Lancashire, Preston, UK. Denise Forshaw and Jane Fitzgerald.

List of AVERT collaborators, countries and recruitment at each participating hospital

Figures in parentheses are the number of patients recruited by the centre. MIs are listed first for each site. Some investigators worked across multiple sites, but they are listed for one site only.

Australia

Austin Hospital (253): E Hibbert, R Melling, S Petrolo, T Purvis, H Williamson (MIs), P Adams, L Augoustakis, S Batcheler, S Berney, V Cobani, B Cohen, H Dewey, S Gangi, N Giofre, C Gordon, L Hegarty, M Hindson, F Horvath, S Kalinowski, A Kleine, S Kramer, J Lawrence, S Lindquist, N Logan, A Macdonell, J Matlioski, N McDonough, S McLennan, M McNamee, L Miller, C Nall, E Nelson, K Ng, Z Nicholas, C Nunn, K Owen, E Plant, L Proud, D Quah, K Rodway, S Sertori, V Sheldon, L Sherry, S Speare, K Stansfeld, N Studden, Z Teoh, L Twist, G Velupillai, L Walker, K Wall, A Warwick, R Wharrie, J Wilson, H Worboys and D Young. **Royal Perth Hospital (149):** J Ancliffe (MI), M Bryant, B Doran, M Field, P Fogliani, A Haber, G Hankey, D Hendrie, V Jackaman, A Jacobsen, S Jose, R Lim, R Louis, S Nanthakumar, S Pain, A Power, B Rappeport, J Reynolds, L Smith, S Tombe, A Wesseldine and T West. **The Royal Melbourne Hospital (95):** K Clarke, H Maccanti, L Marr, S Plumb, J Quiney, L Werner (MIs), E Abeykoon, W Apirutvorrachod, L Attard, S Behanan, D Brown, K Buchanan, D Butler, M Camac, S Davis, D Diocera, N Gan, C Gendre, J Germaine, P Hand, L Maurenbrecher, J McCulloch, S Mcritchie, M Ong, R Pachett, L Pesavento, H Power, R Reilly, M Sawers, G Silva, C Stevens, L Taylor, T Timms, M Ugalde, A Vardy, J Wallace, S Walsh, E Whatley and E Winter. **Frankston Hospital (90):** M Baxter, M Davis, L Sundararajan (MIs), E Butler, K Caspers, E Coulter, S Shaw, F Kent, H Lack, F Leavold, J Lord, J Martin-Francisco, R Mohanraj, R Nelson, T O'Neill, R Otto, J Parker, V Rees and B Stevens. **Westmead Hospital (84):** R Chen (MI), RI Lindley, J Bindra, R Dongre, N Downey, M Ferris, L Gibson, R Gonzalez, M Kinniburgh, M Lazaridou, D McCormack, R Singh, A Stepney and Y Tria. **Geelong Hospital (74):** K Bainbridge, B Killey, R Sheedy (MIs), O Aitchison, L Bray, K Clatworthy, S Coghill, M Collins, L Cornwall, J Dow, P Gates, S Gillett, N Johnson, S Joseph, K Kopelke, R Lam, R Levy, N Lloyd, S Logan, G McPherson, M Newth, C Parsons, K Powles, M Rebis, T Samakowidic, L Sanders, S Savickas, J Shrimpton, H Smith, L Smith, J Spehr, J Summers, G Taylor, M Thackeray and B Wilkinson. **The Alfred (42):** K Richardson (MI), J Frayne, E Barber, L Bode, A Brakey, K Chand, P Christin, G Crook, D Delrosario-Kelly, R Descallar, A Deutsch, S Easo, M Farquhar, P Fergus, J Ford, E Hamson, M Hlaing, E Hope, J Lacivita, J Laurenson, K Lock, N Ly, K McKay, C Mill,

K Moloney, L Price, Tristan Terry, A Tyers, S Willems and R Woolstencroft. **Flinders Medical Centre (40):** N Crawshaw, J Luker, C Wood, S Choat (MIs), C Archer, D Benham, M Billinger, M Bronca, S Curchin, C Dickie, M Dixon, D Douglass, M Enomoto, K Ernst, L Fries, S George, E Green, L Hamilton, Z Harris, T Heard, G Hunt, N Jamieson, M Mackenzie, H McKearney, B Oermann, C O'Reilly, T Pearson, N Reid, L Rodda, D Scutcheon, C Simons, R Smith, L Tait, J Troake and D Usher. **Western Hospital (37):** L Mackey, T Wijeratne (MIs), C Abela, S Ashoka, C Chen, T Cheng, V Chong, S Cooke, A Fok, L Galang, C Grant, S Karageorge, K Kat, L Keo, B Lee, A Luscombe, J Mackay, M Minett, J Mizen, P Nim, N Nunlist, V Patel, M Pathirage, A Paton, M Pombuena, N Rathnayake, L Rhodes, M Sequeira, S Smart, S Somaratne, N Sta Maria, L Talbot and R Tecle. **Epworth Richmond (23):** M Shannon, R Gerraty (MIs), S Allen, R Boyle, N Fatchen, N Hendley, A Hyde, M Inal, P Kalubowilage, M Laverde, K Lawless, A McFadyen, K Peters, C Pugh, C Qin, J Robertson, S Smee, R Tomlinson, V Wang, F Williams, D Woolley and R Yawieriin. **St George Hospital (23):** N Austin, S Pomfret, M Tinsley (MIs), L Allport, C Ang, L Armitage, E Blundell, A Courtney, M Dela Costa, T Devi Thapa, P Diwakar, M Dulleh, J Francis, P Cic, G Gellie, C Gill, D James, S Lee, T Mai, K Majcher, C Mawson, G Newton, N Qiu, E Ragonton, L Roberts, H Saitamis, L Stanwell, L Ting, P Xu and L Yin. **Albury Hospital (23):** V Crosby (MI), K Broadhead, J Church, R Collins, K Everitt, M Fisher, K Hochmuth, N Jones, A Lieschke, E McCarthy, C McGlone, D Morey, D Neilson, S Spry and M Vile. **Nambour General Hospital (20):** R Grimley, D Rowley (MIs), I Rosbergen, E Ahern, L Anderson, J Boreham, R Devin, R Doolan, M Dyke, L Griffiths, K Guest, D Hecita, N Kendal, J Koltermann, M Lacy, S Lebeter, D Lloyd, M Matthews, C McAuley, A Pollock, M Pyke, T Rogers, S Street, G Styles, A Tampiyappa, J Trinder, T Verral, K Walker and C White. **Sir Charles Gairdner Hospital (15):** T Beckwith, L Cormack (MIs), J Arriagada, C Babenschneider, D Blacker, S Bennett, S Connor, J Cowmeadow, N Daniel, G Edmonds, M Faulkner, M Garcia-Vega, K Kruger, B Martial, P McGinley, H Mountford, V Riley, N Smith, F Stepan, S Tilley and S Whisson. **Warrnambool Base Hospital (15):** P Groot (MI), J Bailey, K Ballinger, C Bell, B Camilleri, C Charnley, D Crabbe, S Crossland, N Edirimanna, C Fitzgerald, C Gibbins, J Gibbs, K Hirst, A Kennedy, E Klose, K McDowall, S Miller, R Morgan, A Noonan, M North, M Oliver, K Richards, T Russell, N Scott, A Shlanski and A Traynor. **West Gippsland Hospital (12):** S Smith (MI), R Adams, C Banks, K Burke, S Hewat, B McKenna, M McKimmie, L Polmear, M Traumanis and S Whiteman. **St Vincent's Hospital (12):** V Bramah, R Errey, M Halpin, V Molan, D Wheelwright, N Wilson, W Zhang (MIs), M Bakshi, S Bracher, M Bryant, W Byrnes, T Denton, N DeVries, P Fay, P Galbraith, T Gallaher, O Haidar, K Holgate, K Hozack, N Jackson, S Kipps, S Lerner, R Marcus, R Merheb, C Naismith, G Nolan, R Odelli, K Page, P Sangvatanakul, T Simpson, P van Vliet, K Walch, S Walker and T Yasue. **Wyong Public Hospital (11):** G Auld (MI), R Baker, K Cousins, M Fairbrother, K Hutchinson, M Maclean, E Maher, D Mills, S Ohlback, J Sturm, M Tooth and J Watkins. **The Wesley Hospital (9):** J Cramb (MI), P Atkinson, J Conrad, D Fichera, S Follent, C Gilbert, M Herzig, S Kohler, S McCracken, L Nunan, S Roberts, J Shelley, S Varendorff and A Wills. **Calvary Mater Newcastle Hospital (8):** A Moore, A Robertson (MIs), J Britton, A Burgess, T Coates, J Croft, E Greening, J Holland, P O'Brien and R Strong. **Wodonga Hospital (8):** L Tighe (MI), S Bilston, J Black, K De Rivera, I Dwyer, S Gissane, K Heckenberg, S Jackson, A Maclagan, L O'Hare, H Patel, J Pearce, C Scanlan, K Seymour, M Symington, A Tyers, A Waite and K Wiesner. **Belmont Hospital (5):** O Katalinic, M Spear (MIs), P Brown, E Difuntorum, S Gilbert, J Henderson, D James, H Janssen, E Lane, S Lowndes, D Smith, S Thompson, D Weaver, S Weston and S Wright. **Wollongong Hospital (4):** S Cox, C Tse (MIs), J Adrian, M Doughty, J Kok, R McGrath, T Morris, A Pickup, E Ray, R Richardson, M Sims, C Thompson, K Trinh, N Walton and F Whittaker. **Gosford Hospital (2):** P Andersen (MI), J Burrows, M Dawson, D Griffiths, G Harris, P Kavalieros, B O'Brien, K Roberts, J Watkins and C Whyatt.

