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

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Title Page

Title

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

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Economic evaluation of AVERT trial

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Objectives While Very Early Mobilisation (VEM) intervention for stroke patients was shown not to be effective at 3 months, 12 -month clinical and economic outcomes remain unknown. It was aimed to assess cost-effectiveness of a VEM intervention within a Phase III randomised controlled trial (RCT).

Design An economic evaluation alongside a RCT

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 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. Dichotomised Modified Rankin Scale (mRS) scores (0-2 vs 3-6) 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 (ITT) basis and 95% confidence intervals (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 significant 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 AUD\$102, 95%CI: -\$6907 to \$7111, from a societal perspective including productivity cost).

The probability of VEM being cost-effective was between 19% and 44%. 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.

Trial registration Australian New Zealand ClinicalTrials Registry, number ACTRN12606000185561.

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Strength and limitations

- 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-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.

Introduction

Stroke is one of the biggest killers and a leading cause of disability worldwide.^{1 2} 65% 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 7}

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 2,104 patients enrolled from Australia, New Zealand, United Kingdom, Singapore and Malaysia.⁸ The evidence from this trial indicated that at three months after stroke, early mobilisation of patients was associated with a reduction in the probability of a favourable outcome as defined by a modified Rankin Scale (mRS) score of 0-2 compared to that in the UC group.⁸ However, it is uncertain whether this intervention effect extended after the acute phase of stroke. Given the implications of stroke burden sustained beyond the acute phase (i.e., 3 months), it is also important to ascertain clinical outcomes at a longer time point. For example, it has been reported that the recurrence rate of stroke between 3 months and 1 year was approximately 3.1%.⁹ Moreover, "steady state" after an acute episode of stroke typically occurs within 3-6 months for patients with lower baseline mRS score (i.e. lower disability after stroke) and longer for those with higher initial mRS (i.e. higher level of disability after stroke).¹⁰

From a decision-maker's perspective, the long-term outcomes of patients after stroke bear substantial economic and policy implications. With increasingly scarce health resources, it is imperative to examine the longer-term cost-effectiveness credentials of VEM in an early rehabilitation setting for patients after stroke even if this intervention was inferior to usual

care at 3-month follow up.⁸ The clinical findings from Phase III AVERT trial were inconsistent with that of our Phase II study;¹¹ however, the short term follow-up (only 3 months), single country study design, and small sample size (N=71) of the Phase II study may account for this discrepancy, and rendered the conclusion of associated economic evaluation not generalizable to a broader context.

This economic evaluation was conducted alongside the Phase III RCT.⁸ 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 (UC).

Methods

The economic analysis was undertaken following the previously published plan.¹² It also conforms to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.¹³ Ethics approval was granted by relevant institutions.

Intervention and comparator

The trial design has been reported in detail elsewhere.⁸ 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 (UC) 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-4D (AQoL-4D)¹⁴ were used as the effectiveness measures in the economic evaluation. The AQoL-4D instrument is a multi-

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attribute utility scale used to assess the health-related quality of life (HRQoL)¹⁵; it was administered at 3 and 12 months.

Outcome of mRS was dichotomised into "favourable" (mRS 0-2) and "poor" (mRS 3-6) based on patients outcomes at 12-month follow up.⁸ The difference in the probability of patients achieving a favourable mRS outcome (mRS 0-2) 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, the mRS score at baseline⁸ was used as a surrogate measure of patient utility during the acute phase. The detailed methods of this work are reported elsewhere¹⁶ 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 and nurses delivering VEM (or UC) to patients. The mean of the total physiotherapist time (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 (Supplementary document 2). Cost CRF from other participating countries could be requested from corresponding author.

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 (Supplementary document 3). Unit costs from a country with a similar economic status and healthcare system were used where local countryspecific unit costs were unavailable.

All costs are expressed in Australian dollars (AUD) for the 2015 reference year value and can be converted to United States dollar (USD) using the Purchasing Power Parity rate 1 USD=1.463 AUD¹⁷. The currency of other countries was converted to AUD using the corresponding exchange rate. The country-specific Consumer Price Index (CPI) from the health sector was employed to adjust costs not valued in the year of 2015.

