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Economic evaluation of a phase III international randomised controlled trial of very early mobilisation after stroke (AVERT)

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ABSTRACT

Objectives While very early mobilisation (VEM) intervention for stroke patients was shown not to be effective at 3 months, 12 month clinical and economical outcomes remain unknown. The aim was to assess cost-effectiveness of a VEM intervention within a phase III randomised controlled trial (RCT).

Design An economic evaluation alongside a RCT, and detailed resource use and cost analysis over 12 months post-acute stroke.

Setting Multi-country RCT involved 58 stroke centres.

Participants 2104 patients with acute stroke who were admitted to a stroke unit.

Intervention A very early rehabilitation intervention within 24 hours of stroke onset

Methods Cost-utility analyses were undertaken according to pre-specified protocol measuring VEM against usual care (UC) based on 12 month outcomes. The analysis was conducted using both health sector and societal perspectives. Unit costs were sourced from participating countries. Details on resource use (both health and non-health) were sourced from cost case report form. Dichotomised modified Rankin Scale (mRS) scores (0 to 2 vs 3 to 6) and quality adjusted-life years (QALYs) were used to compare the treatment effect of VEM and UC. The base case analysis was performed on an intention-to-treat basis and 95% CI for cost and QALYs were estimated by bootstrapping. Sensitivity analysis were conducted to examine the robustness of base case results.

Results VEM and UC groups were comparable in the quantity of resource use and cost of each component. There were no differences in the probability of achieving a favourable mRS outcome (0.030, 95% CI −0.022 to 0.082), QALYs (0.013, 95% CI −0.041 to 0.016) and cost (AUD1082, 95% CI -$2520 to $4685 from a health sector perspective or AUD102, 95% CI -$6907 to $7111, from a societal perspective including productivity cost). Sensitivity analysis achieved results with mostly overlapped CIs.

Conclusions VEM and UC were associated with comparable costs, mRS outcome and QALY gains at 12 months. Compared with to UC, VEM is unlikely to be cost-effective. The long-term data collection during the trial also informed resource use and cost of care post-acute stroke across five participating countries.

Strengths and limitations of this study

- ► This is the first economic evaluation assessing the cost-effectiveness of a very early rehabilitation intervention within the largest phase III randomised controlled trial in patients with stroke.
- ► The study assessed the long-term cost and cost-effectiveness of this very early rehabilitation intervention at 12 month.
- ► The difficulty posed by the multi-country design of the trial and the percentage of missing data may undermine the confidence in the results.

Trial registration number ACTRN12606000185561; Results.

INTRODUCTION

Stroke is one of the biggest killers and a leading cause of disability worldwide.[1 2] Sixty five per cent of stroke survivors live with some degree of disability that impedes their ability to carry out daily living activities unassisted.[3] Therefore, ways of improving the outcomes of patients after stroke is an important focus of research.[4 5] Early mobilisation after stroke is believed to contribute to better patient outcomes and clinical trials have been conducted globally.[6–9]

The short-term efficacy and safety of a very early rehabilitation trial after stroke (AVERT) has been evaluated in a phase III randomised controlled trial (RCT) with 2104 patients enrolled from Australia, New Zealand, UK, Singapore and Malaysia.[10] The evidence from this trial indicated that at 3 months after stroke, very early mobilisation (VEM) of patients was associated with a reduction in the probability of a favourable outcome as defined by a modified Rankin Scale (mRS) score of 0 to 2 compared with that in the

usual care (UC) group.[10] In the research field of stroke, primary endpoint is usually assessed at month 3 after stroke,[11–14] which means there is a paucity of data in terms of long-term resource use and cost of care for patients with stroke. Given AVERT provided a longer-term (ie, 12 months) comprehensive measurement of costs relating to stroke care (ie, direct medical, direct non-medical and indirect costs), and the broader representativeness of patients across countries and regions (>2000 patients were recruited from both developing and developed world), together with the implications of stroke economic burden sustained beyond the acute phase (ie, 3 months), holistically examining the cost of stroke care that falls within health and non-health sectors could potentially advance understanding of pattern of resource use post stroke and identify any gaps to improve care for stroke and chances to curb the increasing economic burden of disease. This examination also benefits healthcare funders (ie, governments, insurance companies) and the public with addition of substantial knowledge of long-term rehabilitation cost for stroke.

This economic evaluation, which was part of the registered trial protocol (Australian New Zealand Clinical Trials Registry, ACTRN12606000185561) and planned prior to knowledge of outcomes, was conducted alongside the phase III RCT,[10] The aim of this paper is to assess the cost-effectiveness of very early mobilisation within 24 hours after stroke in terms of improving patient outcomes at 12 months, in comparison to usual care, with a particular focus on examining the resource use and cost of care after stroke.

METHODS

The economic analysis was undertaken following the previously published plan.[15] It also conforms to the Consolidated Health Economic Evaluation Reporting Standards checklist.[16] Ethics approval was granted by relevant institutions.

Intervention and comparator

The trial design has been reported in detail elsewhere.[10] In brief, patients with confirmed stroke who were admitted to a stroke unit within 24 hours of stroke onset were randomised to receive usual stroke-unit care alone or VEM in addition to UC in a multinational phase III trial.

Outcomes

The mRS at 12 months, a secondary outcome of the trial, and quality-adjusted life years (QALYs) derived from the assessment of quality of life-4 dimension (AQoL-4D)[17] were used as the effectiveness measures in the economic evaluation. The AQoL-4D instrument is a multi-attribute utility scale used to assess the health-related quality of life (HRQoL)[18]; it was administered at 3 and 12 months.

