Appendix 1.

Economic Evaluation Plan

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Abbreviations

Acronym	Definition
AQoL	Assessment of Quality of Life
AUD	Australian Dollars
AVERT	A Very Early Rehabilitation Trial
CEA	Cost-Effectiveness Analysis
Cost CRF	Cost Case Report Form
CUA	Cost-Utility Analysis
FCA	Friction Cost Approach
GBP	British Pound
HCA	Human Capital Approach
ICER	Incremental Cost-Effectiveness Ratio
MAR	Missing At Random
mRS	modified Rankin Scale
RM	Malaysian Ringgit
NHCDC	National Hospital Cost Data Collection
NZD	New Zealand Dollar
PPP	Purchasing Power Parity
QALY	Quality Adjusted Life Year
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCU	Stroke Care Unit
SGD	Singapore Dollar
UC	Usual Care
UK	United Kingdom
VEM	Very Early Mobilisation

Section A. Key parameters of the economic evaluation

1.1 Target population and subgroups

Patients are eligible for participation in the trial: following a first or recurrent ischaemic or haemorrhagic stroke (but not transient ischaemic attack); recruited within 24 hours of onset of stroke symptoms; informed consent is obtained from the patient or responsible third party; aged 18 years or more; admitted to a Stroke Care Unit (SCU); and are conscious: at a minimum, must at least react to verbal commands. Exclusion criteria also apply with a full list available in the AVERT Statistical Analysis Plan (SAP) [1].

1.2 Setting and location

Participants are recruited from 56 stroke units (typically acute hospitals with a SCU) in three geographic regions– Australia (Australia and New Zealand); Asia (Malaysia and Singapore); United Kingdom (UK: Northern Ireland, Scotland, England and Wales).

1.3 Study perspective

The analyses will be carried out both from a societal and health sector perspective.

1.4 Comparators

The intervention comprises Very Early Mobilisation (VEM) in addition to usual care (UC). VEM patients commence out of bed activity within 24 hours of stroke onset, receive usual stroke unit care, and in addition, are assisted by trained therapy and nursing staff to continue out of bed activity as guided by an intervention protocol. The intervention is task specific, targets recovery of sitting, standing and walking, and is delivered for 14 days or until discharge whichever occurs first. Further details of the intervention are provided in the AVERT SAP [1].

UC patients receive usual stroke unit care. The economic evaluation detailed in Section B will measure the incremental difference in outcomes and costs between VEM and UC.

1.5 Time horizon

The study time horizon is 12 months. Follow up data are collected at 3 and 12 months to minimise recall bias.

1.6 Discount rate

No discounting is required as costs and outcomes are tracked for a period of only 12 months.

2. Outcomes

A comprehensive discussion of safety, efficacy and quality of life outcomes, their measurement and planned analysis is detailed in the AVERT SAP [1].

2.1 Primary outcome: modified Rankin Scale

The primary outcome is a favourable outcome at 3 months, measured by the mRS score 0-2 (no or minimal disability). The mRS is a standard stroke outcome measure using an ordinal scale ranging from 0 (no disability) to 5 (severe disability) and patients who die are assigned a score of 6. Three month mRS outcomes and analysis methods have been published elsewhere [1, 2].

The mRS is measured at 12 months and this outcome will be used in the cost-effectiveness analysis described in Section B.

2.2 Secondary outcome: Preference based outcome

Health related quality of life is measured at 3 months and at 12 months using the Assessment of Quality of Life (AQoL), a multi attribute utility instrument used to derive a utility score across a range of conditions [3]. The utility score falls on a scale of 0 (death) – 1 (good health), with a score below 0 indicating that a health state is worse than death. Utility scores will be estimated using published algorithms for the AQoL instrument [4].

The mRS score determined at baseline (day 0) by a trained clinician will be used as a surrogate measure of quality of life in the acute phase because measuring the quality of life immediately following a stroke was not possible. mRS scores will be mapped to AQoL utility values guided by methods described in the literature [5] and previous work in the pilot AVERT study. Ordinary Least Squares will be used however as the relationship between mRS and AQoL is not expected to be linear and variance in utility for each mRS score anticipated, other potential mapping models (eg. linear, polynomial and Classification And Regression Tree analysis) will be tested. Cross validation techniques will be used for this purpose. Each candidate model will be run to validate the prediction

model at 3 and 12 months and the root mean squared error; mean absolute error and mean absolute percentage error; will be used as model selection criteria.

Quality Adjusted Life Years (QALYs) will be calculated using (mapped) AQoL scores at baseline and measured at 3 and 12 months using the Area Under the Curve method [6]. If a baseline difference in utility is observed between groups, adjustment will be made using multiple regression methods [6]. Potential country heterogeneity will be taken into account in the model if necessary.

The mean QALY gain for VEM and UC will be used in the cost-utility analysis described in Section B.