The details of resource use and unit cost for acute stroke hospitalisation, rehospitalisation, rehabilitation, non-health sector costs and productivity cost are provided in Supplementary document 3.

Statistical analysis

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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 interquartile ranges (IQRs) due the skewness of the raw data. Means and standard deviations (SDs) were also reported. Base case analysis of the economic evaluation was performed based on the Intention-to-Treat (ITT) population¹⁸ 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 NIHSS, baseline mRS¹² 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.¹⁹ While for the secondary effectiveness outcome (i.e. 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% confidence intervals (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 perspective, all the costs borne by healthcare system were counted (i.e. excluding non-healthcare costs and productivity cost). The differences between groups in terms of costs and benefits (i.e. QALYs) were compared regardless of the statistical significance of the difference.²⁰ 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 \leq AUD50,000 per QALY.²¹ All the analyses were performed using the STATA 14.0 statistical package (StataCorp. 2015. Release 14. StataCorp LP.)

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.²² 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 missing²³ (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.

Results

Between July 2006 and October 2014, 2,104 patients (VEM 1,054; UC 1,050) were recruited across 58 sites from Australia (1,054), New Zealand (189), United Kingdom (610), Singapore (128) and Malaysia (123). 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

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patients; 26% aged over 80 years and 24% had received recombinant tissue plasminogen activator prior to randomisation⁸. Baseline characteristics were similar between the two treatment groups⁸.

Outcomes

In terms of the mRS score, a comparable percentage of patients from both treatment groups achieved a favourable outcome at 12 months after stroke, resulting in a non-significant difference (0.030, 95%CI:-0.022 to 0.082, p=0.252) between groups in the analyses adjusted for baseline age and NIHSS (Supplementary document 5: Table III). Since there was no significant intervention effect together with no accepted willingness-to-pay (WTP) per unit increase in probability of achieving a better mRS outcome, further estimation of the ICER was considered not meaningful (i.e. no cost-effectiveness plane or cost-effectiveness acceptability curve could be generated). For the outcome of QALY gains across 12 months, a non-significant treatment effect was also observed (0.013, 95%CI:-0.041 to 0.016, p=0.389) (Supplementary document 5: Table III).

Given the excessive variability in observed AQoL (i.e. 3 and 12 months) within the same mRS category, it was considered inappropriate to apply the mapped utility to measure the incremental QALY gains between two treatment groups. Instead, the differences in AQoL-4D utility value measured at 12 months follow-up between treatment groups were used to approximate the incremental QALY gains across 12 months provided that patients were well balanced between two groups and there were no significant discrepancies in patients characteristics across all baseline variables, including baseline AQoL-4D utility value.

The results of estimation in QALY gains based on the mapping (i.e. deriving the baseline utility from the baseline mRS score) are provided in the supplementary documents. Generally, the difference in QALY gains between VEM and UC groups were fairly consistent across different methods (Supplementary document 5).

Costs

Generally, the differences between VEM and VC groups was \$1082 (95%CI: -\$2399, \$44563) for the total medical cost (Supplementary document 6: Table III) and \$3 (95%CI: - \$5, \$12) for the productivity cost per person at 12 months. Similarly, the between-group difference in the total non-health care cost was -\$1300 (95%CI: -\$3361, \$760) over the same period of time. The detailed costs of each resource item and summary costs are presented in Supplementary document 6: Table III.

The details relating to the resource use item collected, quantities of resource utilisation and intervention costs are summarized in Supplementary documents 6 and 7.

Cost-effectiveness analysis

The between group difference in both efficacy and cost outcomes generated from the GLM model are presented in Supplementary document 5: Table III.

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: -

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0.041 to 0.016) at 12 months, with a 19% probability being a cost-effective intervention compared to UC. 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), with a higher probability (42-44%) of being cost-effective (Table 1).

The cost-effectiveness planes and cost-effectiveness acceptability curves from the two perspectives are shown in Figures 1 and 2, and Supplementary document 8: Figures I to IV. Sensitivity analyses

Inclusion of a country dummy variable in the analysis produced similar results to the base case (Supplementary document 5: Table I).

