



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

Protocol Summary Version 1.0 – 4 April 2006

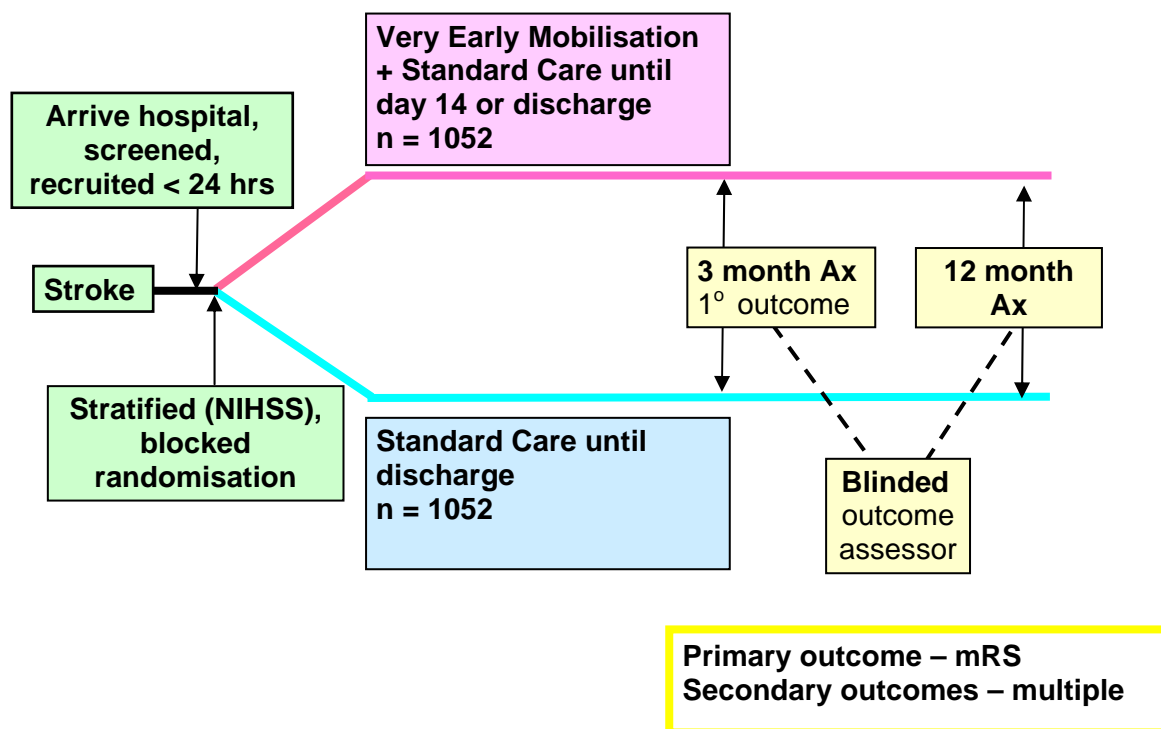


National Stroke Research Institute

Glossary of Abbreviations

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| ARR | Absolute Risk Reduction |
| AQoL | Assessment of Quality of Life |
| AVERT | A Very Early Rehabilitation Trial |
| CRF | Case Report Form |
| DSMC | Data Safety and Monitoring Committee |
| IDA | Irritability, Depression and Anxiety scale |
| HREC | Human Research Ethics Committee |
| ICU | Intensive Care Unit |
| mRS | modified Rankin Score |
| 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