New Zealand

Auckland City Hospital (189): A McRae, G Wavish (MIs), F Anos, J Armstrong, E Au, A Barber, C Bates, M Bertulfo, A Boggs, F Burgess, K Cassels-Brown, M Chiu, S Dass, N Duff, J Farrell, W Foster, D Fuertez, C Gadhvi, S George, A Green, L Harvey-Fitzgerald, L Hau, L Hayward, D Holman, K Huggins, M Jacobs, A John, H Kaur, T Lagerstedt, J Lee, R Llenes, L Lyons, S Magandi, M Martin, S Mathew, T Mathew, D McKellar, E Moss, KL Nand, K Nicol, F Peterson, A Prasad, K Quick, E Revell, S Roy, J Ryan, N Samadi, B Scrivener, J Slow, S Tharakan, J Torrens, E van Bysterveldt, C Villaluz and S Yang.

Malaysia

UKM Medical Centre (123): Katijjahbe MA (MI), Ai Sing G, Azlina A, Azmi MI, Efri MH, Fadilah AZ, Fathuddeen H, Haryani H, H Hussien, Izuani M, ZC Man, Man Ying C, Mashitoh KM, Noor Azah A, Norlinah MI, Norliza I, Ravinder KB, Rohaizah R, Rosnita K, Rozita A, Safwan J, R Sahathevan, Shahrul I, Sharifah SM, Tan HJ, Wan Nafisah WY, YL Yee, Zaharah MA and Zunaidah AS.

Singapore

Singapore General Hospital (128): D Tan, MT Ahmad, S Hameed (MIs), MFB Bakari, J Britto, JJ Chen, S Choo, M Faizal, FK Fong, S Hong, J Ja'afar, Z Ke, G Koh, CK Lee, YF Lee, P Lim, GM Lim, SH Ninhadi, G Ong, T Pei Pei, V Penero, N Rahim, P Ratnagopal, K Saleh, HC Seow, E Sim, CK Tan, PY Tay, I Teo, S Thilarajah, PHJ Wong, WP Wong and S Yeap.

UK

Forth Valley Royal Hospital (65): M Macleod (MI), A Anderson, K Armstrong, K Baird, D Balfour, M Boyd, J Cameron, C Carswell, C Clanachan, L Cuthill, I Devoy, S Forsyth, J Gavin, M Hughes, E Marr, S McAuley, E McCagherty, K McCallum, N McDonald, C McGhee, TA McIntyre, L Noonan, A Smart and R Walshe. **Yeovil District Hospital (61):** D Neal (MI), J Allison, G Ball, S Board, H Brunt, C Buckley, C Carroll, D Hayward, T Hutchinson, E Jones, E Keeling, E Marsh, N Mead, H Smith, C Vickers, B Williams-Yesson and D Wood. **York Hospital (54):** J Coyle, M Keeling (MIs), L Ackroyd, C Brown, K Donnan, N Dyer, H Green, G Kilbride, C Nicholson and M Porteous. **Royal Victoria Infirmary (35):** S Louw (MI), A Annamalai, A Barkat, S Crawford, M Fawcett, D Harvey, V Hogg, A Hughes, J Kemp, J Morrison, K Storey and T Thompson. **Aberdeen Royal Infirmary (33):** J Furnace, MJ Macleod (MIs), J Bell, K Bennett, M Bruce, R Clarke, H Cowie, H Gow, J Irvine, A Joyson, S MacDonald, A Macvicar, N Murphy and J Robertson. **Royal Bournemouth Hospital (32):** C Gordon, J Kwan, L Redpath, K Saunders (MIs), J Bell, R Burrow, C Clarke, C Dickson, G Hann, M Heath, S Heath, A Hewett, R Humphrey, B Longland, A Orpen, C Ovington, J Page, E Rogers and K Toombs. **Imperial College Healthcare, St Mary's Hospital (29):** R Howes, A Lacey, P Meakin (MIs), D Ames, S Banerjee, E Beranova, S Berry, MJ Burke, V Cassama, K Collins, J Crow, A Dunne, C Gomez, A Hawkins, K Hellier, SA Howard, A Kar, E Lambert, H Lee, C Mandri, J Moye, E Murtagh, J Pushpa-Rajah, J Richardson, T Sachs, J Stilwell, V Tilley, P Wilding and N Wilson. **Wishaw General Hospital (28):** E Feely, S Kirk (MIs), P Cassidy, A Chalmers, C Duguid, N Hughes, J Hutton, K Lapsley, J Lee, A Murray, L Weir and M Whitelaw. **Monklands Hospital (26):** M Barber, D Esson (MIs), H Armit, C Devlin, R Duncan, C Forman, K Frame, L Hogg, J Lee, P McLeod, R McWhinney, J Porter, M Purves and L Snowball. **Ulster Hospital (25):** B Wroath (MI), L Fearson, M Gibson, S Gillespie, N Ignatius, T Kane, J Kwant, M Matthews, C McCallion, C McConville, M McDowell, C McNally, L Moore, P Murphy, A Nesbitt, J Newell, M Power, E Reid and K Robinson. **Royal Devon and Exeter Hospital (23):** C Charnley, M James (MIs), S Bacon, N Booth, A Bowring, L Boxall, J Burt, J Cageao, N Green, K Gupwell, S Keenan, H Kingwell, M Kryszkowska, J Mortimore, B Peace and C Roughan. **Queen Elizabeth The Queen Mother Hospital (21):** G Gunathilagan, J Sampson, G Thomas (MIs), T Allen, G Dane, K Harris, S Hart, SA Jones, M Reader, J Sampson and G Thomas. **Antrim Area Hospital (18):** P Browne, C McGoldrick, D Mullan (MIs), P Adair, J Armstrong, E Beggs, I Bell, C Edwards, L Gilligan, C Kelly, M Kennedy, J Kurian, L Leal, A McAtamney, E McKay, E Rogan, M Smyth, E Wiseman and J Vahidassr. **Wansbeck General Hospital (18):** C Price, V Riddell (MIs), E Bendix, K Craig, R Davison, A Harrison and A Smith. **Blackpool Hospital (17):** V Green (MI), K Ashton, W Barkhuizen, A Daniel, C Dickinson, H Durdu, D Eastwood, H Goddard, R Hodkin, J Howard, C Jeffs, S Joyce, C Kelly, G Kerr, J Lanes, B Magnall, M McMahon, M Moody, S Patton, R Taylor and A Watson. **North Tyneside General Hospital (17):** K Mitchelson, L Mokoena (MIs), L Aird, R Lakey, J Murdy, K Nelson and G Storey. **Belfast City Hospital (15):** R McGeown, S Tauro (MIs), R Brady, D Holland, M Kinnaird, L Maltman, D Martin, K McCord, S McKenna, C Morgan, C Shannon, A Steele and I Wiggam. **Harrogate District Hospital (15):** S Appleby, S Brotheridge, M Prescott (MIs), P Bagot, D Baston, C Bennett, J Featherstone, C Hare, A McCluskey, S Wade and R Worton. **St Mary's Hospital, Isle of Wight (13):** E Hakim, J Herman, T Norman (MIs), L Beale, E Buckley, K Byrne, M Gasior, B Robles, C Smallwood, S Stevens, M Thomas and V Williams. **Nevill Hall Hospital (12):** K Buck (MI), S Armstrong, V Brice, A Edwards, S Gething, A Griffiths, T Hills, D Howells, S Langdon, S Moseley, G Powell, G Reynolds, B Richard, E Scott, R White and J Zebedee. **Western Infirmary (10):** M Walters (MI), J Alexander, L Brand,

E Colquhoun, A Hill, D Macartney, H MacDonald, B Manak, H Morgan and C Ritchie. **South Tyneside District Hospital (8):** H Hunter (MI), T Blair, M Duffy, J Graham, J Scott, T Vu and P Yorston. **Calderdale Royal Hospital (7):** A Nair (MI), I Shakir, C Button, M Friend, J Greig, B Hairsine, S Wade and S Williamson. **St George's Hospital (7):** G Cloud (MI), T Adedoyin, N Dayal, S Gawned, R Ghatala, N Jeyaraj, L Kerin, L Montague, C Orefo, J O'Reilly, J Styles, S Trippier, C Watchurst and F Watson. **North Devon District Hospital (6):** J Hunt, R Latif (MIs), C Barrett, J Cox, F Hammonds, K Quick, K Robinson, A Skinner and C Vernon. **Royal Infirmary of Edinburgh (6):** S Burgess, T Elder-Gracie (MIs), C Browne, W Cameron, V Coleman, C Fulgencio, L Gibson, P Halliday, D Heaney, L Main, K McGavin, G Mead, F Proudfoot, A Redpath, C Rodger and S Scott. **Hexham General Hospital (5):** K. Robinson. **Crosshouse Hospital (3):** K Mason (MI), L Baxter, A Bryce, M Halkett, J Halliday, A McAllister, M McGuiness, M Munro, A Robb, A Thompson, B Tougher, J Weadon and J Young. **Daisy Hill Hospital (1):** C Douglas (MI), M McParland, S Boyle, B Byrne, L Comiskey, J Gilpin, S Gilpin, A Harris, S Harshaw, J Haughey, F McArdle, L McConnell, E McEneaney, M Millar, M Murphy and J Tilley.