2.3 Other secondary and tertiary outcomes

Full details of secondary and tertiary outcomes are provided in the AVERT SAP [1]. Other secondary outcomes include: differences in 3 month mRS outcome across the full mRS scale; difference between VEM and UC groups in ability to walk unassisted over 50 metres sooner or in greater number; serious complications (serious adverse events: SAE) and death at 3 months. Other tertiary outcomes include: dose-response, serious complications and deaths at 14 days; all falls, regardless of severity at 3 months; and length of hospital stay (acute and rehabilitation).

These outcomes will be incorporated into the exploratory analysis where appropriate, as described in Section C.

3. Resource Use

3.1 Identification

Pathway analysis was used to identify the cost items associated with AVERT and previous research was also consulted to identify major cost categories relevant to stroke [7]. Cost items were limited to those expected to vary between VEM and UC patients (eg. medications were not expected to change as a result of the intervention and therefore were not collected in the trial) and that were related to a patient's stroke. A list of major cost categories collected during the trial is provided in Table 1.

3.2 Measurement

Resource use is being collected for the economic evaluation using standardised methods and tools across multiple hospital sites within the participating countries at three time points: baseline (day 0-14), 3 and 12 months.

During the acute phase from day 0-14 (or until hospital discharge), resources utilised in the delivery of UC and VEM are recorded using an online data entry system (AVERT Online) by nursing and therapy staff. A standardised Cost Case Report Form (Cost CRF) is used to collect resource use information at 3 and 12 months. The Cost CRF was trialled and refined during the pilot AVERT study [8]. Subsequent minor modifications were made for each country of the trial sites to reflect local service provision or differences in terminology.

Where a patient dies during the trial, the Cost CRF is completed to capture resources used prior to death either through medical record review and/or discussion with the permitted proxy where possible.

3.3 Valuation

Unit prices will be applied to resource use data using 2015 as the reference year. Where the 2015 price is not available, adjustment to the real price in the reference year will be made using the appropriate country specific health sector price deflator (for example [9]).

3.3.1 Unit costs

Unit costs will be obtained from each participating country (Australia, New Zealand, Malaysia, Singapore and United Kingdom [England/Wales/Scotland/Northern Ireland]) and applied to patient-level data collected within that country.

Given the large number of centres involved in this trial it is not practical to collect centre-specific unit costs. National cost estimates will therefore be used to value resources used by each patient for pragmatic reasons and for consistency with pilot study methods [8]. Centre-specific unit costs may only be used where a national estimate cannot be obtained.

Resource use will be valued using nominal prices (which will be adjusted to real prices as needed) taken from published sources such as national datasets (e.g. Australian National Hospital Cost Data Collection, NHCDC; UK Unit Costs of Health and Social Care) and fee schedules (Australian Medicare Benefits Schedule: MBS). The exception to this is informal care which will be valued as an opportunity cost by the proxy good method using the hourly wage rate of a professional care giver. Productivity gains/losses will be estimated via both the Human Capital Approach (HCA) and Friction Cost Approach (FCA) method [10].

In the absence of published estimates, unpublished unit prices will be obtained with appropriate permission. The source of unpublished prices will vary but may include hospital financial records or provider specific fee schedules/invoicing. Trial collaborators in each country will facilitate the collection of accurate unit costs and of published and unpublished prices.

Where there is a large variation in unit prices for a specific item, a mean cost will be applied and a range around the mean cost tested in uncertainty analysis. If a unit price cannot be obtained, an average price will be imputed from another country/countries similar in terms of development and health care expenditure. This valuation method is consistent with published economic evaluation work [11] and any uncertainty in a unit price will be reported and its effect on the final results tested in sensitivity analysis.

3.3.2 Economic modelling

Multilevel hierarchical regression modelling will be used to analyse resource use data using a combination of mixed effect models and generalised estimating equations. The hierarchy of the model will be: SCU as the higher-level; and patients nested within the units. Country/geographic region will be accounted as a factor in the regression analysis. The model will estimate the effect of intervention group (independent variable) on resource use (dependent variable) at 12 months with adjustment for treatment covariates.

The main output of the analysis will be reported as an estimate of the mean cost of VEM and UC. Median values and/or other descriptive statistics will to be reported to further illustrate cost findings.

The following subgroup analyses will be carried out on resource use data, and is guided by the AVERT SAP [1]:

- Age (<65; 65-79; >80)
- Stroke severity (mild: NIHSS <7 moderate: NIHSS 8-16 and severe: NIHSS>16)
- Stroke type (ischaemic versus haemorrhagic)

- Time to first mobilisation (<12 hours; 12 to <24 hours)
- Discharge destination following acute hospital admission

The analysis will be conducted primarily using STATA 14 software.

3.3.3 Unit cost heterogeneity

Assessment of the comparability of unit prices between countries will be made during the analysis process and adjustments made where practicable to eliminate identified differences. For example, inpatient bed day rates in participating countries may invariably include overhead expenses. Any adjustment made to a unit price will be documented and reported alongside main findings.