The analysis from imputed data including all randomised participants produced consistent results with regard to the incremental cost and effectiveness between treatment groups. 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. Likewise, if a societal perspective was taken, VEM was associated with comparable costs (\$1413, 95%CI:-\$4044 to \$6871, including productivity cost; \$1704, 95%CI:-\$3817 to \$7226, excluding productivity cost) and QALY gains (-0.019, 95%CI:-0.044 to 0.005) (Supplementary document 6: Table IV). Even though the point estimate of difference in total costs between groups from a societal perspective varied considerably, the 95% confidence interval derived from base case and multiple imputation analyses were nearly identical (Supplementary document 5: Table IV). The cost-effectiveness plane derived from the multiple imputation

analysis from the two different perspectives are shown in Supplementary document 8: Figures V to VII.

From a health sector perspective, the between-group difference for each participating country yielded consistent conclusions with the base case analysis. VEM was associated with both non-significantly different costs and benefits (i.e. QALY gains at 12 months) compared to the UC, although the point estimate of the cost difference between groups varied from country to country, ranging from -\$2836 (New Zealand) to \$2937 (UK) (Supplementary document 5: Table II).

The country-specific analysis showed an inconsistent trend in the between-group differences for both costs and QALYs. It was found that VEM was likely to cost less and associated with a greater gain in QALYs in comparison to UC in New Zealand and Singapore. Meanwhile, except for total medical cost, VEM seemed to incur less cost while leading to less gain in QALYs at month 12 months for participants from Australia, whilst in the United Kingdom, VEM was associated with higher cost and lower QALY gains than UC. Lastly, for patients from Malaysia, VEM contributed to higher cost while greater QALY gains at 12 month follow-up. It is worth noting that none of the afore-mentioned between-group differences were statistically significant (Supplementary document 5: Table II).

When a societal perspective was assumed, again, the point estimate of difference in costs between groups across countries varied substantially, with the 95% confidence intervals mostly overlapping (Supplementary document 5: Table II).

Discussion

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The 12 months within-trial cost-effectiveness analysis showed that VEM was associated with a low probability (19-49%) of being more cost-effective than 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 one year study period were not significant, even though the point estimates indicated that VEM was dominated (less effective, more costly) by UC from a health sector perspective. The base case analysis showed that the probability of VEM being cost-effective was 21% from a health sector perspective and 45% from a societal perspective.

The cost-effectiveness acceptability curve showed that, with the increasing WTP per QALY threshold, the probability of the VEM intervention being cost-effective actually decreases. This is probably due to the fact that VEM was both less costly and less effective than UC, so the lower WTP/QALY threshold (<\$50,000) afforded a higher probability of being the cost-effective intervention, and vice versa.

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 to UC.¹¹ 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 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 health care 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% confidence intervals 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.²² 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 tended to receive rehabilitation services in an outpatient rather than inpatient setting, compared to participants from other countries. Patients from western countries consumed more community services than their Asian counterparts, which reflects the difference in social welfare systems. The country-specific subgroup analysis also echoed these findings. It was

observed that, except for Malaysia, VEM was associated with less total non-medical cost than UC. The cost-effectiveness credentials varied from country to country: VEM was dominated by UC in United Kingdom and dominates UC in New Zealand and Singapore, while it was cost saving but had less QALY gains in Australia. This indicates that even though, compared with UC, VEM is unlikely to be cost-effective when compared to UC. However, in some countries (e.g. United Kingdom) where patients tend to have heavy use of non-medical health resources, VEM might be cost-saving in comparison to UC.

Economic evaluations have been conducted for other types of stroke rehabilitation interventions including early-supported discharge service, community- or home-based rehabilitation. ²⁴⁻³² Generally, these interventions trended towards being cost-saving measured against usual practice. In regards to health-related quality of life (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.^{24-28 30 31 33} Only one study reported a significant difference improvement in the overall HRQoL score.³² The conclusions drawn from these economic evaluations of stroke rehabilitation interventions were fairly consistent; the interventions were likely to cost less.^{29 30 33-38} although the difference in costs was statistically significant in only one study.³⁷ 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.³⁹

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.¹² Whilst 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 to approximate the difference in QALY gains over one 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, and the difference was unanimously statistically insignificant.