References

1. Langhorne P, Sandercock P, Prasad K. Evidence-based practice for stroke. *Lancet Neurol* 2009;**8**:308–9. https://doi.org/10.1016/S1474-4422(09)70060-2
2. Gilligan AK, Thrift AG, Sturm JW, Dewey HM, Macdonell RA, Donnan GA. Stroke units, tissue plasminogen activator, aspirin and neuroprotection: which stroke intervention could provide the greatest community benefit? *Cerebrovasc Dis* 2005;**20**:239–44. https://doi.org/10.1159/000087705
3. Stroke Unit Trialists Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev* 2007;**4**:CD000197.
4. Sandercock P, Counsell C, Gubitz G, Tseng MC. Antiplatelet therapy for acute ischaemic stroke. *Cochrane Database Syst Rev* 2008;**3**:CD000029. https://doi.org/10.1002/14651858.CD000029.pub2
5. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, *et al.* Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014;**384**:1929–35. https://doi.org/10.1016/S0140-6736(14)60584-5
6. Balami JS, Sutherland BA, Edmunds LD, Grunwald IQ, Neuhaus AA, Hadley G, *et al.* A systematic review and meta-analysis of randomized controlled trials of endovascular thrombectomy compared with best medical treatment for acute ischemic stroke. *Int J Stroke* 2015;**10**(Suppl. 8):1168–78. https://doi.org/10.1111/ijs.12618
7. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, *et al.* Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurol* 2007;**6**:215–22. https://doi.org/10.1016/S1474-4422(07)70036-4
8. Langhorne P, de Villiers L, Pandian JD. Applicability of stroke-unit care to low-income and middle-income countries. *Lancet Neurol* 2012;**11**:341–8. https://doi.org/10.1016/S1474-4422(12)70024-8
9. Indredavik B, Bakke F, Slordahl SA, Rokseth R, Hâheim LL. Treatment in a combined acute and rehabilitation stroke unit: which aspects are most important? *Stroke* 1999;**30**:917–23. https://doi.org/10.1161/01.STR.30.5.917
10. Bernhardt J, English C, Johnson L, Cumming TB. Early mobilization after stroke: early adoption but limited evidence. *Stroke* 2015;**46**:1141–6. https://doi.org/10.1161/STROKEAHA.114.007434
11. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. *Lancet* 2011;**377**:1693–702. https://doi.org/10.1016/S0140-6736(11)60325-5
12. Allen C, Glasziou P, Del Mar C. Bed rest: a potentially harmful treatment needing more careful evaluation. *Lancet* 1999;**354**:1229–33. https://doi.org/10.1016/S0140-6736(98)10063-6
13. Mutin-Carnino M, Carnino A, Roffino S, Chopard A. Effect of muscle unloading, reloading and exercise on inflammation during a head-down bed rest. *Int J Sports Med* 2014;**35**:28–34. https://doi.org/10.1055/s-0033-1343407
14. Langhorne P, Stott DJ, Robertson L, MacDonald J, Jones L, McAlpine C, *et al.* Medical complications after stroke: a multicenter study. *Stroke* 2000;**31**:1223–9. https://doi.org/10.1161/01.STR.31.6.1223
15. Bamford J, Dennis M, Sandercock P, Burn J, Warlow C. The frequency, causes and timing of death within 30 days of a first stroke: the Oxfordshire Community Stroke Project. *J Neurol Neurosurg Psychiatry* 1990;**53**:824–9. https://doi.org/10.1136/jnnp.53.10.824

16. Govan L, Langhorne P, Weir CJ, Stroke Unit Trialists Collaboration. Does the prevention of complications explain the survival benefit of organized inpatient (stroke unit) care? Further analysis of a systematic review. *Stroke* 2007;**38**:2536–40. https://doi.org/10.1161/STROKEAHA.106.478842

17. Bernhardt J, Dewey H, Thrift A, Donnan G. Inactive and alone: physical activity within the first 14 days of acute stroke unit care. *Stroke* 2004;**35**:1005–9. https://doi.org/10.1161/01.STR.0000120727.40792.40

18. West T, Bernhardt J. Physical activity in hospitalised stroke patients. *Stroke Res Treat* 2012;**2012**:813765. https://doi.org/10.1155/2012/813765

19. Murphy TH, Corbett D. Plasticity during stroke recovery: from synapse to behaviour. *Nat Rev Neurosci* 2009;**10**:861–72. https://doi.org/10.1038/nrn2735

20. Johansson BB. Brain plasticity and stroke rehabilitation. The Willis lecture. *Stroke* 2000;**31**:223–30. https://doi.org/10.1161/01.STR.31.1.223

21. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: what can be learned from animal models? *Neurorehabil Neural Repair* 2012;**26**:923–31. https://doi.org/10.1177/1545968312440745

22. Pekna M, Pekny M, Nilsson M. Modulation of neural plasticity as a basis for stroke rehabilitation. *Stroke* 2012;**43**:2819–28. https://doi.org/10.1161/STROKEAHA.112.654228

23. Skarin M, Bernhardt J, Sjöholm A, Nilsson M, Linden T. 'Better wear out sheets than shoes': a survey of 202 stroke professionals' early mobilisation practices and concerns. *Int J Stroke* 2011;**6**:10–5. https://doi.org/10.1111/j.1747-4949.2010.00534.x

24. Olavarría VV, Arima H, Anderson CS, Brunser AM, Muñoz-Venturelli P, Heritier S, Lavados PM. Head position and cerebral blood flow velocity in acute ischemic stroke: a systematic review and meta-analysis. *Cerebrovasc Dis* 2014;**37**:401–8. https://doi.org/10.1159/000362533

25. Bernhardt J, Dewey H, Thrift A, Collier J, Donnan G. A very early rehabilitation trial for stroke (AVERT): phase II safety and feasibility. *Stroke* 2008;**39**:390–6. https://doi.org/10.1161/STROKEAHA.107.492363

26. Cumming TB, Thrift AG, Collier JM, Churilov L, Dewey HM, Donnan GA, *et al.* Very early mobilisation after stroke fast tracks return to walking: further results from the phase II AVERT randomized controlled trial. *Stroke* 2011;**42**:153–8. https://doi.org/10.1161/STROKEAHA.110.594598

27. Langhorne P, Stott DJ, Knight A, Barer D, Bernhardt J, Watkins C. Very Early Rehabilitation or Intensive Telemetry after Stroke (VERITAS): a pilot randomised controlled trial. *Cerebrovasc Dis* 2010;**29**:352–360. https://doi.org/10.1159/000278931

28. Craig LE, Bernhardt J, Langhorne P, Wu O. Early mobilization after stroke: an example of an individual patient data meta-analysis of a complex intervention. *Stroke* 2010;**41**:2632–6. https://doi.org/10.1161/STROKEAHA.110.588244

29. Tay-Teo K, Moodie M, Bernhardt J, Thrift AG, Collier J, Donnan G, Dewey H. Economic evaluation alongside a phase II, multi-centre, randomised controlled trial of very early rehabilitation after stroke (AVERT). *Cerebrovasc Dis* 2008;**26**:475–81. https://doi.org/10.1159/000155984

30. Bernhardt J, Churilov L, Dewey H, Lindley R, Moodie M, Collier J, *et al.* for the AVERT Collaborators. Statistical Analysis Plan (SAP) for A Very Early Rehabilitation Trial (AVERT): An international trial to determine the efficacy and safety of commencing out of bed standing and walking training (very early mobilisation) within 24 h of stroke onset vs usual stroke unit care. *Int J Stroke* 2015;**10**:23–4. https://doi.org/10.1111/ijs.12423

31. The AVERT Trial Collaboration Group. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet* 2015;**386**:46–55. https://doi.org/10.1016/S0140-6736(15)60690-0

32. Bernhardt J, on behalf of the AVERT Investigators. Could upright posture be harmful in the early stages of stroke? – Author's Reply. *Lancet* 2015;**386**:1734–5. https://doi.org/10.1016/S0140-6736(15)00692-3

33. Bernhardt J, Churilov L, Ellery F, Collier J, Chamberlain J, Langhorne P, *et al.* on behalf of the AVERT Collaboration Group. Pre-specified dose response analysis for A Very Early Rehabilitation Trial (AVERT). *Neurology* 2016;**86**(Suppl. 23):2138–45. https://doi.org/10.1212/WNL.0000000000002459

34. Sheppard L, Dewey H, Bernhardt J, Collier JM, Ellery F, Churilov L, *et al.* on behalf of the AVERT Trial Collaboration Group. Economic Evaluation Plan (EEP) for A Very Early Rehabilitation Trial (AVERT): An international trial to compare the costs and cost-effectiveness of commencing out of bed standing and walking training (very early mobilization) within 24 hours of stroke onset with usual stroke unit care. *Int J Stroke* 2016;**11**(Suppl. 4):492–4. https://doi.org/10.1177/1747493016632254

35. Bernhardt J, Lindley RI, Lalor E, Ellery F, Chamberlain J, Van Holsteyn J *et al.* on behalf of the AVERT Collaboration Group. AVERT2 (a very early rehabilitation trial, a very effective reproductive trigger): retrospective observational analysis of the number of babies born to trial staff. *BMJ* 2015;**351**:h6432. https://doi.org/10.1136/bmj.h6432

36. van Wijk R, Cumming T, Churilov L, Donnan G, Bernhardt J. An early mobilization protocol successfully delivers more and earlier therapy to acute stroke patients: further results from phase II of AVERT. *Neurorehabil Neural Repair* 2012;**26**:20–6. https://doi.org/10.1177/1545968311407779

37. Luker JA, Craig L, Bennett L, Ellery F, Langhorne P, Wu O, Bernhardt J. Implementing a complex rehabilitation intervention in a stroke trial: a qualitative process evaluation of AVERT. *BMC Med Res Methodol* 2016;**16**:52. https://doi.org/10.1186/s12874-016-0156-9

38. Bernhardt J, Raffelt A, Churilov L, Lindley RI, Speare S, J. A, Katijjahbe MA, *et al.* on behalf of the AVERT Trialists' Collaboration. Exploring threats to generalisability in a large international rehabilitation trial (AVERT). *BMJ Open*. 2015;**5**:e008378. https://doi.org/10.1136/bmjopen-2015-008378

39. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;**19**:604–7. https://doi.org/10.1161/01.STR.19.5.604

40. Brott T, Adams H, Olinger C, Marler J, Barsan W, Biller J, *et al.* Measurements of acute cerebral infarction: A clinical examination scale. *Stroke* 1989;**20**:864–870. https://doi.org/10.1161/01.STR.20.7.864

41. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991;**337**:1521–6. https://doi.org/10.1016/0140-6736(91)93206-O

42. Briggs DE, Felberg RA, Malkoff MD, Bratina P, Grotta JC. Should mild or moderate stroke patients be admitted to an intensive care unit? *Stroke* 2001;**32**:871–6. https://doi.org/10.1161/01.STR.32.4.871

43. Simondson J, Goldie P, Brock K, Nosworthy J. The Mobility Scale for Acute Stroke patients: intra-rater and inter-rater reliability. *Clin Rehab* 1996;**10**:295–300. https://doi.org/10.1177/026921559601000406

44. Borg G. Perceived exertion as an indicator of somatic stress. *Scand J Rehabil Med* 1970;**2**:92–8.

45. Snaith RP, Constantopoulos AA, Jardine MY, McGuffin P. A clinical scale for the self-assessment of irritability. *Br J Psychiatry* 1978;**132**:164–71. https://doi.org/10.1192/bjp.132.2.164

46. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J* 1965;**14**:61–5.