Outcome of mRS was dichotomised into 'favourable' (mRS 0 to 2) and 'poor' (mRS 3 to 6) based on patients outcomes at 12 month follow-up.[10] The difference in the probability of patients achieving a favourable mRS outcome (mRS 0 to 2) was used to estimate the incremental benefits between treatment groups for the primary efficacy outcome.

Due to the inherent difficulties of administering the AQoL instrument to acute stroke patients (ie, most of patients were not able to respond to these questions at baseline), the mRS score at baseline[10] was used as a surrogate measure of patient utility during the acute phase. The detailed methods of this work are reported elsewhere[19] and a brief description is supplied in the online supplementary document 1.

Costs

A societal perspective with a key focus on the health sector was adopted.

Intervention delivery

Intervention delivery costs consisted of the time costs of physiotherapists (PT) and nurses delivering VEM (or UC) to patients. The mean of the total physiotherapist time (recorded by a log documented by each participating PT across whole hospital stay) per patient was calculated. Given insufficient data, physiotherapist's mean time per session was used as a proxy for nurse time spent on delivering either VEM or UC.

Resource use

All resource use during the study period was electronically collated using a validated cost case report form (Cost CRF) administered and recorded by trained staff at 3 and 12 months using face-to-face assessments with patients and carers, and medical records. Cost CRF used in Australia is supplied as an example (online supplementary document 2). Cost CRF from other participating countries could be requested from corresponding author.

Healthcare resource use

The quantity of resources used for the following healthcare resource items was recorded: number of ambulance transfers (emergency and non-emergency), acute hospitalisation (including length of stay (LoS)), rehospitalisation (number of occasions and LoS for each occasion), rehabilitation hospital admission (number of occasions and LoS for each occasion), outpatient rehabilitation programme (number of occasions and number of days for each occasion), rehabilitation provided at home/nursing facility (number of occasions and number of sessions for each occasion), private physiotherapy (number of sessions), respite care (number of sessions) and individual outpatient (including physiotherapy, occupational therapy and speech and language therapy) visits (service type and number of sessions) for patients from UK, Singapore and Malaysia only.

Non-healthcare resource use

The quantity of resources used was recorded for the following non-healthcare resource items: accommodation

move due to stroke (location moved to and date of move), community service (type of service use and number of service used both for prior to and post stroke), home modification (type of modification, supplier and cost), special equipment and aids (type of equipment/aids and quantity consumed), informal care (purpose of the care and hours used), live-in maids (number of maids prior to and post stroke) (for Singapore and Malaysia only), changes to employment (employment status and weekly hours of working both prior to and post stroke).

Resource use reported at 3 (ie, resources used between 0 and 3 months) and 12 (ie, resources used between 4 and 12 months) months was used to calculate the total annual resource use for each participant. Generally, where patients were still using a particular resource at the time of 12 month data collection, the last day of 12 months' follow-up (calculated from the day of index stroke) was used to estimate the duration of that resource utilisation. In the event of a patient dying, resource use data for the period prior to death was ascertained from their carer and medical records, wherever possible.

Unit costing

Costs were computed by applying country-specific unit costs to each resource item utilised. Therefore, five sets of unit costs (one for each of the participating countries) were compiled from the most up-to-date and reliable source (online supplementary document 3). Unit costs from a country with a similar economic status and healthcare system were used where local country-specific unit costs were unavailable.

All costs are expressed in Australian dollars (AUD) for the 2015 reference year value and can be converted to US dollar (USD) using the purchasing power parity rate 1 USD=1.463 AUD[20] (December 2015). The currency of other countries was converted to AUD using the corresponding exchange rate. The country-specific consumer price index from the health sector was employed to adjust costs not valued in the year of 2015.

The details of unit cost for acute stroke hospitalisation, rehospitalisation, rehabilitation (inpatient and outpatient), non-health sector costs (home modifications, community services, aids, etc) and productivity cost are provided in online supplementary document 3.

Statistical analysis

All the costs that were attributable to stroke including healthcare costs, non-healthcare costs and productivity costs were accounted for in the economic analysis. Since a 12 month economic evaluation was undertaken, no discounting was applied to either costs or benefits.

Quantity of resource use and costs were summarised using medians and IQRs due the skewness of the raw data. Means and SDs were also reported. Base case analysis of the economic evaluation was performed based on the intention-to-treat (ITT) population[21] with an assumption for the main analysis that data were missing at random (MAR). The difference in costs was analysed using generalised linear regression model (GLM) with gamma family and a log link, with treatment groups as an independent variable, including baseline National Institutes of Health Stroke Scale (NIHSS), baseline mRS[15] and age as treatment covariates.

For the primary outcome, the mRS score at 12 months was compared following the method detailed in the statistical analysis plan.[22] While for the secondary effectiveness outcome (ie, the QALY gains at 12 months), a linear regression model with treatment group as the factor variable and 12 months AQoL-4D utility value as the dependent variable, adjusted for age, baseline mRS was utilised to estimate the difference in QALY gains over 12 months. Non-parametric bootstrap simulations with 2000 replications were used to calculate 95% CIs around mean difference in costs and effects for cost-effectiveness analysis. To examine the cost-effectiveness of VEM measured against UC, incremental cost-effectiveness ratios (ICERs) were calculated where applicable. For the ICER from a societal perspective, all the costs from health and non-health sector were summed together, including the productivity cost; for ICER of a health sector perspective, all the costs borne by healthcare system were counted (ie, excluding non-healthcare costs and productivity cost). The differences between groups in terms of costs and benefits (ie, QALYs) were compared regardless of the statistical significance of the difference.[23] Cost-effectiveness acceptability curves were plotted to show the probability of VEM being the optimal choice. The ICERs were compared with a common benchmark in Australia of ≤AUD50,000 per QALY.[24] All the analyses were performed using the STATA V.14.0 statistical package.