Whilst 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.⁴⁰

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-effectiveness under this setting reflects the actual value for money of this intervention.

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

BMJ Open

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 (i.e. base case of pooling all countries) and disaggregated (i.e. 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. ²⁴ It is believed that this practice can be recommended to other multi-country studies.

A couple of limitations of the study are acknowledged. Firstly, 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 (i.e. no significant difference in costs and benefits between treatment groups). Secondly, unit costs originating from individual countries were assigned to value resource use. The differences in health care 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 associated with higher costs from health sector and societal perspectives, lower QALYs at 12 months, and was unlikely to be cost-effective compared to UC, although the between-group difference in cost and QALYs gains were not statistically significant. The sensitivity analyses based on the multiple imputation and subgroup analyses by each country separately yielded fairly consistent results. Overall, the VEM intervention was demonstrated to be comparable with UC in terms of both benefits and costs at one-year, however given its poorer outcomes at 3 months, VEM cannot be recommended to clinicians, patients or policymakers.

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Figure Legends

Figure 1 cost-effectiveness plane_ health sector perspective

Figure 2 cost-effectiveness plane_ societal perspective (including productivity cost)

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Table 1. Baseline cost-utility analysis_ ITT

	QALYs	Per capita mean cost (AUD)	Probability of being cost-effective
Health care perspective			
Total medical costs	-0.013	\$1082	19%
	(-0.041, 0.016)	(-\$2520, \$4685)	
Societal perspective			
Total medical and non-medical	-0.013	-\$6	42%
costs (excl. productivity cost)	(-0.041, 0.016)	(-\$5476, \$5463)	
Total medical and non-medical	-0.013	\$102	44%
costs (incl. productivity cost)	(-0.041, 0.016)	(-\$6907, \$7111)	

or of the terms only

ITT: Intention-to-treat; QALYs: Quality-adjusted Life Years; AUD: Australian dollar; excl: excluding; incl: including

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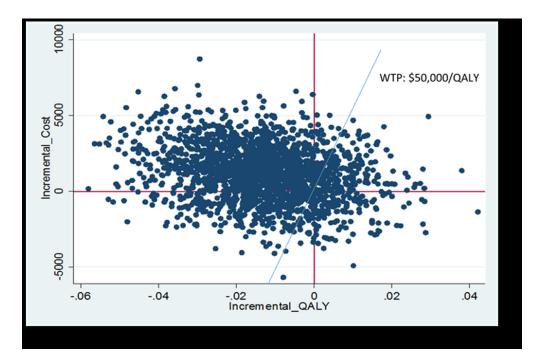


Figure 1 cost-effectiveness plane_ health sector perspective

174x114mm (150 x 150 DPI)

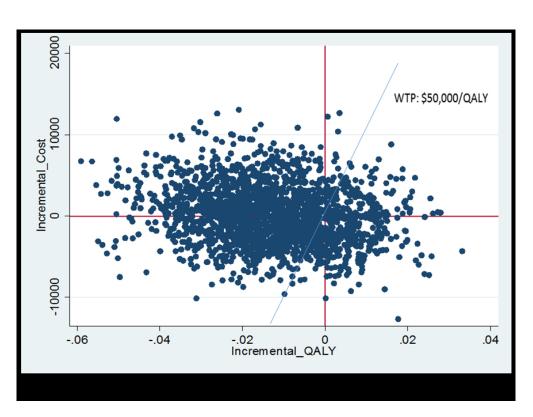


Figure 2 cost-effectiveness plane_ societal perspective (including productivity cost)

146x109mm (150 x 150 DPI)

Supplementary document 1: Mapping baseline mRS score to utility of AQoL-4D

Methods

Generalized additive model (GAM) with spline smother was used to map AQoL from premorbid mRS, stroke severity, and/ or age group. The performance of the models was evaluated using mean absolute, mean squared errors (MAE and MSE) and R2. 10-fold crossvalidation was implemented for model validation. The mapped baseline utility of AQoL-4D was used in the following models.