47. Hawthorne G, Richardson J, Osborne R. The Assessment of Quality of Life (AQoL) instrument: a psychometric measure of health-related quality of life. *Qual Life Res* 1999;**8**:209–24. https://doi.org/10.1023/A:1008815005736

48. Collen FM, Wade DT, Bradshaw CM. Mobility after stroke: reliability of measures of impairment and disability. *Int Disabil Stud* 1990;**12**:6–9. https://doi.org/10.3109/03790799009166594

49. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, *et al.* The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;**53**:695–9. https://doi.org/10.1111/j.1532-5415.2005.53221.x

50. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. *BMJ* 2011;**342**:d40. https://doi.org/10.1136/bmj.d40

51. Howard G, Waller JL, Voeks JH, Howard VJ, Jauch EC, Lees KR, *et al.* A simple, assumption-free, and clinically interpretable approach for analysis of modified Rankin outcomes. *Stroke* 2012;**43**:664–9. https://doi.org/10.1161/STROKEAHA.111.632935

52. Churilov L, Arnup S, Johns H, Leung T, Roberts S, Campbell BC, *et al.* An improved method for simple, assumption-free ordinal analysis of the modified Rankin Scale using generalized odds ratios. *Int J Stroke* 2014;**9**:999–1005. https://doi.org/10.1111/ijs.12364

53. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, *et al.* Consolidated health economic evaluation reporting standards (CHEERS) statement. *BMJ* 2013;**346**:f1049. https://doi.org/10.1136/bmj.f1049

54. James G, Witten D, Hastie T, Tibshirani R. An Introduction to Statistical Learning with Applications. In James G, Witten D, Hastie T, Tibshirani R, editors. *An Introduction to Statistical Learning with Applications in R.* 1st edn. New York, NY: Springer Science and Business Media; 2013. p. 303. https://doi.org/10.1007/978-1-4614-7138-7_8

55. Kwakkel G. Impact of intensity of practice after stroke: issues for consideration. *Disabil Rehabil* 2006;**28**:823–30. https://doi.org/10.1080/09638280500534861

56. Bernhardt J, Thuy MN, Collier JM, Legg LA. Very early versus delayed mobilisation after stroke. *Cochrane Database Syst Rev* 2009;**1**:CD006187. https://doi.org/10.1002/14651858.CD006187.pub2

57. Brady MC, Stott DJ, Norrie J, Chalmers C, St George B, Sweeney PM, *et al.* Developing and evaluating the implementation of a complex intervention: using mixed methods to inform the design of a randomised controlled trial of an oral healthcare intervention after stroke. *Trials* 2011;**12**(Suppl. 1):168. https://doi.org/10.1186/1745-6215-12-168

58. Neergaard MA, Olesen F, Andersen RS, Sondergaard J. Qualitative description – the poor cousin of health research? *BMC Med Res Methodol* 2009;**9**:52. https://doi.org/10.1186/1471-2288-9-52

59. Nayer S, Stanley M. *Qualitative Research Methodologies for Occupational Science and Therapy*. London: Routledge; 2015.

60. Chippala P, Sharma R. Effect of very early mobilisation on functional status in patients with acute stroke: a single-blind randomized controlled trial. *Clin Rehabil* 2015;1–7.

61. Poletto SR, Rebello LC, Valenca MJM, Rossato D, Almeida AG, Brondani R, *et al.* Early mobilization in ischemic stroke: a pilot randomized trial of safety and feasibility in a public hospital in Brazil. *Cerebrovasc Dis Extra* 2015;**5**:31–40. https://doi.org/10.1159/000381417

62. Herisson F, Godard S, Volteau C, Le Blanc E, Guillon B, Gaudron M, SEVEL study group. Early sitting in ischemic stroke patients (SEVEL): a randomized controlled trial. *PLOS ONE* 2016;**11**:e0149466. https://doi.org/10.1371/journal.pone.0149466

63. Chippala P, Sharma R. Effect of Very early mobilisation on disability and adverse events in the first 3 months post stroke: a single-blind, randomisd controlled trial. *Int J Health Sci Res* 2015;**5**(Suppl. 10):166–74.

64. Bernhardt J, Indredavik B, Langhorne P. When should rehabilitation begin after stroke? *Int J Stroke* 2013;**8**:5–7. https://doi.org/10.1111/ijs.12020

65. Sundseth A, Thommessen B, Rønning OM. Outcome after mobilization within 24 hours of acute stroke: a randomized controlled trial. *Stroke* 2012;**43**:2389–94. https://doi.org/10.1161/STROKEAHA.111.646687

66. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex inter- ventions: the new Medical Research Council guidance. *BMJ* 2008;**337**:979–83.

67. Austin MW, Ploughman M, Glynn L, Corbett D. Aerobic exercise effects on neuroprotection and brain repair following stroke: a systematic review and perspective. *Neurosci Res* 2014;**8**:8–15. https://doi.org/10.1016/j.neures.2014.06.007

68. Egan KJ, Janssen H, Sena ES, Longley L, Speare S, Howells DW, *et al.* Exercise reduces infarct volume and facilitates neurobehavioral recovery: results from a systematic review and meta-analysis of exercise in experimental models of focal ischemia. *Neurorehabil Neural Repair* 2014;**28**:800–12. https://doi.org/10.1177/1545968314521694

69. Humm JL, Kozlowski DA, James DC, Gotts JE, Schallert T. Use-dependent exacerbation of brain damage occurs during an early post-lesion vulnerable period. *Brain Res* 1998;**783**:286–92. https://doi.org/10.1016/S0006-8993(97)01356-5

70. Dromerick AW, Lang CE, Birkenmeier RL, Wagner JM, Miller JP, Videen TO, *et al.* Very early constraint-induced movement during stroke rehabilitation (VECTORS): a single-centre RCT. *Neurology* 2009;**73**:195–201. https://doi.org/10.1212/WNL.0b013e3181ab2b27

71. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, *et al.* Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2016;**47**:e1–72. https://doi.org/10.1161/STR.0000000000000098

72. Herbert D, Lindsay MP, McIntyre A, Kirton A, Rumney PG, Bragg S, *et al.* Canadian stroke best practice recommendations: stroke rehabilitation practice guidelines, update 2015. *Int J Stroke* 2016;**11**(Suppl. 4):459–84. https://doi.org/10.1177/1747493016643553

73. Intercollegiate Stroke Working Party/Fifth Edition 2016/Royal College of Physicians, London. *Stroke Guidelines*. www.rcpLondon.ac.uk/guidelines-policy/stroke-guidelines (accessed 28 August 2017).

74. Stroke Foundation. *2017 Draft Guidelines*. 2017. URL: https://strokefoundation.org.au/What-we-do/Treatment-programs/Clinical-guidelines (accessed 28 August 2017).

Appendix 1 Project outputs

Publications

The main aspects of this project have already been published.

Bernhardt J, Lindley RI, Lalor E, Ellery F, Chamberlain J, Van Holsteyn J, *et al.* on behalf of the AVERT Collaboration Group. AVERT2 (a very early rehabilitation trial, a very effective reproductive trigger): retrospective observational analysis of the number of babies born to trial staff. *BMJ* 2015;**351**:h6432.

The AVERT Trial Collaboration Group. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet* 2015;**386**:46–55.

Bernhardt J, Raffelt A, Churilov L, Lindley RI, Speare S, Ancliffe J, *et al.* on behalf of the AVERT Trialists' Collaboration. Exploring threats to generalisability in a large international rehabilitation trial (AVERT). *BMJ Open* 2015;**5**:e008378.

Bernhardt J, Churilov L, Ellery F, Collier J, Chamberlain J, Langhorne P, *et al.* on behalf of the AVERT Collaboration Group. Pre-specified dose response analysis for A Very Early Rehabilitation Trial (AVERT). *Neurology* 2016;**86**(Suppl. 23):2138–45.

Bernhardt J, Churilov L, Dewey H, Lindley R, Moodie M, Colier J, *et al.* for the AVERT Collaborators. Statistical analysis plan (SAP) for A Very Early Rehabilitation Trial (AVERT): an international trial to determine the efficacy and safety of commencing out of bedstanding and walking training (very early mobilisation) within 24 h of stroke onset vs. usual stroke unit care. *Int J Stroke* 2015;**10**:23–4.