3.4 Currency, price date, and conversion

Unit prices will be converted to a common currency using the Purchasing Power Parity (PPP) [12, 13]. The British Pound (GBP) or Australian Dollar (AUD) are most relevant to use however the final currency chosen will be dependent on the journal publishing the economic evaluation results.

Where specific analysis is undertaken by country, results will additionally be reported in local currencies as follows: AUD Australia; NZD New Zealand; RM Malaysia; SGD Singapore; and GBP England, Scotland, Wales and Northern Ireland.

3.5 Missing data

Minimal missing data are anticipated [1] and any missing resource use data will be assumed missing at random (MAR) with this assumption tested. Imputation of missing data will only be undertaken where indicated. The pattern of missingness will be explored as a function of patient characteristics, geographic region, who reported resource use (patient versus proxy) and other important variables deemed relevant at the time of analysis.

Section B. Economic evaluation analysis and reporting

1.1 Study question

From a societal and health sector perspective, what is the cost-effectiveness of a rehabilitation practice that consists of very early mobilisation (VEM) of stroke patients in addition to usual care (UC), in comparison to UC alone?

1.2 Cost-effectiveness analysis

The primary economic evaluation of AVERT will be a cost-effectiveness analysis (CEA [10]) using the favourable (independence) outcome (mRS score 0-2) at 12 months, combined with resource use collected to 12 months.

1.3 Cost-utility analysis

Cost-utility analysis (CUA [10]) will be undertaken using health-related quality of life, reported as QALYs over the 12 month period as measured by the mRS (baseline) and AQoL (12 months).

1.4 Incremental Cost Effectiveness Ratio

Incremental cost effectiveness ratios (ICER) will be used to jointly assess costs and outcomes. The additional cost/saving of the intervention VEM compared to UC will be expressed as a ratio by dividing the net benefits derived and reported as the: incremental cost per favourable (independence) outcome at 12 months; and incremental cost per QALY. The final ICER will be

reported with and without productivity effects. Any assumptions made during the analysis will be documented and reported alongside the economic evaluation results

Results will be reported as trial-wide cost-effectiveness ratios and reported alongside geographic region and/or country specific results (dependant on participant numbers and to be determined at the time of analysis).

1.5 Uncertainty analysis

Bootstrapping of costs and QALYs will be undertaken to assess the degree of uncertainty in reported ICERs. Multivariate sensitivity analysis will be conducted to test various assumptions identified during analysis.

A plot on a cost-effectiveness plane will be drawn to illustrate the distribution of cost and effectiveness iterations. A cost-effectiveness acceptability curve will be plotted in order to assess the degree of uncertainty associated with the conclusion using a commonly used appropriate cost-effectiveness threshold (e.g. AUD50,000 for Australasia region; GBP20,000-30,000 for United Kingdom).

Section C. Exploratory economic analysis

Exploratory analysis of resource use will be undertaken, with the purpose of informing patterns of resource use and their relationship to outcomes.

The following areas will be explored in the analysis:

- Resource use and outcomes at different time points during the first year following stroke (baseline; 3 months, 12 months; other relevant time points);
- Resource use by 'payer' (Government, patient/family, employer);
- Resource use by other subgroups (eg. exposure to early mobilisation)
- Health related quality of life by subgroup including: levels of exposure to early mobilisation (dose-response), place of residence at time of measurement;
- Resource use by secondary and tertiary outcomes specified in Section A 2.1.3 not explored in the main economic evaluation analysis; and
- One year and lifetime economic costs of stroke using pooled data from UC and VEM patients.

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TABLE 1. Items of cost being collected during the acute phase and at follow up

	Item	Measurement unit
Acute phase[1]	Physiotherapy time	Minutes/number of services
	Nursing attendance	Number of services
	Length of inpatient stay	Days
	Complications and adverse events	Number/type of event
Follow up at 3 and 12 months	Inpatient rehabilitation	Days
	Outpatient rehabilitation program	Days
	Rehabilitation in the home	Number of sessions
	Stroke-related problems (that lead to re hospitalisation or prolongation of original admission)[2]	Days
	Home modifications	Type of modification, cost to patient/family
	Special equipment and aids	Type of equipment/aid
	Community services	Type, number and hours per service
	Community Rehabilitation Centre	Days/sessions
	Informal care	Hours
	Respite care	Days
	Employment status	Returned to work; hours
	Changes in accommodation (home, nursing home, hostel etc)	Days
	Ambulance transfer	Number of trips
	Private physiotherapy	Number of sessions
	Live in maids[3]	Number of maids

[1] Acute phase: From day 1 to day 14 or until discharged, whichever is earlier.

2 Stroke-related problems were identified and pre-specified on the Cost CRF

[3] Collected in Singapore and Malaysia