The analyses are structured as follows:

Model 1:

a) A complete case model with the utility value at 12 months as an output, group as an input, and pre- morbid mRS as a covariate;

b) A complete case model with the utility value at 12 months as an output, group as an input, and pre- morbid mRS + stroke severity as covariates;

c) A complete case model with the utility value at 12 months as an output, group as an input, and pre- morbid mRS + stroke severity + age group as covariates;

d) Sensitivity analyses for the unadjusted model using pattern-mixture models that confirm that there is no statistically significant difference between the groups for the plausible range of changes of a parameter that describes the departure from the assumed "missing-at-random" pattern.

Model 2:

a) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output and group as an input;

b) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output and group as an input + stroke severity as a covariate;

c) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output and group as an input + stroke severity and age group as covariates;

d) Sensitivity analyses for the unadjusted model using pattern-mixture models that confirm that there is no statistically significant difference between the groups for the plausible range of changes of a parameter that describes the departure from the assumed "missing-at-random" pattern.

Model 3:

a) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output, group as an input, and baseline mapped utility value as a covariate;

b) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output, group as an input, and baseline mapped utility value + stroke severity as covariates;

c) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output, group as an input, and baseline mapped utility value + stroke severity + age group as covariates;

d) Sensitivity analyses for the unadjusted model using pattern-mixture models that confirm that there is no statistically significant difference between the groups for the plausible range of changes of a parameter that describes the departure from the assumed "missing-at-random" pattern.

Model 4:

a) A complete case model with the utility value at 12 months as an output, group as an input, and baseline mapped utility value as a covariate;

b) A complete case model with the utility value at 12 months as an output, group as an input, and baseline mapped utility value + stroke severity as covariates;

c) A complete case model with the utility value at 12 months as an output, group as an input, and baseline mapped utility value + stroke severity + age group as covariates;

d) Sensitivity analyses for the unadjusted model using pattern-mixture models that confirm that there is no statistically significant difference between the groups for the plausible range of changes of a parameter that describes the departure from the assumed "missing-at-random" pattern.

Results

Table I. Difference in utility values between treatment groups by different models

	a	b	c	d	
				1	2
Model 1	-0.011	-0.015	-0.016	-0.026	0.006
	(-0.042, 0.020)	(-0.042, 0.011)	(-0.042,0.010)	(-0.062,	(-0.030,
				0.009)	0.041)
Model 2 [*]	-0.001	-0.007	-0.008	-0.007	0.005
	(-0.046, 0.044)	(-0.047, 0.034)	(-0.048, 0.031)	(-0.062,	(-0.050,
				0.048)	0.060)
Model 3 [*]	-0.008	-0.014	-0.015	-0.014	0.002
	(-0.043, 0.026)	(-0.043, 0.016)	(-0.043, 0.014)	(-0.052,	(-0.050,
				0.033)	0.045)
Model 4	-0.008	-0.014	-0.015	-0.026	0.006
	(-0.043, 0.026)	(-0.043, 0.016)	(-0.043, 0.014)	(-0.062,	(-0.030,
				0.010)	0.042)

*models 2 and 3 used the mapped baseline AQol utility to estimate the QALY gains over 12 month for each patient.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml As shown in Table 1, using the mapped baseline AQoL utility value and the 12 month AQoL

utility value to calculate the difference in QALYs between treatment groups (results from models 2 and 3) yielded similar results to the primary analysis (-0.013, 95%CI [-0.043, 0.018]), and the 95% confidence

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Supplementary document 2: Cost Case Report Form (CRF)

The Cost CRF was originally developed via pathway analysis during Phase II of AVERT to identify resource items associated with the trial11. Since the Phase II of AVERT trial was a national project and resource utilisation tools were tailored to the Australian setting, the form was further modified to accommodate international differences in the acute service delivery, rehabilitation and post-acute care. An extensive review of country-specific literature and consultation with international AVERT project team members based in each country were e Cost L. undertaken to tailor the Cost CRF tool to each participating country.