Luker JA, Craig L, Bennett L, Ellery F, Langhorne P, Wu O, Bernhardt J. Implementing a complex rehabilitation intervention in a stroke trial: a qualitative process evaluation of AVERT. *BMC Med Res Methodol* 2016;**16**:52.

Bernhardt J, Dewey H, Collier J, Thrift A, Lindley R, Moodie M, Donnan G. A Very Early Rehabilitation Trial (AVERT). *Int J Stroke* 2006;**1**(Suppl. 3):169–71.

Bernhardt J, Churilov L, Dewey H, Lindley R, Moodie M, Collier J, *et al.* for the AVERT Collaborators. Statistical Analysis Plan (SAP) for A Very Early Rehabilitation Trial (AVERT): an international trial to determine the efficacy and safety of commencing out of bed standing and walking training (very early mobilisation) within 24 h of stroke onset vs usual stroke unit care. *Int J Stroke* 2015;**10**:23–4.

The AVERT Trial Collaboration group, Bernhardt J, Langhorne P, Lindley RI, Thrift AG, Ellery F, *et al.* Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet* 2015;**386**:46–55.

Bernhardt J, AVERT investigators. Could upright posture be harmful in the early stages of stroke? - Author's reply. *Lancet* 2015;**386**:1734–5.

Bernhardt J, Lindley RI, Lalor E, Ellery F, Chamberlain J, Van Holsteyn J, *et al.* on behalf of the AVERT Collaboration Group. AVERT2 (a very early rehabilitation trial, a very effective reproductive trigger): retrospective observational analysis of the number of babies born to trial staff. *BMJ* 2015;**351**:h6432.

Bernhardt J, Churilov L, Ellery F, Collier J, Chamberlain J, Langhorne P, *et al.* on behalf of the AVERT Collaboration Group. Pre-specified dose response analysis for A Very Early Rehabilitation Trial (AVERT). *Neurology* 2016;**86**(Suppl. 23):2138–45.

Sheppard L, Dewey H, Bernhardt J, Collier JM, Ellery F, Churilov L, *et al.* on behalf of the AVERT Trial Collaboration Group. Economic Evaluation Plan (EEP) for A Very Early Rehabilitation Trial (AVERT): an international trial to compare the costs and cost-effectiveness of commencing out of bed standing and walking training (very early mobilization) within 24 hours of stroke onset with usual stroke unit care. *Int J Stroke* 2016;**11**(Suppl. 4):492–4.

Conference presentations

There have been a large number of conference presentations (> 30) by various members of the AVERT team. These included European Stroke Organisation Conference 2015 and 2016, International Stroke Conference 2015, 2016, Stroke Society of Australia 2014–16, and the UK Stroke Forum 2014–15.

Presentations to investigators, professional associations and UK stroke network

A large number of local and regional presentations were carried out and have been reported in the investigators newsletters. This has included presentations at the UK Stroke Forum (2011, 2012, 2013, 2014), local meetings (March 2013, April 2013, European Stroke congress 2013). In addition, we hosted two large UK contributor meetings in Glasgow in October 2013 and April 2015.

Consumers

We have disseminated the 3-month results for distribution from each hospital to the patients recruited. After the 12-month results are published, patients will be allowed to find out what group they were in (from the local hospital) and we will publish a final patient report. Alongside this, we plan to disseminate results to consumers via consumer organisations [e.g. the Stroke Association (UK) and the National Stroke Foundation (Australia)].

Media/social media

We have promoted and publicised the trial on social media [Twitter (www.twitter.com; Twitter, Inc., San Francisco, CA, USA), Facebook (www.facebook.com; Facebook, Inc., Menlo Park, CA, USA) and blogs].

Clinical guidelines

Two stroke clinical practice guidelines (USA,[71] Canada[72]) have recently changed. Updates of the UK[73] and Australian[74] guidelines are underway.

Clinical trials websites

The NIHR HTA and AVERT websites are up to date, with grant publications online. www.nets.nihr.ac.uk/projects/hta/120116 (accessed 28 August 2017).

www.gla.ac.uk/researchinstitutes/icams/staff/peterlonghorne/#/grants,researchinterests (accessed 28 August 2017).

www.florey.edu.au/very-early-rehabilitation-trial-avert (accessed 28 August 2017).

Appendix 2 Participating sites

Hospital site	Numbers recruited	Principal investigator
Australia	1043	
Austin Hospital	253	H Williamson
Royal Perth Hospital	149	J Ancliffe
Royal Melbourne Hospital	95	L Werner
Frankston Hospital	90	L Sundararajan
Westmead Hospital	84	R Chen
Geelong Hospital	74	R Sheedy
Alfred Hospital	42	K Richardson
Flinders Medical Centre	40	S Choat
Western Hospital	37	T Wijeratne
Albury Hospital	23	V Crosby
Epworth Hospital, Richmond	23	S Gerraty
St George Hospital	23	M Tinsley
Nambour Hospital	20	D Rowley
Warrnambool Hospital	15	P Groot
Sir Charles Gairdner Hospital	15	L Cormack
St Vincent's Hospital	12	W Zhang
West Glippsland Hospital	12	S Smith
Wyong Public Hospital	11	G Auld
The Wesley Hospital	9	J Cramb
Calvary Mater Newcastle	8	A Robertson
Wodonga Hospital	8	L Tighe
Belmont Hospital	5	M Spear
Wollongong Hospital	4	C Tse
Gosford Hospital	2	P Andersen
New Zealand	189	
Auckland Hospital	189	G Wavish
Singapore and Malaysia	251	
Singapore General Hospital	128	S Hameed
UKM Malaysia	123	MA Katijjahbe

APPENDIX 2

Hospital site	Numbers recruited	Principal investigator
UK	610	
Forth Valley Royal Hospital	65	M Macleod
Yeovil District Hospital	61	D Neal
York Hospital	54	M Keeling
Royal Victoria Infirmary	35	S Louw
Aberdeen Royal Infirmary	33	MJ Macleod
Royal Bournemouth	32	K Saunders
Imperial College Hospital (St Marys)	29	P Meakin
Wishaw General Hospital	28	S Kirk
Monklands Hospital	26	M Barbour
Ulster Hospital	25	B Wroath
Royal Devon & Exeter Hospital	23	C Charnley, *et al.*
Queen Elizabeth The Queen Mother Hospital	21	J Sampson, *et al.*
Antrim Area Hospital	18	D Mullan, *et al.*
Wansbeck General Hospital	18	C Price, *et al.*
Blackpool Hospital	17	V Green
North Tyneside General Hospital	17	L Mokoena, *et al.*
Belfast City Hospital	15	S Tauro, *et al.*
Harrogate District Hospital	15	S Brotheridge, *et al.*
St Mary's Hospital Isle of Wight	13	T Norman, *et al.*
Nevill Hall Hospital	12	K Buck
Western Infirmary	10	M Walters
South Tyneside District Hospital	8	H Hunter
Calderdale Royal Hospital	7	A Nair
London St George Hospital	7	G Cloud
North Devon District Hospital	6	R Latif, *et al.*
Royal Infirmary Edinburgh	6	T Elder-Gracie, *et al.*
Hexham General Hospital	5	K Robinson
Crosshouse Hospital	3	K Mason
Daisy Hill	1	C Douglas

Appendix 3 Protocol version 3

A phase 3, multicentre, randomised controlled trial

of very early rehabilitation after stroke (AVERT).

Protocol Version 3 – 25 April 2008

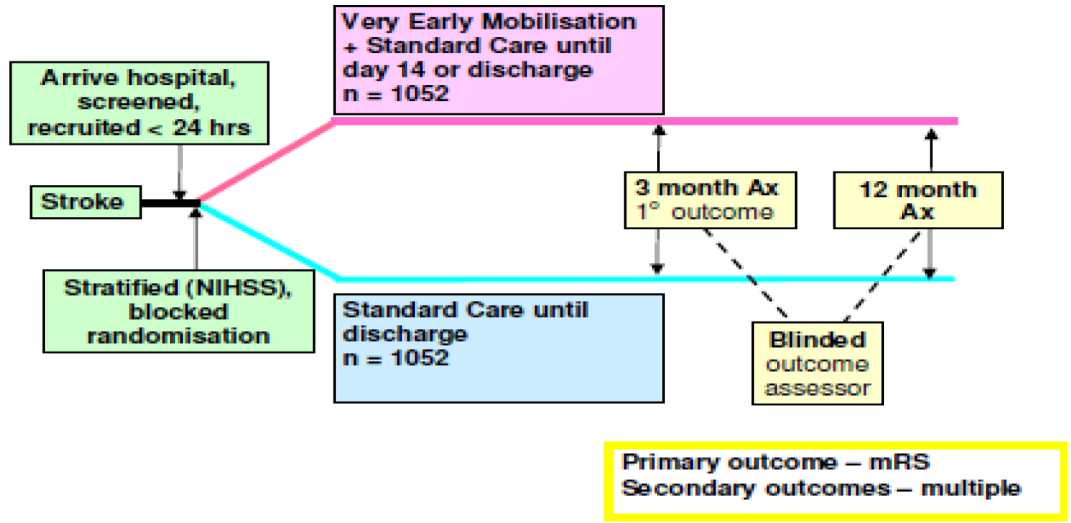
National Stroke Research Institute

Table of Contents

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

Management Committee

Associate Professor Julie Bernhardt (Chair)
Associate Professor. Helen M Dewey
Dr Amanda G Thrift
Dr Janice M Collier
Professor Geoffrey A Donnan
Professor Richard Lindley
Dr Leonid Churilov (Trial Statistician)
Fiona Ellery (Trial Manager)