Sensitivity analyses

To investigate the impact of using country-specific costs, a country dummy variable was added to the GLM analysis to adjust for country effect.[25] Subgroup analysis on the basis of individual countries were also conducted to explore the difference in costs and benefits across countries.

Multiple imputation was performed to test the sensitivity of results to the missing data assumption. The missing patterns were explored with the use of logit regression to investigate if any of the other variables predicted whether a given variable was missing[26] (online supplementary document 4).

Secondary analyses were undertaken to assess the robustness of the base case results. Subgroup analyses were performed at the country-specific level to test for differences in efficacy and costs.

Patient and public involvement

No patient and public were involved.

RESULTS

Between July 2006 and October 2014, 2104 patients (VEM 1054, UC 1050) were recruited across 58 sites from Australia (n=1054, 24 sites), New Zealand (n=189, one site), UK (n=610, 29 sites), Singapore (n=128, one

site) and Malaysia (n=123, one site). At recruitment, over 80% of patients had no prior history of stroke; NIHSS was greater than 7 points (indicating a moderate-to-severe stroke) for around 45% of patients; 26% aged over 80 years and 24% had received recombinant tissue plasminogen activator prior to randomisation.[10] Baseline characteristics were similar between the two treatment groups.[10]

Outcomes

There was no difference between VEM and UC groups in terms of favourable mRS outcome and quality of life (as measured by AQoL-4D) at month 12. Specifically, a comparable percentage of patients from both treatment groups achieved a favourable outcome at 12 months after stroke (between-group difference in probability: 0.030, 95% CI −0.021 to 0.082, adjusted for baseline age and NIHSS). Likewise, for the outcome of AQoL-4D at 12 months, no between-group difference was observed (−0.013, 95% CI −0.043 to 0.017). The detailed mRS outcomes are presented in online supplementary document 5: table I.

Resource use and costs

The proportion of patients reporting use of a specific resource varied from item to item (table 1). In relation to the healthcare resource items, nearly half of the patients experienced rehabilitation hospital admission and more than a quarter of the patients had a stroke-related rehospitalisation, rehabilitation service use (outpatient/provided at home or nursing facility) and ambulant transfers whereas only a small proportion of the patients (less than 10%) recorded the use of private physiotherapy and/or respite care. Regarding non-health-related resource use, the majority of patients (>50%) used some form of special aids or equipment during the 12 months after their index stroke, while nearly 40% of patients received informal care and around 27% reported the use of community services and home modifications. Only 16% (VEM) and 17% (UC) of patients respectively, experienced accommodation changes due to the index stroke. For maid's service use in the home in Singapore and Malaysia, a small proportion (less than 10%) of the patients hired a maid both before and after the index stroke.

With respect to productivity, nearly one in four patients were employed prior to their stroke; this proportion fell to only one in eight patients at 12 months follow-up. Generally, resource use was comparable between VEM and UC groups (p>0.05) across all items (table 1).

The median total medical cost was marginally higher in the UC group ($20 411, IQR $7238 to $63 835) than in the VEM group ($19 271, IQR $6294 to $52 637), primarily due to the higher rehabilitation admission cost in UC. In both groups, the major cost component was acute hospitalisation which accounted for around 30% of medical costs. The median non-medical cost was also marginally higher in the UC group ($438, IQR $0 to $4561) than in the VEM group ($358, IQR $0 to $3334). The median productivity cost was zero for both treatment groups given that less than one quarter of patients were in paid employment before the index stroke. Overall, the median total cost (including productivity cost and non-medical costs) were nominally higher in the UC group ($27 042, IQR $7257 to $63 824) compared with the VEM group ($25 675, IQR $6766 to $63 617). The detailed costs of each resource item and summary costs are presented in table 2. The costs for VEM and UC interventions are summarised in online supplementary document 5: table II.

Generally, the cost from VEM and UC groups were comparable: the differences between VEM and UC groups was $1082 (95% CI -$2399 to $4563) for the total medical cost (online supplementary document 6: table I) and $3 (95% CI -$5 to $12) for the productivity cost per person at 12 months; the between-group difference in the total non-healthcare cost was -$1300 (95% CI -$3361 to $760) over the same period of time.

Cost-effectiveness analysis

The between-group difference in both efficacy and cost outcomes generated from the GLM model are presented in online supplementary document 6: table I.

In the base case health sector perspective analysis, the VEM yielded comparable total medical costs ($1082, 95% CI -$2520 to $4685, p=0.544) and QALY gains (−0.013, 95% CI −0.041 to 0.016) at 12 months. When a societal perspective was adopted, the VEM entailed, again, similar costs with the UC group ($102, 95% CI -$6907 to $7111, p=0.982, including productivity costs) or (-$6, 95% CI -$5476 to $5463, p=0.933, excluding productivity costs) (table 3).

The cost-effectiveness planes and cost-effectiveness acceptability curves from the two perspectives are shown in online supplementary document 7: figures I to V.

Sensitivity analyses

Inclusion of a country dummy variable in the analysis produced similar results to the base case (online supplementary document 6: table II).

The analysis from imputed data including all randomised participants produced consistent results with regard to the incremental cost and effectiveness between treatment groups. For example, from a health sector perspective, VEM was associated with similar costs ($940, 95% CI $−4622 to $4682) and QALY gains (−0.019, 95% CI−0.044 to 0.005) over 12 months. (online supplementary document 6: table III and online supplementary document 7: figures VI-VIII)

The country-specific analysis showed similar results in the between-group differences for both costs and QALYs, indicating that VEM and UC yielded comparable results within each participating countries (table 4).