Case Report Form - Cost

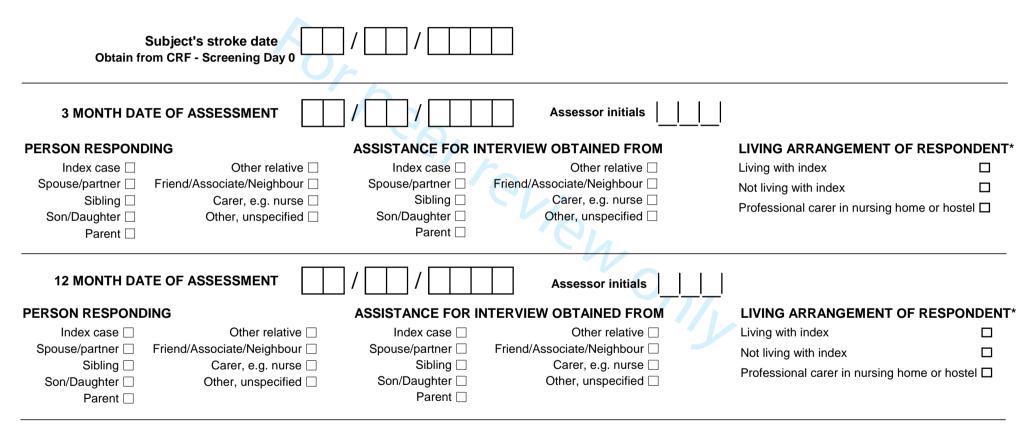


National Stroke PATIENT STUDY NUMBER Research Institute

PATIENT INITIALS

NOTE: this one form is to be completed AND faxed following BOTH the 3 and 12 month interviews.	
When CRF Cost complete at 3 months AND at 12 months, fax all pages 25-36 to the Data Fax.	

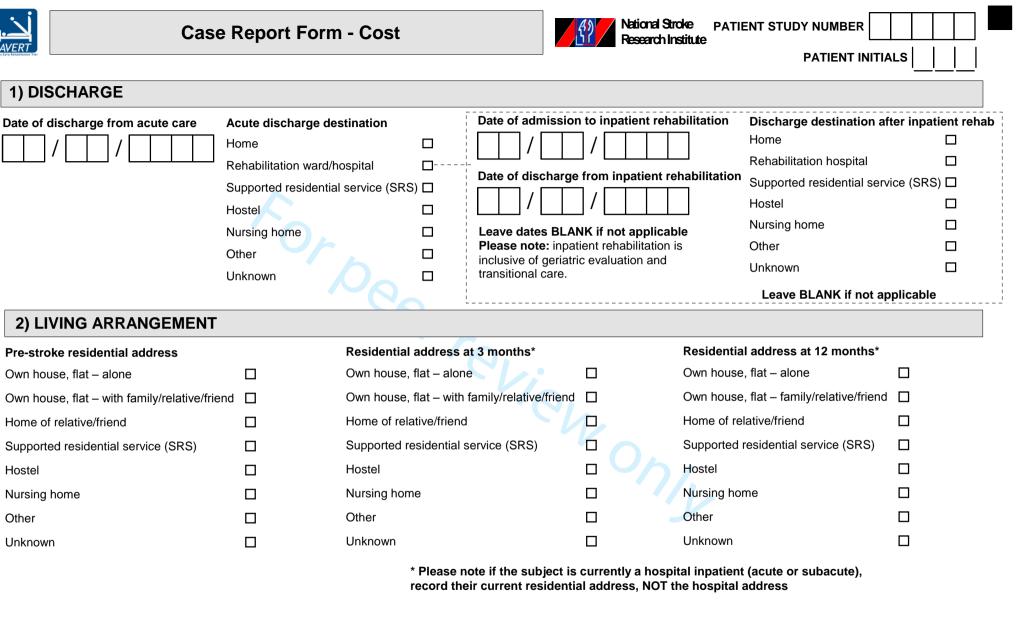
Instructions to the person responding: These questions are about health care provided as a consequence of the stroke which occurred on (give date of stroke) or as a result of any further stroke. I will be asking about health care such as visits to hospital, rehabilitation, therapy at home, equipment and work. To help us work out the cost of stroke to the community, and to you and your family, I will be asking about how often services were provided and their cost.