International Advisors

Professor Peter Langhorne
Professor Bent Indredavik

Steering Committee

Associate Professor. Helen M Dewey (Co-Chairman)
Professor Geoffrey A Donnan (Co-Chairman)
Associate Professor Julie Bernhardt (Principle Investigator)
Professor Richard Lindley (Westmead Hospital, NSW)
Associate Professor Robert Carter (Health Economist, Deakin University) [Dr Marjorie Moodie will substitute for Professor Carter as required]
Brooke Parsons (Consumer)
Tara Purvis (Austin Health, Vic)
Jacqueline Ancliffe (Royal Perth Hospital, WA)
Heidi Maccanti /Samantha Plumb (Royal Melbourne Hospital, Vic)
Julie Luker (Flinders Medical Centre, SA)
Ruth Chen (Westmead Hospital, NSW)
Glen Auld (Wyong Hospital, NSW)
Michael Davis (Frankston Hospital, Vic)
Susan Smith (West Gippsland Hospital, Vic)
Andrea Moore (Newcastle Calvary Mater Hospital, NSW)
Jacky Cramb (Wesley Private Hospital, QLD)
Bruce Killey (Geelong Hospital, VIC)
Gemma Wavish (Auckland City Hospital, NZ)
Julie Sansom (Royal Hobart Hospital, TAS)
Leanne Cormack/Tracy Beckwith (Sir Charles Gairdner Hospital, WA)
Other members to be announced

Outcome Committee

Professor Sandy Middleton (Chairman)
Dr Judith Frayne
Dr Velandai Shrikanth

Data Safety Monitoring Committee (DMC)

Professor Phillip Bath (Chairman)
Professor Chris Bladin
Dr Chris Reid
Dr Stephen Read
Dr Cathy Said

Committee members can be contacted via the:

National Stroke Research Institute, Level 1, Neurosciences Building
Repatriation Hospital, 300 Waterdale Road, Heidelberg Heights
Victoria, Australia, 3081.
Phone: +613 9496 2888
Fax: +613 9496 2251
Email: avert@nsri.org.au

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 unexpected 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_____

21 References

1. World Health Organization. The World Health Report 2003. Geneva, Switzerland, 2003.
2. Bonita R. Epidemiology of stroke. *Lancet* 1992;339:342-344.
3. Wolfe C. The impact of stroke. *British Medical Bulletin* 2000;56:275-286.
4. Australian Institute of Health and Welfare (AIHW). Heart, stroke and vascular diseases - Australian facts 2001: Australian Institute of Health and Welfare, National Heart Foundation, National Stroke Foundation of Australia, 2001:108.
5. Dewey H, Thrift A, Mihalopoulos C, Carter R, Macdonell R, McNeil J, et al. The cost of stroke in Australia from a societal perspective: results from the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke* 2001;32:2409-2416.
6. Dewey HM, Thrift AG, Mihalopoulos C, Carter R, Macdonnell RAL, McNeil JJ, et al. Informal care for stroke survivors: results from the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke* 2002;33(4):1028-1033.
7. Rothwell PM. The high cost of not funding stroke research: a comparison with heart disease and cancer. *Lancet* 2001;357:1612-1616.
8. Langhorne P, Williams BO, Gilchrist W, Howie K. Do stroke units save lives? *Lancet*, 1993:395-398.
9. Wardlaw JM, del Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke (Cochrane review). *The Cochrane Library* 2003(4).
10. Indredavik B, Bakke F, Slordahl S, Rokseth R, Haheim L, Holme I. Benefits of a stroke unit: A randomized controlled trial. *Stroke* 1991;22:1026-1031.
11. Indredavik B, Bakke RPT, Slordahl SA, Rokseth R, Haheim LL. Treatment in a combined acute and rehabilitation stroke unit: which aspects are most important? *Stroke* 1999;30:917-923.
12. The working group of the National Stroke Foundation. National Clinical Guidelines for Acute Stroke Management. Australia, 2003.
13. Holloway R, Vickery B, Benesch C, Hinchey J, Bieber J. Development of performance measures for acute ischemic stroke. *Stroke* 2001;32(9):2058-2074.
14. Allen C, Glasziou P, Del Mar C. Bed Rest: A potentially harmful treatment needing more careful evaluation. *Lancet* 1999;354(9186):1229-1233.
15. Bloomfield S. Changes in musculoskeletal structure and function with prolonged bed rest. *Medicine and Science in Sports and Exercise* 1997;29(2):197-206.
16. Convertino VA. Cardiovascular consequences of bed rest: effect on maximal oxygen uptake. *Medicine and Science in Sports and Exercise* 1997;29(2):191-196.
17. Bernhardt J, Dewey HM, Thrift AG, Donnan GA. Inactive and alone: Physical activity in the first 14 days of acute stroke unit care. *Stroke* 2004;35:1005-1009.
18. Birschel, P., Ellul, J., & Barer, D. 2004. Progressing stroke: towards an internationally agreed definition. *Cerebrovascular Diseases*, 2004;*17*(2-3), 242-252.
19. Borg G. Perceiced exertion as an indicator of somatic stress. *Scandinavian Journal of Rehabilitation Medicine* 1970;2-3:93-98.
20. Bernhardt J, Dewey HM, Thrift AG, Collier J, Donnan GA. A Very Early Rehabilitation Trial (AVERT) Phase II Safety and Feasibility. *Stroke* 2008; 29:390-396.
21. Thrift AG. Personal communication. NEMESIS database: Stroke deaths at 3 months for patients admitted to hospital, 2006.
22. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJA, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604-607.
23. Sulter G, Steen C, De Keyser J. Use of the Barthel Index and Modified Rankin Scale in acute stroke trials. *Stroke* 1999;30:1538-1541.
24. D'Olhaberriague L, Litvan I, Mitsias P, Mansbach HH. A reappraisal of reliability and validity studies in stroke. *Stroke* 1996;27:2331-2336.

25. Donnan G, Davis S. Stroke care outcomes: providing effective services (SCOPES): An evaluation of Victorian Stroke Services. Melbourne: Public Health Division, NSRI, 2002:1-328.
26. Hawthorne G, Richardson J, Osborne R. The Assessment of Quality of Life (AQoL) instrument: A psychometric measure of health-related quality of life. *Quality of Life Research* 1999;8:209-224.
27. Sturm J, Osborne R, Dewey HM, Donnan GA, Macdonnell RAL, Thrift AG. Brief comprehensive quality of life assessment after stroke: the Assessment of Quality of Life (AQoL) Instrument in the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke* 2002;33:2888-2894.
28. Herrman H, Hawthorne G, Thomas R. Quality of life assessment in people living with psychosis. *Psychiatry Epidemiology* 2002;37:510-518.
29. Snaith RP, Constantopolous AA, Jardine MY, McGuffin P. A clinical scale for the self-assessment of irritability. *British Journal of Psychiatry* 1978;132:164-171.
30. Collen F, Wade D, Bradshaw C. Mobility after stroke: reliability of measures of impairment and disability. *International Disability Studies* 1990;12:6-9.
31. Adams S, Pickering R, Ashburn A, Lincoln N. The scalability of the Rivermead Motor Assessment in non-acute stroke patients. *Clinical Rehabilitation* 1997;11:52-59.
32. Mahoney F, Barthel D. Functional evaluation: the Barthel Index. *Maryland State Medical Journal* 1965;14:61-65.
33. Brott T, Adams H, Olinger C, Marler J, Barsan W, Biller J, et al. Measurements of acute cerebral infarction: A clinical examination scale. *Stroke* 1989;20:864-870.
34. Briggs D, Felberg R, Malkoff M, Bratina P, Grotta J. Should mild or moderate strokes be admitted to an intensive care unit? *Stroke* 2001;32:871-876.
35. Samsa GP, al. e. Performing cost-effectiveness analysis by integrating randomized trial data with a comprehensive decision model: application to treatment of acute ischemic stroke. *Journal of Clinical Epidimiology* 1999;52(3):259-271.
36. Australian Government Department of Health and Ageing. Medicare Benefits Schedule (MBS), 2003.
37. Australian Government Department of Health and Ageing. Schedule of Pharmaceutical Benefits for approved pharmacists and medical practitioners, 2003.
38. Simondson J, Goldie P, Brock K, Nosworthy J. The Mobility Scale for Acute Stroke Patients: intra-rater and inter-rater reliability. *Clinical Rehabilitation* 1996;10:295-300.
39. Peto R, Pike M, Armitage P, Breslow N, Cox D, Howard S. Design and analysis of randomised clinical trials requiring prolonged observation of each patient. II. analysis and examples. *British Journal of Cancer* 1977;35:1-39.