When a societal perspective was assumed, again, the point estimate of difference in costs between groups across countries varied substantially, with the 95% CIs mostly overlapping (table 4).

DISCUSSION

The 12 months within-trial cost-effectiveness analysis showed that VEM was unlikely to be cost-effective than

Table 1 Quantity of resource use over 12 months (ITT) (median, IQR)

	AU (n=1054)		NZ (n=189)		UK (n=610)		SG (n=128)		MA (n=123)		All Countries	
	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC
Acute hospitalisation												
% of patients using	100	100	100	100	100	100	100	100	100	100	100	100
LoS (days)	21 (6-42)	22 (7-46)	23 (6-57)	25 (8-48)	12 (4-45)	13 (5-4)	16 (4-25)	18 (4-25)	5 (3–8)	4 (2–8)	16 (4-41)	17 (5-41)
Stroke-related rehospitalisation												
% of patients using	30	29	28	33	28	23	20	20	18	23	28	27
No. readmission/s	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	2 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)
Admission to rehabilitation hospital‡												
% of patients using	62	56	60	65	35	34	45	56	0	2	50	47
No. of admission/s	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	1 (0–1)	0 (0–0)	0 (0–0)	0 (0–1)	1 (1–1)
Outpatient rehabilitation programme												
% of patients using	40	39	23	19	12	10	19	25	52	48	30	28
No. of services	15 (6-29)	12 (6-28)	16 (7-28)	17 (12-34)	12 (6-21)	7 (4–14)	32 (20-77)	29 (3-116)	15 (7-24)	16 (4-22)	15 (6-28)	12 (6-27)
Rehabilitation provided at home/nursing facility												
% of patients using	30	33	57	52	50	46	3	2	2	2	35	34
No. of services	9 (4–22)	10 (4-25)	18 (8-29)	16 (9-30)	12 (6-28)	12 (6-30)	81 (63-99)	9 (9–9)	104 (104-104)	8 (8–8)	12 (5-27)	12 (5-28)
Ambulance transfer												
% of pts using	51	53	34	48	41	38	36	28	5	8	43	44
No. of trips	2 (1–3)	2 (1–3)	2 (1–3)	1 (1–3)	2 (1–3)	2 (1–3)	1 (1–2)	1 (1–2)	2 (2–3)	2 (1–3)	2 (1–3)	2 (1–3)
Individual allied health therapy												
% of pts using	N/A	N/A	N/A	N/A	19	15	–	2	20	25	–	–
No. of services	N/A	N/A	N/A	N/A	8 (2–12)	8 (4–15)	–	2 (2–2)	8 (3–10)	16 (8-31)	–	–
Private physiotherapy												
% of pts using	9	8	11	1	5	5	8	8	3	2	8	6
No. of services	5 (3–19)	6 (4–19)	13 (6-18)	3 (3–3)	12 (6-33)	7 (1–14)	18 (16-24)	14 (7-24)	12 (11-13)	8 (8–8)	15 (4-20)	24 (3-19)
Respite care												
% of pts using	3	2	3	2	2	3	–	–	–	2	2	2
No. of services	21 (10-43)	15 (11-35)	12 (10-20)	7 (5–8)	24 (9-40)	21 (12-80)	–	–	–	30 (N/A)	18 (9-39)	18 (9-41)
Accommodation moves												
% of pts using	18	17	19	28	13	14	11	20	23	10	16	17
No. of moves	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–2)	2 (1–2)	1 (1–1)	1 (1–1)
Community services used prior to having a stroke over the past year												
% of pts using	13	17	6	7	5	5	–	–	–	–	9	11
No. of services	26 (26-52)	26 (26-52)	52 (39-88)	46 (14-52)	52 (25-104)	40 (15-131)	–	–	–	–	27 (26-52)	26 (26-52)
Community services used over 12 months after stroke												
% of pts using	30	35	32	28	31	28	–	3	6	–	27	28

Continued

Table 1 Continued

	AU (n=1054)		NZ (n=189)		UK (n=610)		SG (n=128)		MA (n=123)		All Countries	
	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC
No. of services	28 (18-72)	32 (12-78)	130 (47-233)	48 (17-256)	42 (12-185)	90 (12-310)	–	3 (3–3)	6 (3–73)	–	39 (14-119)	39 (12-124)
Home modifications undertaken over 12 months												
% of pts using	27	30	20	17	36	33	16	19	3	10	27	28
No. of mods	2 (1–2)	2 (1–2)	1 (1–2)	2 (1–2)	1 (1–2)	2 (1–2)	1 (1–2)	1 (1–2)	1 (1–1)	1 (1–1)	1 (1–2)	2 (1–2)
Aids and appliances used over 12 months												
% of pts using	46	47	55	63	58	51	44	45	58	59	51	50
No. of aids/appliance used	2 (1–5)	2 (1–4)	3 (2–6)	2 (1–4)	4 (2–6)	4 (2–6)	2 (2–3)	2 (1–3)	2 (1–3)	2 (1–3)	3 (1–5)	3 (1–5)
Working prior to stroke												
% of patients	24	23	38	34	19	21	52	52	45	33	27	26
Hrs worked/week	40 (27-50)	40 (30-50)	40 (37-40)	40 (37-40)	40 (25-48)	37 (25-40)	48 (40-56)	45 (36-50)	42 (40-56)	45 (32-50)	40 (30-50)	40 (30-50)
Proportion working at 12 months												
% of patients	15	12	20	16	7	9	25	22	24	15	14	12
Hrs worked/week	38 (18-40)	25 (12-40)	40 (20-40)	40 (38-40)	35 (26-40)	30 (24-37)	39 (16-46)	35 (23-44)	40 (32-47)	45 (30-50)	38 (20-41)	30 (16-40)
Patients from Malaysia and Singapore who had a maid prior to stroke												
% of patients	–	–	–	–	–	–	19	16	5	10	–	–
No. of maids	–	–	–	–	–	–	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	–	–
Patients from Singapore and Malaysia who had a maid at 12 months following stroke												
% of patients	–	–	–	–	–	–	23	22	5	7	–	–
No. of maids	–	–	–	–	–	–	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	–	–
Receipt of informal care at 12 months												
% of patients	35	39	37	33	41	40	30	36	42	44	37	39
No. of hrs/week	15 (6-34)	12 (4-31)	8 (3–21)	14 (6-30)	21 (9-34)	17 (7-35)	35 (13-46)	16 (4-30)	22 (10-38)	16 (5-26)	18 (7-35)	14 (5-32)