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| Title | A Very Early Rehabilitation Trial (AVERT). A phase 3, multicentre, randomised controlled trial of very early rehabilitation after stroke. |
| Protocol | AVERT Protocol Version 1.0 - 4 April 2006 |
| 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 to a stroke unit within 24 hours of first or recurrent stroke. |
| Primary Outcome | Modified Rankin Score at 3 months. |
| Secondary Outcomes | <p>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.</p> <p>Health-related quality of life: Assessment of Quality of Life and Irritability, Depression and Anxiety scale; at 3 and 12 months.</p> <p>Cost effectiveness and cost utility: Comprehensive questionnaire at 3 and 12 months and baseline mRS.</p> <p>Long term efficacy: mRS at 12 months.</p> <p>Activity limitations: Time to walking 50 metres; Rivermead Motor Assessment and Barthel Index at 3 and 12 months.</p> <p>Dose-response: Intervention dose and Modified Rankin Score at 3 and 12 months.</p> <p>Patient severity and efficacy: Mild, moderate and severe stroke (NIHSS) and mRS at 3 and 12 months</p> <p>Staff injury: The number, severity and type of staff injury for AVERT patients during the intervention period.</p> |
| Hypotheses | <p>Compared to standard care (SC) alone, very early mobilisation (VEM) of stroke patients (in addition to standard care):</p> <ol style="list-style-type: none"> 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 | Ten sites located within Australia. A combination of larger metropolitan institutions and smaller regional hospitals will be involved. |
| Inclusion Criteria | <p>Patients with first or recurrent stroke diagnosis, haemorrhage or infarct</p> <p>Admitted to a stroke unit within 24 hours of onset of symptoms</p> <p>Consciousness: Must at least react to verbal commands</p> |

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| Exclusion Criteria | <p>Pre-stroke (retrospective) modified Rankin Score of 3, 4 or 5 (indicating significant previous disability).</p> <p>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.</p> <p>Concurrent diagnosis of rapidly deteriorating disease (e.g. terminal cancer).</p> <p>Unstable coronary or other medical condition that is judged by the investigator to impose a hazard to the patient by involvement in the trial.</p> <p>A suspected or confirmed lower limb fracture at the time of stroke preventing the implementation of the mobilisation protocol.</p> <p>Patients who have received rt-PA can be recruited if the attending physician permits and if mobilisation within 24 hours of stroke is permitted.</p> <p>Patients cannot be concurrently recruited to drug or other intervention trials.</p> <p>Patients may participate in AVERT if they are also recruited to non intervention trials.</p> <p>Systolic blood pressure less than 110, or greater than 220mmHg.</p> <p>Oxygen saturation of less than 92% with supplementation.</p> <p>Resting heart rate of less than 40 or greater than 110 beats per minute.</p> <p>Temperature of greater than 38.5°C.</p> |
| Intervention Groups | <p>Control Intervention: Standard Care is usual stroke unit care.</p> <p>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.</p> |
| Randomisation Procedures | <p>A remote, web-based, computer-generated randomisation procedure is used. Assessors have certified reliability for NIHSS and mRS.</p> |
| Trial Progress | <p>The Data Safety and Monitoring Committee will monitor compliance with the AVERT Protocol Version 1.0 - 4 April 2006 and make recommendations to the Steering Committee.</p> |
| Safety Parameters | <p>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.</p> |
| Clinical Analysis | <p>Outcomes will be reported in clinical terms of absolute risk reduction, relative risk reduction, and numbers needed to treat.</p> |
| Statistical Analysis | <p>The primary efficacy analysis will be an intention to treat, between-group comparison of mRS at 3 months, using a proportional odds ordinal logistic regression model, subject to the validity of the proportional odds assumption. Secondary analyses include evaluations of safety, health-related quality of life, cost effectiveness and cost utility, long term efficacy, activity limitation, dose response, patient severity and staff injury.</p> |

2 AVERT Committees

Management Committee

Associate Professor Julie Bernhardt (Chairman)
Dr. Helen M Dewey
Dr. Amanda G Thrift
Dr. Janice M Collier
Professor Geoffrey A Donnan
Professor Richard Lindley
Dr. Marcus Nicol
Fiona Ellery

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Steering Committee

Dr. Helen M Dewey (Co-Chairman)
Professor Geoffrey A Donnan (Co-Chairman)
Associate Professor Julie Bernhardt (Principle Investigator)
Professor Richard Lindley (Westmead Hospital, NSW)
Professor Robert Carter (University of Melbourne, Melbourne)
Tara Sharpley (Austin Health, Vic)
Brooke Parsons (Consumer)
Other members to be announced

Outcome Committee

Professor Mary Galea (Chairman)
Dr. Judith Frayne
Dr. Velandai Shrikanth

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