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	Score 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	☐

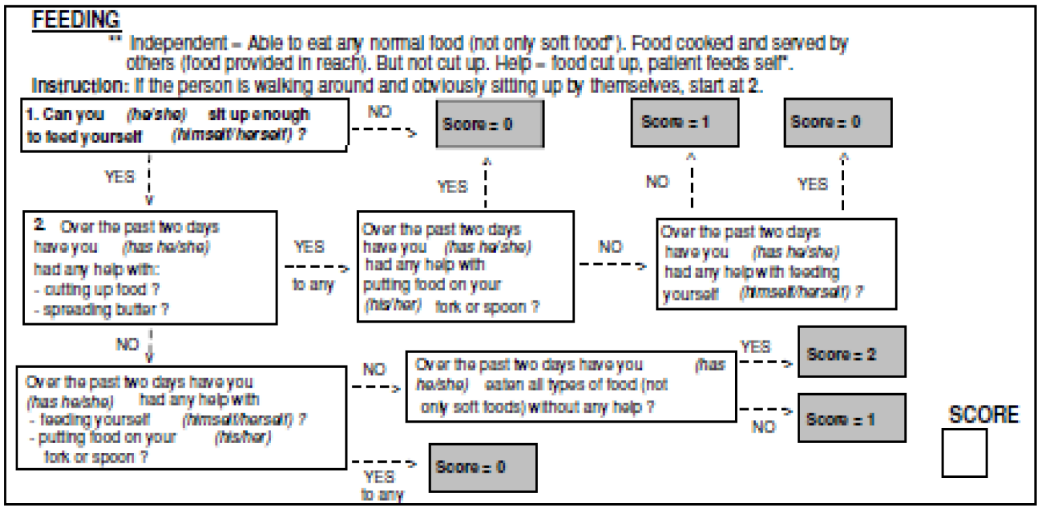
BARTHEL INDEX

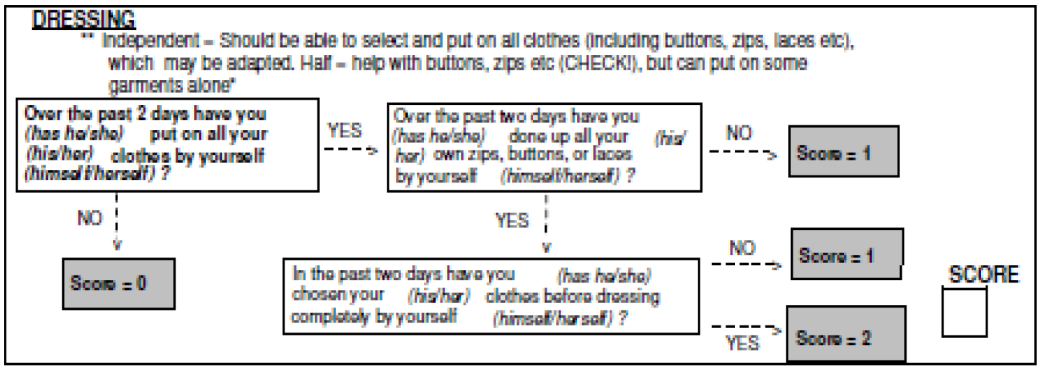
PATIENT STUDY NUMBER			-				TIME OF ASSESSMENT	3 months ☐ 12 months ☐

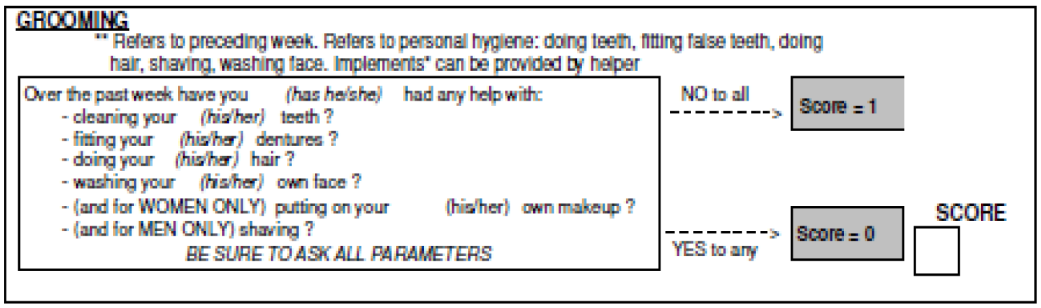
PERSON RESPONDING				ASSISTANCE FOR INTERVIEW OBTAINED FROM			
Index Case	☐	Other Relative	☐	Index Case	☐	Other Relative	☐
Spouse/Partner	☐	Friend/Associate/ Neighbour	☐	Spouse/Partner	☐	Friend/Associate/ Neighbour	☐
Sibling	☐			Sibling	☐		
Son/Daughter	☐	Carer, e.g. nurse	☐	Son/Daughter	☐	Carer, e.g.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

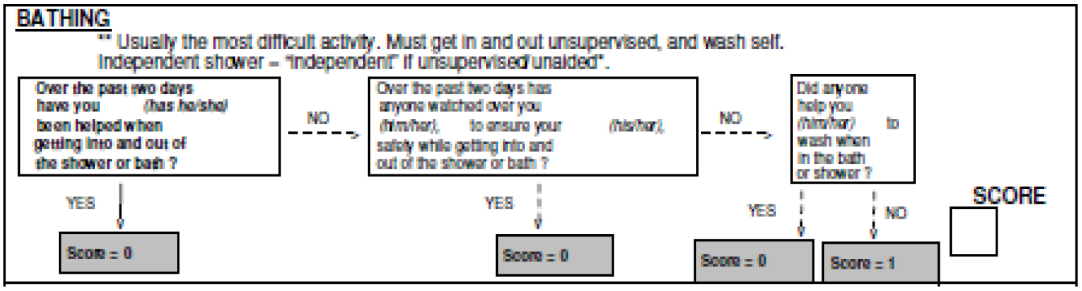
BARTHEL ACTIVITIES OF DAILY LIVING

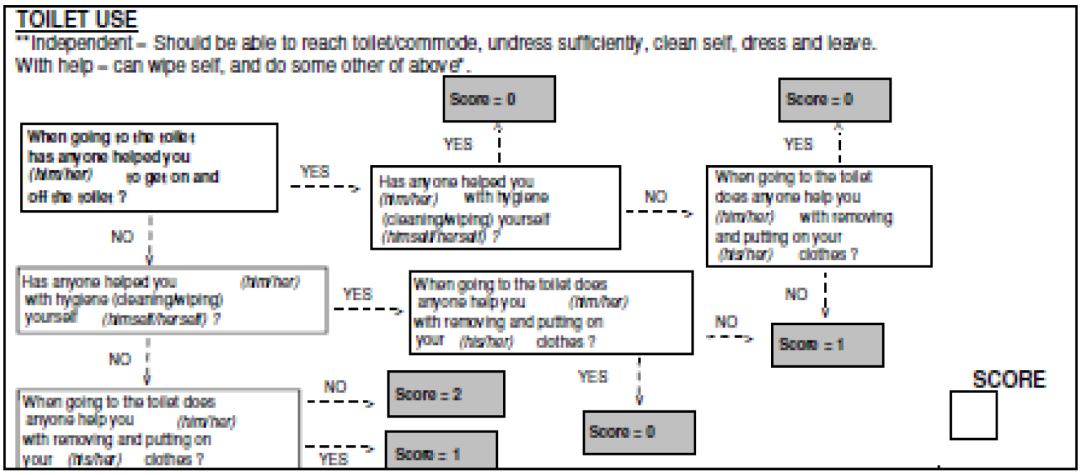
If the participant indicates that they are not independent in any of these activities, ask "Who helps you with these tasks?", and note which person is the chief carer on the patient contact sheet.