–, no such resource use; all numbers were expressed as median and IQR; AU, Australia; hrs, hours; ITT, Intention-to-treat; LoS, length of stay; MA, Malaysia; mod, modification; No.: number; NZ, New Zealand; pts, patients; SG, Singapore; UC, usual care; UK, United Kingdom; VEM, very early mobilisation; ǂ includes any admissions to rehabilitation hospital following the indexed stroke.

Table 2 Cost of all the resources used over 12 months (AUD)

	AU (n=1054)		NZ (n=189)		UK (n=610)		SG (n=128)		MA (n=123)		All Countries	
	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC
Healthcare cost (AUD)												
Acute hospitalisation												
Median, IQR	$6294 (6294, 9553)	$6294 (6294, 9553)	$6104 (4370, 6104)	$6104 (4370, 6104)	$2763 (1382, 6563)	$3109 (1727, 6563)	$1493 (1493, 1809)	$1493 (1493, 1493)	$1363 (1363, 1572)	$1363 (1363, 1572)	$6294 (2279, 9535)	$6294 (2418, 9553)
Mean, SD	$9883 (9484)	$10 010 (10 508)	$6635 (3244)	$6549 (3555)	$5714 (7876)	$5885 (7101)	$1721 (547)	$1676 (432)	$1482 (212)	$1472 (200)	$7369 (8469)	$7521 (8916)
Stroke-related rehospitalisation												
Median, IQR	$0 (0, 3850)	$0 (0, 3850)	$0 (0, 325)	$0 (0, 2243)	$227 (227, 1401)	$227 (227, 227)	$111 (111, 111)	$111 (111, 111)	$68 (68, 68)	$68 (68, 68)	$111 (0, 1401)	$111 (0, 610)
Mean, SD	$6030 (17 114)	$6473 (21 590)	$651 (1371)	$1507 (2828)	$4524 (13 968)	$3494 (11 349)	$2756 (7565)	$1679 (3465)	$714 (1608)	$603 (1479)	$4610 (14 518)	$4551 (16 707)
Admission to rehab hospital												
Median, IQR	$13 134 (0, 36 371)	$13 134 (0, 38 391)	$11 262 (0, 30 983)	$11 262 (0, 26 486)	$0 (0, 29 788)	$0 (0, 29 788)	$0 (0, 2921)	$1298 (0, 3570)	$0 (0, 0)	$0 (0, 0)	$0 (0, 29 788)	$1136 (0, 29 788)
Mean, SD	$25 667 (38 892)	$26 648 (38 315)	$16 871 (18 536)	$15 573 (16 848)	$12 539 (19 682)	$11 758 (18 390)	$1815 (2759)	$2798 (5082)	$0 (0)	$43 (234)	$18 197 (31 241)	$18 458 (30 811)
Outpatient rehab programme												
Median, IQR	$0 (0, 2451)	$0 (0, 1913)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 36)	$33 (0, 265)	$0 (0, 249)	$0 (0, 478)	$0 (0, 239)
Mean, SD	$2081 (4183)	$1934 (5316)	$821 (2236)	$721 (1991)	$266 (1026)	$155 (676)	$364 (1090)	$562 (1478)	$174 (286)	$126 (206)	$1246 (3244)	$1142 (3976)
Rehab provided at home/nursing facility												
Median, IQR	$0 (0, 717)	$0 (0, 956)	$1168 (0, 4299)	$212 (0, 3821)	$922 (0, 11 064)	$0 (0, 11 064)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 1913)	$0 (0, 1913)
Mean, SD	$1382 (4069)	$1551 (4252)	$3171 (4960)	$3111 (5754)	$12 085 (28 516)	$11 051 (26 723)	$93 (570)	$5 (42)	$97 (719)	$7 (53)	$4447 (16 294)	$4180 (15 203)
Individual allied health visit												
Median, IQR	N/A	N/A	N/A	N/A	$0 (0,0)	$0 (0,0)	$0 (0,0)	$0 (0,179)	$0 (0,0)	$0 (0,0)	N/A	N/A
Mean, SD	N/A	N/A	N/A	N/A	$375 (1144)	$329 (1291)	$432 (1521)	$1126 (3150)	$0 (0)	$0.2 (2)	N/A	N/A
Ambulance transfers												
Median, IQR	$508 (0, 1015)	$508 (0, 1015)	$0 (0, 646)	$0 (0, 646)	$0 (0, 1150)	$0 (0, 575)	$0 (0, 265)	$0 (0, 265)	$0 (0, 0)	$0 (0, 0)	$0 (0, 611)	$0 (0, 610)
Mean, SD	$671 (1057)	$623 (946)	$543 (1082)	$605 (928)	$790 (3209)	$701 (3150)	$164 (348)	$113 (208)	$6 (26)	$14 (64)	$627 (1920)	$578 (1838)
Private physiotherapy												
Median, IQR	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)
Mean, SD	$70 (375)	$124 (797)	$245 (1308)	$4 (36)	$128 (780)	$174 (2102)	$238 (1096)	$333 (1938)	$4 (19)	$1 (9)	$109 (693)	$132 (1336)
Respite care												
Median, IQR	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)