* Please note: this is the 'normal' living arrangement of the respondent with respect to the subject, even if the subject is currently in hospital

Page 35 of 76

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3) CHANGE IN LIVING ARRANGE	IENTS					
As a consequence of your stroke, have you no If NO, proceed to question 4.	eded to change your place of residence?	3	months	Yes 🗌	No 🗌 🛛 U	nknown 🗖
	Please note: if subject has been a hospital inpatient this is NOT a change of residence				No 🗌 🛛 U	nknown 🗖
DATE OF MOVE	LOCATION					
1) / /	Own home or unit Image: Constraint of the second					
2) / /	Own home or unit Home of relative/friend SRS Hostel Nursing home Other					
3)	Own home or unit Image: Constraint of the second secon					
4) / /	Own home or unit Image: Constraint of the second					
4) AMBULANCE TRANSFERS: EN	ERGENCY AND NON-EMERGEN	CY				
As a consequence of your stroke, have you re If NO, please proceed to question 5	equired ambulance transport after your acut	e admission to hospital?*	3 months	Yes 🗌	No 🗖	Unknown 🗌
· · · · · · · · · · · · · · · · · · ·			3-12 mon	ths Yes 🛛	No 🗖	Unknown 🗌
Count number of ambulance trips (recruit		acute transfers (eg - acute to	rehab)			
Count number of ambulance trips (fro	n 3 to 12 months)					



Case Report Form - Cost



National Stroke PATIENT STUDY NUMBER Research Institute

PATIENT IN	ΙΤΙΑ	LS	

) Have you been readmitted to hospital or attended the for any stroke related problems?	e emergency depart	ment as a consequence of another stroke	3 months	Yes 🛛 No 🗖	Unknow
			3-12 months	Yes 🗌 No 🗌	Unknow
NLY include information for admissions and attendar oke-related problems and CRF completion manual fo			of		
NO, proceed to question 6					
) If YES, Start with the earliest admission or attendance. tes BLANK (complete dates at 12 month assessment)	If patient NOT discha	rged at 3 month assessment, leave discharg	e		If patient discharg
Admission or Attendance 1 - Hospital name	Hospital code	Date admitted	Date d	ischarged	<u>12 mont</u> assessn
					cross be
Admission or Attendance 2 - Hospital name	Hospital code	Date admitted	Date d	lischarged	
Admission or Attendance 3 - Hospital name	Hospital code	Date admitted	Date o	lischarged	
				/	
Admission or Attendance 4 - Hospital name	Hospital code	Date admitted	Date o	lischarged	
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Admission or Attendance 5 - Hospital name	Hospital code	Date admitted	Date o	lischarged	