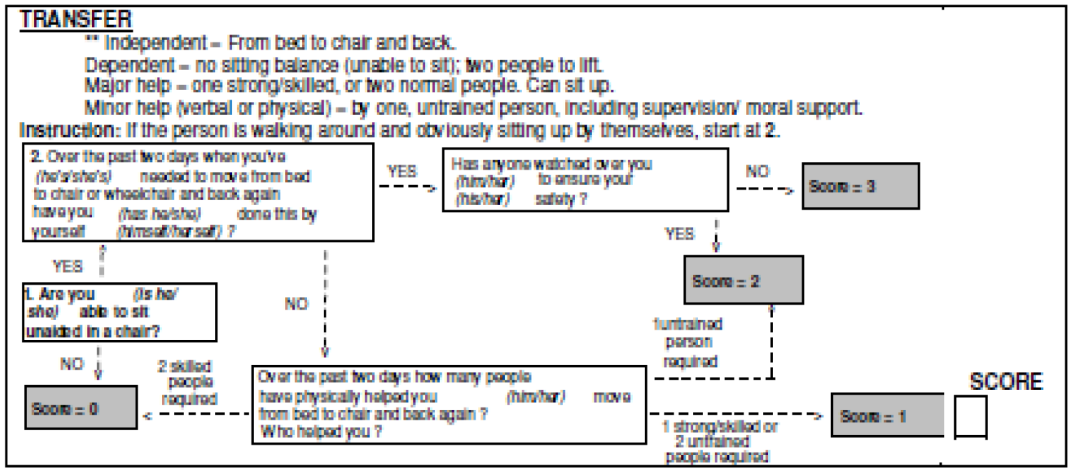


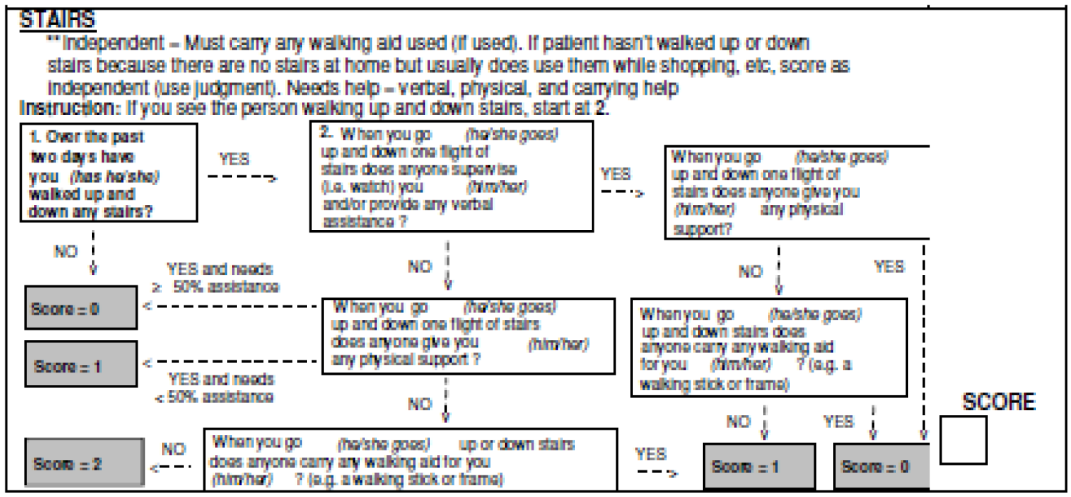


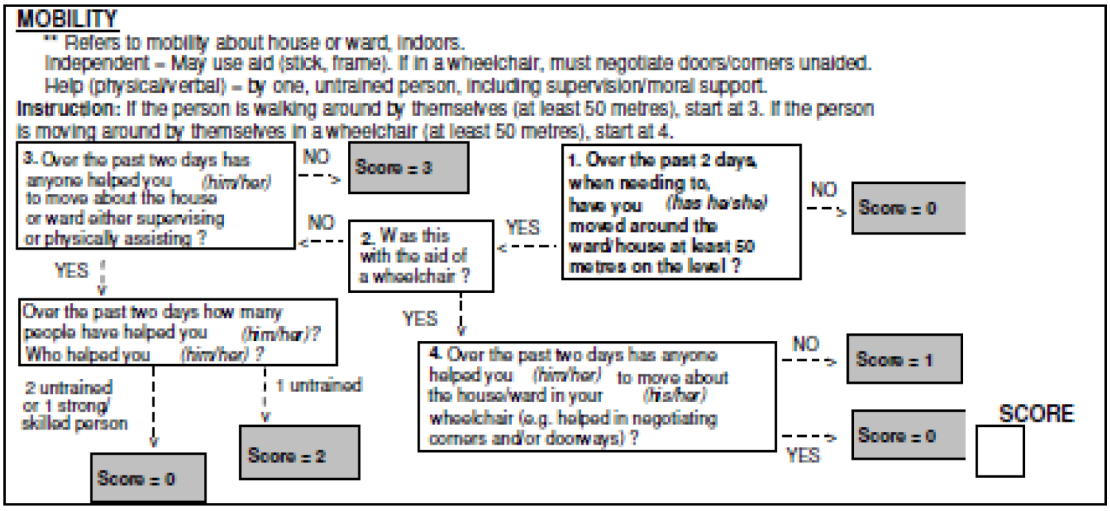


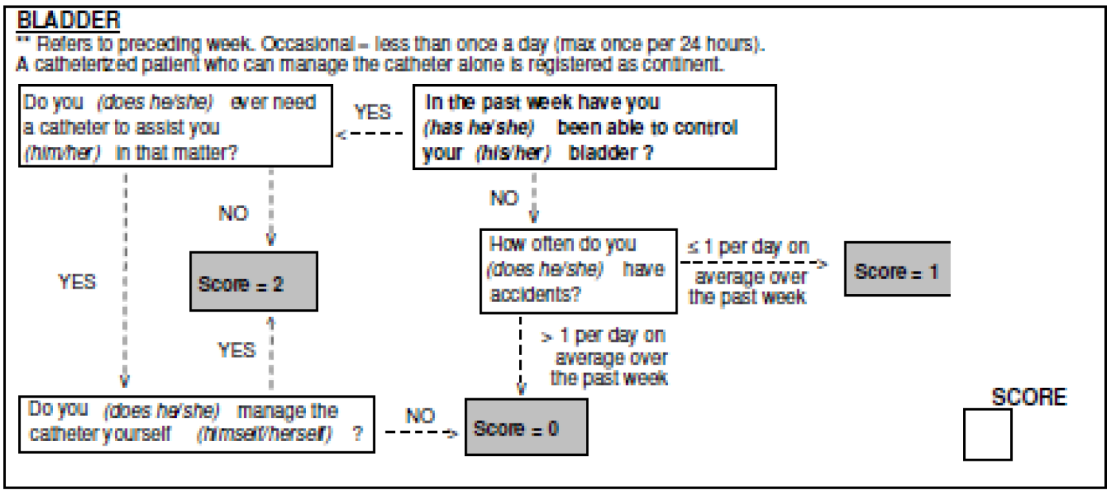


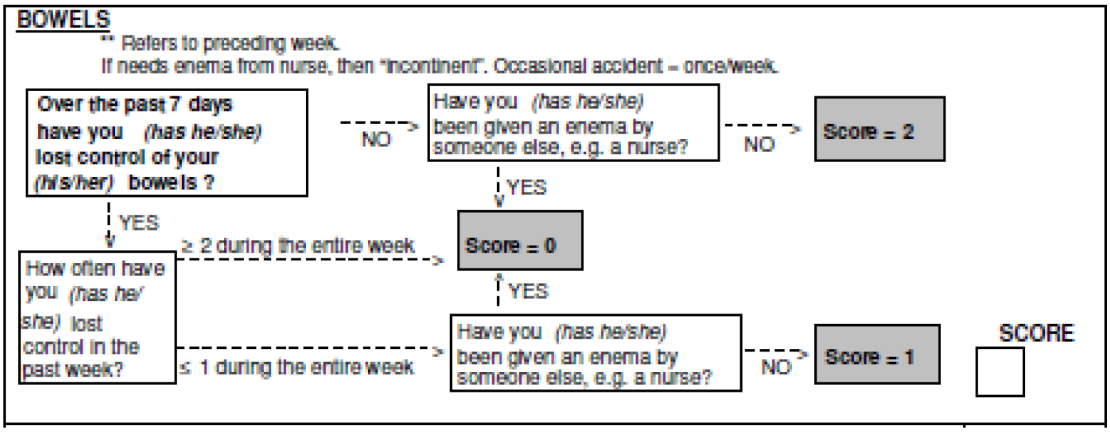












BARTHEL INDEX TOTAL		

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

	PATIENT STUDY NUMBER			-				

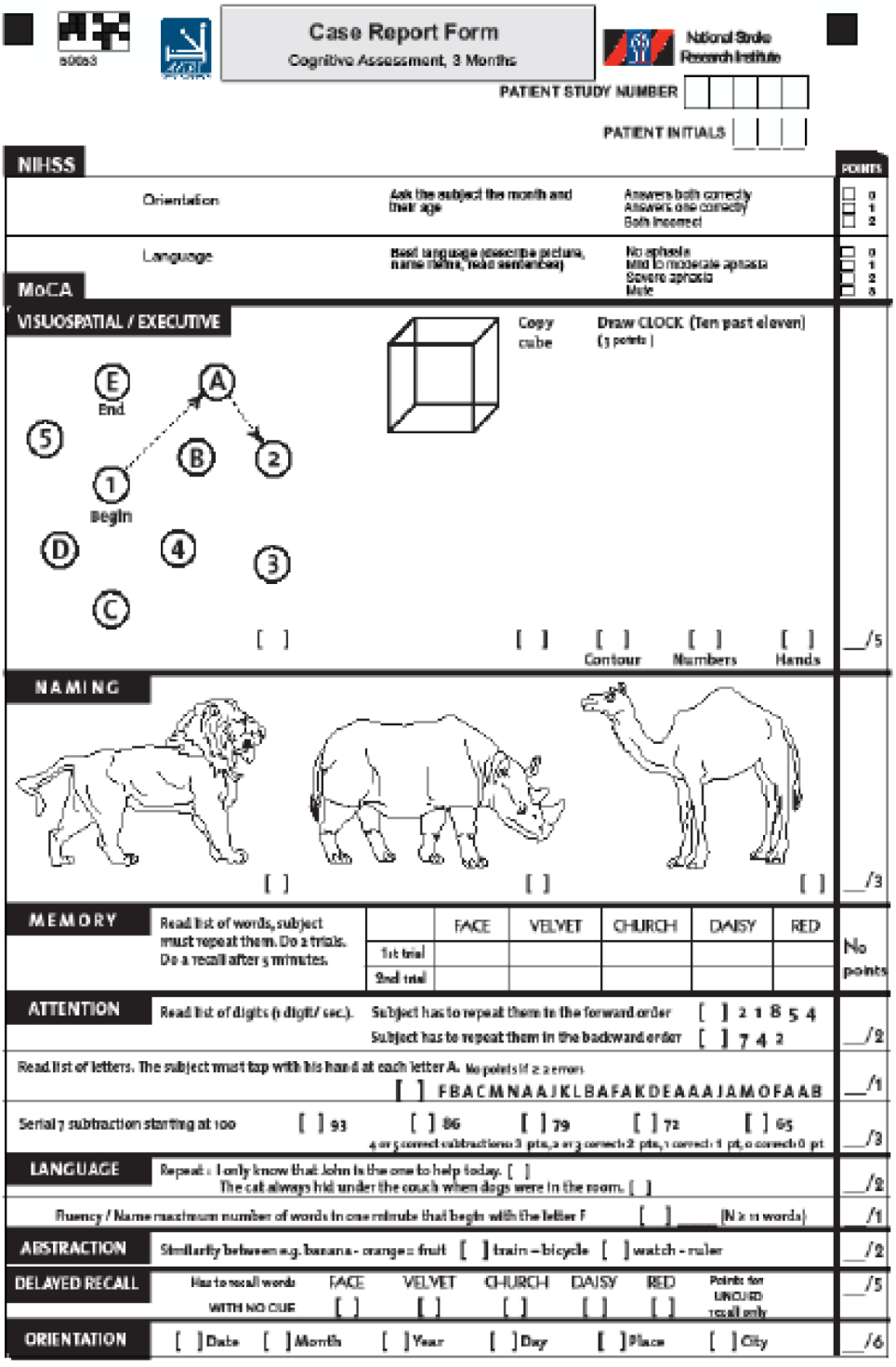
Instructions: Scores should reflect what the patient does, not what the clinician thinks the patient can do.
The clinician should record answers while administering the examination and should work quickly.
Except where indicated, the patient should not be coached (ie. Repeated requests to make a special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

Page 39 of 41
AVERT Protocol Version 3 25 April 08



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	Read 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						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

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

EME
HS&DR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library