Continued

Table 2 Continued

	AU (n=1054)		NZ (n=189)		UK (n=610)		SG (n=128)		MA (n=123)		All Countries	
	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC
Mean, SD	$48 (355)	$20 (182)	$7 (46)	$2 (15)	$9 (95)	$58 (686)	$0 (0)	$0 (0)	$0 (0)	$1 (8)	$27 (259)	$27 (386)
Sub-total												
Median (IQR)	$29 278 (8218, 63 622)	$29 441 (9811, 62 489)	$20 621 (6068, 46 909)	$23 722 (7316, 40 162)	$18 896 (4030, 48 999)	$20 843 (3682, 47 908)	$4525 (1604, 8668)	$4687 (2724, 10 926)	$1713 (1431, 2532)	$1746 (1431, 2348)	$19 271 (6294, 52 637)	$20 411 (7238, 63 835)
Mean (SD)	$45 620 (51 458)	$47 453 (53 715)	$28 898 (25 011)	$27 986 (22 676)	$34 863 (42 509)	$32 842 (39 517)	$7681 (8828)	$8358 (8787)	$2385 (1587)	$2269 (1574)	$36 351 (45 620)	$36 604 (46 309)
Non-healthcare cost												
Accommodation moves												
Median, IQR	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)
Mean, SD	$2089 (8518)	$2482 (9323)	$5975 (19 614)	$9135 (26 918)	$2901 (12 958)	$2532 (11 125)	$72 (578)	$108 (507)	$425 (1893)	$104 (501)	$2460 (11036)	$2821 (12 212)
Community services												
Median, IQR	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 430)	$0 (0, 174)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)
Mean, SD	$570 (2681)	$1091 (8556)	$238 (950)	$1022 (4113)	$22 275 (294 988)	$10 738 (57 306)	$0 (0)	$244 (1902)	$21 (110)	$0 (0)	$6870 (160 318)	$3786 (31 893)
Home modifications												
Median, IQR	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)
Mean, SD	$805 (6338)	$751 (7715)	$833 (4862)	$565 (3204)	$352 (2133)	$834 (7091)	$234 (1079)	$62 (299)	$49 (369)	$64 (237)	594 (4840)	$676 (6734)
Special aids and equipment												
Median, IQR	$0 (0, 332)	$0 (0, 318)	$70 (0, 549)	$103 (0, 357)	$27 (0, 786)	$0 (0, 846)	$0 (0, 240)	$0 (0, 210)	$15 (0, 218)	$36 (0, 186)	$0 (0, 414)	$0 (0, 414)
Mean, SD	$1986 (7668)	$2787 (10 396)	$2198 (7993)	$1798 (7229)	$1354 (3649)	$1720 (5083)	$1117 (5843)	$1079 (5483)	$153 (252)	$193 (658)	$1660 (6426)	$2141 (8328)
Informal care												
Median, IQR	$24 (0, 503)	$48 (0, 455)	$14 (0, 283)	$0 (0, 149)	$29 (0, 471)	$29 (0, 375)	$0 (0, 114)	$0 (0, 238)	$24 (0, 60)	$9 (0, 50)	$24 (0, 407)	$24 (0, 407)
Mean, SD	$414 (747)	$405 (758)	$236 (536)	$152 (311)	$324 (516)	$324 (645)	$144 (285)	$159 (300)	$43 (57)	$27 (34)	$335 (633)	$322 (660)
Living-in maids												
Median, IQR	N/A	N/A	N/A	N/A	N/A	N/A	$0 (0,0)	$0 (0,0)	$0 (0,0)	$0 (0,0)	N/A	N/A
Mean, SD	N/A	N/A	N/A	N/A	N/A	N/A	$3154 (8146)	$4268 (11 338)	$179 (930)	$83 (504)	N/A	N/A
Sub-total												
Median (IQR)	$459 (0, 3334)	$673 (0, 5209)	$381 (0, 3674)	$638 (103, 14 551)	$758 (0, 5097)	$471 (0, 4725)	$25 (0, 1293)	$194 (0, 6999)	$74 (0, 285)	$57 (0, 318)	$358 (0, 3334)	$438 (0, 4561)
Mean (SD)	$6104 (15 582)	$6985 (17 554)	$7752 (17 751)	$11 981 (27 676)	$27 892 (306 917)	$15 345 (61 750)	$4802 (10 366)	$6177 (13 942)	$861 (2272)	$484 (1113)	$12 043 (164 026)	$9360 (36 504)
Productivity cost												

Continued

Table 2 Continued

	AU (n=1054)		NZ (n=189)		UK (n=610)		SG (n=128)		MA (n=123)		All Countries	
	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC
Median, IQR	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)	$0 (0, 0)
Mean, SD	$75 (317)	$84 (391)	$29 (130)	$14 (54)	$17 (152)	$44 (245)	$6 (29)	$8 (35)	$1 (4)	$0.4 (3)	$46 (246)	$58 (312)
Total cost												
Median (IGR)	$33 203 (9687, 71 902)	$35 143 (12 696, 74 070)	$29 934 (8528, 65 781)	$32 216 (15 710, 68 292)	$25 374 (4712, 64 285)	$30 537 (4629, 67 012)	$6960 (1674, 26 187)	$8810 (3426, 19 493)	$2016 (1561, 3994)	$1816 (1537, 3301)	$25 675 (6766, 63 617)	$27 042 (7257, 63 824)
Mean (SD)	$52 456 (57 264)	$56 408 (62 536)	$40 381 (37 242)	$43 901 (43 170)	$65 530 (332 044)	$49 627 (78 644)	$15 036 (16 921)	$16 340 (19 650)	$3609 (3985)	$2938 (2350)	$50 448 (184 931)	$47 627 (64 249)

Where only a low proportion (ie, less than 50%) of patient reported certain types of resource utilisation, zero median and/or IQR are reported.
*In Malaysia, the length of stay for acute stroke hospitalisation includes a patient's immediate admission to rehabilitation hospital on discharge from hospital as the rehabilitation service immediately following the acute stroke hospitalisation is not routinely provided.
AU, Australia; AUD, Australian dollars; MA, Malaysia; N/A, not available; NZ, New Zealand; SG, Singapore; UC, usual care; UK, United Kingdom; VEM, very early mobilisation.

UC in patients with stroke. Between-group differences in costs and benefits (probability of achieving a favourable outcome of mRS and differences in QALYs) over the 1 year study period were comparable from a health sector perspective. The findings from this economic evaluation is also underpinning an adapted version of trial under way to investigate the effectiveness of optimal rehabilitation in patients with mild-to-moderate stroke (ie, AVERT-DOSE, National Health and Medical Research Council Australia, project grant #1139712).

Our earlier economic evaluation of the phase II AVERT trial which consisted of only 71 patients (38 VEM and 33 UC) from two Australian centres reported that VEM was likely to be a cost-effective intervention with both less cost and more benefit when compared with UC.[27] Since it was a national pilot study with a limited sample, the direct comparison between the results from this and our current economic evaluation is problematic. In addition, inconsistent with the pilot study, no service shifting was observed in the current study. Across all resource use components, the proportion of patients consuming specific types of resources were comparable between the two groups in this study. On the contrary, in the phase II AVERT trial, patients from VEM group were more likely to be discharged earlier from hospital than their UC counterparts; those discharged early tended to use more care provided in the outpatient setting, which incurred lower costs and informal care was not costed. In the current study, the LoS for acute hospitalisation and rehabilitation were similar between treatment groups (median: VEM 16 vs UC 17 days). These differences between the two studies highlight the importance of large, adequately powered studies to inform healthcare policy.

In this study, resources used were valued on the basis of country-specific unit costs sourced for each participating country. To counteract any concern arising from the adoption of this approach, extensive sensitivity analyses were performed to test the robustness of the results. The conduct of incorporation of a country dummy variable into the model or country-specific analysis did not alter the outcomes substantially, with the resultant 95% CIs overlapping to a great extent. Ramsey *et al* 2015 suggest that a country-specific costing approach is likely to yield few qualitative differences in summary measures of cost-effectiveness among countries with similar levels of economic development.[25] Therefore, it was believed that any differences in economic status of the participating countries (as reflected by the unit costs applied in our study) are unlikely to bear a major influence on the results of the cost-effective analysis.

This multinational trial also revealed that in managing patients post-stroke, practice of stroke care varied from country to country. Although 100% of patients with stroke were hospitalised for the initial acute care, the LoS differs significantly greatly, ranging from 4 days (Malaysia) to 25 days (New Zealand), which might be attributable to the different severity of stroke and/or differences in clinical practice care processes. Moreover, in Malaysia, patients

Table 3 Baseline cost-utility analysis ITT

	QALYs	Per capita mean cost (AUD)
Healthcare perspective		
Total medical costs	–0.013 (–0.041, 0.016)	$1082 (-$2520, $4685)
Societal perspective		
Total medical and non-medical costs (excl. productivity cost)	–0.013 (–0.041, 0.016)	-$6 (-$5476, $5463)
Total medical and non-medical costs (incl. productivity cost)	–0.013 (–0.041, 0.016)	$102 (-$6907, $7111)

AUD, Australian dollar; excl., excluding; incl., including; ITT, intention-to-treat; QALYs, quality-adjusted life years.

tended to receive rehabilitation services in an outpatient (ie, up to 52% of patients received the outpatient rehabilitation programme services) rather than inpatient (ie, only up to 2% patients were admitted to rehabilitation hospital) setting; and patients were less likely to use ambulant transfer and apply home modifications, as compared with participants from other countries. This might be a signal for future study around stroke care in Malaysia, research potentially could be helpful to improve the service delivery for outpatient rehabilitation programme. Patients from western countries consumed more community services and rehabilitation services that provided at home/nursing home than their Asian counterparts, which reflects the difference in social welfare and healthcare systems.

Economic evaluations have been conducted for other types of stroke rehabilitation interventions including early-supported discharge service, community- or home-based rehabilitation.[28–36] Generally, these interventions trended towards being cost-saving measured against usual practice. In regards to HRQoL outcomes measured by a series of quality of life instruments (including SF-36, WHOQoL-Bref, Nottingham Health Profile, Sickness Impact Profile and EQ-5D), most studies did not detect an overall significant effect.[28–32 34 35 37] Only one study reported a significant difference improvement in the overall HRQoL score.[36] The conclusions drawn from these economic evaluations of stroke rehabilitation interventions were fairly consistent; the interventions were likely to cost less,[33 34 37–42] although the difference in costs was statistically significant in only one study.[41] None of these studies evaluated the costs and benefits, particularly benefits measured in terms of QALYs, in an aggregated manner, and all were limited by small sample sizes. Another study using a Markov model explored the increased intensity of physiotherapy for stroke patients from a health system perspective, concluding that increased physiotherapy could be cost-effective by improving health outcomes and reducing costs due to the resultant shorter stay in rehabilitation facilities.[43]

Given that it is not practical to obtain a baseline utility value from patients with stroke, in this study, the baseline AQoL value was mapped from mRS score at baseline.[15] While the mapping exercise was carried out using the baseline mRS score and AQoL values at 3 and 12 months, the significant variation in the mapped baseline utility values for patients falling within the same category of mRS hampered its application to the current economic evaluation. Instead, only the 12 month utility values were compared with to approximate the difference in QALY

Table 4 Results of country-specific analysis of costs and benefits

	AU (n=1054)	NZ (n=189)	UK (n=610)	SG (n=128)	MA (n=123)
Total medical costs	$948 (–$4352, $6248)	–$2836 (–$8403, $2730)	$2937 (–$3635, $9509)	–$81 (–$2789, $2627)	$137 (–$324, $599)
Total non- medical costs	–$1318 (–$3038, $403)	–$3959 (–$7769, -$150)	–$1387 (–$7331, $4557)	–$3164 (–$6834, $505)	$200 (–$232, $631)
Total cost (incl. productivity)	–$1735 (–$8482, 5013)	–$8981 (–$18 380, $418)	$1870 (–$13 955, $17 694)	–$2636 (–$9233, $3961)	$479 (–$487, $1446)
Total cost (excl. productivity)	-$1185 (-$7184, $4815)	–$7610 (–$15 302, $82)	$2552 (–$11377, $16 481)	–$1534 (–$6464, $3395)	$416 (–$364, $1196)
QALY gains	–0.036 (–0.076, 0.003)	0.086 (–0.003, 0.176)	–0.010 (–0.064, 0.044)	0.008 (–0.106, 0.123)	0.003 (–0.126, 0.132)

*The p value was >0.05 for the between-group difference in QALYs and cost.
AU, Australia; excl., excluding; MA, Malaysia; NZ, New Zealand; QALY, quality-adjusted life year.; SG, Singapore; UK, United Kingdom.

gains over 1 year between the two treatment groups. Comprehensive sensitivity analyses were undertaken surrounding this assumption. It was observed that there was no noticeable difference among approaches examining the annual QALY gain difference between VEM and UC.

While the results from the clinical study showed that there were no significant differences in either costs or effects between treatment groups, the cost-effectiveness analysis was still performed to investigate the possible ICER of the VEM intervention. It is possible to have greater confidence in the joint outcome of costs and QALYs than looking at them individually.[44]

To the best of our knowledge, this study evaluated the cost-effectiveness of the largest international acute stroke rehabilitation trial ever conducted. The cost-effectiveness analysis was performed alongside the randomised controlled trial, where the costs and benefits data were collected prospectively. Moreover, the Cost CRF was completed by trained and blinded assessors via interviews with individual patients/carers and accessing medical records, which provides for greater accuracy than resource use questionnaires or diaries completed by participants themselves. Since the trial was designed in a pragmatic manner, with close resemblance to real clinical practice, it is believed that the assessment of its cost and cost-effectiveness under this setting reflects the real-life resource use (health and non-health).

This study provides some insights for future economic evaluation alongside multi-country, multi-centre clinical trials. It is important to note that given the large number of centres involved (56 stroke units across five geographical jurisdictions), it was not practical or reasonable to collect centre-specific unit costs which probably leads to huge variations even within a single country. Country-level unit costs were therefore applied to the valuation of resource uses across the trial sites. However, the heterogeneity in the resource utilisation and unit cost among the included countries undermines confidence in the conclusion. A country-specific economic evaluation might be more appropriate in this regard but the lacking of statistical power poses another concern. The current study made a trade-off between them both approaches by presenting both the aggregated (ie, base case of pooling all countries) and disaggregated (ie, sensitivity analysis of individual countries) form of results. The resource utilisation, costs and benefits were also tabulated across all sites and individually to allow close scrutiny from various perspectives.[28] It is believed that this practice can be recommended to other multi-country studies.

A couple of limitations of the study are acknowledged. First, the missing data on total costs from a societal perspective was around 24%, and related mainly to the missing information on community services (10.9%) and productivity loss (10.7%). The base case analysis was based on the ITT population with an assumption of missing pattern being MAR. To account for this, the sensitivity analysis using multiple imputation was undertaken and yielded the identical conclusion (ie, comparable results in costs and benefits between treatment groups). Second, unit costs originating from individual countries were assigned to value resource use. The differences in healthcare systems and cost structures among the five participating countries may potentially confound the cost comparisons between groups. However, analysis by country produced results consistent with the base case, which overcomes any concern that the latter were heavily weighted towards Australia, the largest sample country.

CONCLUSIONS

This economic evaluation alongside a phase III RCT evidenced that based on the ITT population, the VEM intervention for patients with stroke was unlikely to be cost-effective compared with UC. The sensitivity analyses based on the multiple imputation and subgroup analyses by each country separately yielded fairly consistent results. Despite substantial differences observed, in resource use and unit costs across the countries, the marginal differences between VEM and UC were consistent. Overall, the VEM intervention was demonstrated to be comparable with UC in terms of both benefits and costs at 1 year, however given its poorer outcomes at 3 months, VEM cannot be recommended to clinicians, patients or policymakers.

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Collaborators The AVERT Trial Collaboration Group.

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