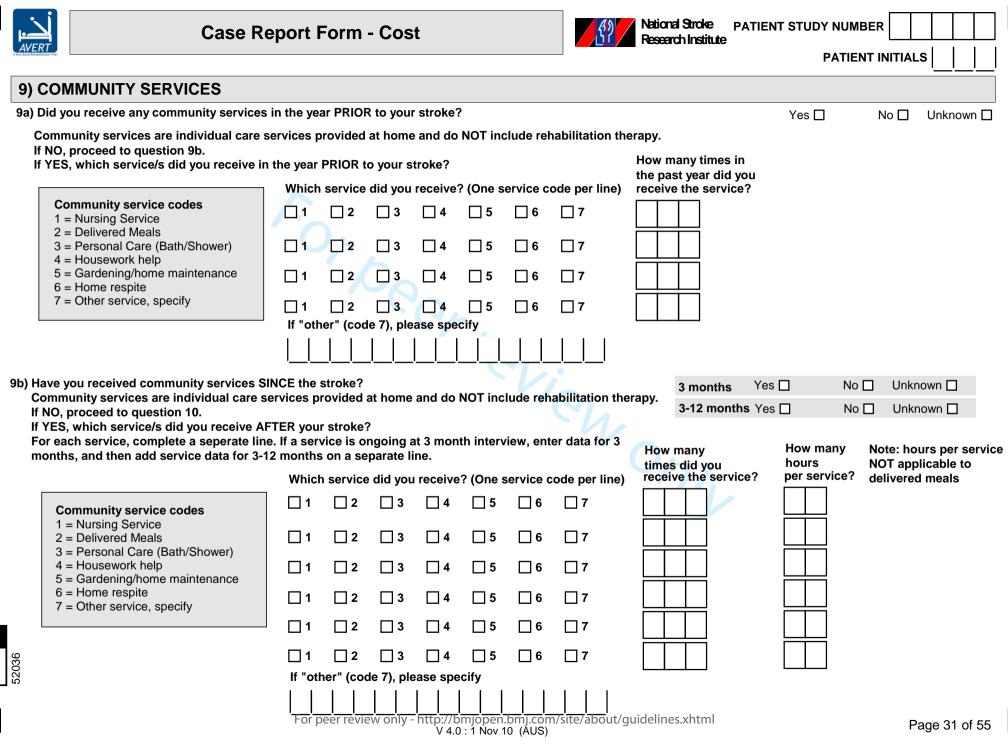


AVER	Case Report Fo	rm - Cost		archinstitute PATIENT STUDY N	
6) I	NPATIENT REHABILITATION ADMISSIO	N			' <u></u> '
-	your stroke on (give date of stroke), were you admitt		ospital or other hospital	3 months Yes	No 🗌 Unknown 🛛
	e you received rehabilitation treatment? Please include			3-12 months Yes □	No 🗌 Unknown 🛛
	ation' and 'transitional care'				
	, proceed to question 7. 5 , complete inpatient rehabilitation admission details, sta	arting from your first inpati	ant rehabilitation admission		If patie
	ent NOT discharged at 3 month assessment, leave discl			nt)	discha
·		Rehab hospital			assess
	Admission 1- Rehabilitation hospital name	code	Date admitted	Date discharg	ged cross
	Admission 2- Rehabilitation hospital name	Rehab hospital code	Date admitted	Date discharg	ged
		Rehab hospital			
	Admission 3- Rehabilitation hospital name	code	Date admitted	Date discharg	jed
7)	OUTPATIENT REHABILITATION PROGE	RAM			
Did	you attend or are you attending an outpatient rehab	ilitation program as a co	insequence of your stroke?	3 months Yes	No 🗌 Unknow
	with physiotherapy, occupational therapy, speech the				
An c	butpatient rehabilitation program is any rehabilitation pro ted at a hospital or community facility.	gram where the patient at	tends a facility. The program can be	e 3-12 months Yes	No 🗌 Unknow
	D, proceed to question 8.				lf p
If YE	ES , complete outpatient rehabilitation details, starting fro	m your first outpatient reh	abilitation visit.		Total dis
If pa	tient NOT discharged at 3 month assessment, leave dis		of days attended BLANK (complete	e dates at 12 month assessment)	
Δ	dmission 1 - Outpatient rehabilitation name	Rehab facility code	Date admitted	Date discharged	of DAYS as: attended cro
		Rehab facility			
A	dmission 2 - Outpatient rehabilitation name	code	Date admitted	Date discharged	
			' /		
a 52036	dmission 3 - Outpatient rehabilitation name	Rehab facility code	Date admitted	Date discharged	
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Page 39 of 76

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	Case Report	t Form - Cost		52	National Stroke Research Institute	PATIENT STU			s
8) REHABILITAT	TION SERVICES PROV	IDED AT HOME OF	R IN A NURSING	HOME					· <u> </u>
	litation program provided to your stroke? e.g. with physic				3 months 3-12 months	Yes 🗌	No 🗆	Unknown Unknown	
sessions.	ilitation details, starting from th ed at 3 month assessment, lea	-		NK	3-12 monuis		Tota	1	If patient no discharged 12 month
Time 1 - Rehabilitation se	prvice name	Rehab service code	Start date		Cease	date /		ber of SIONS	assessmen cross box.
Time 2 - Rehabilitation se	rvice name	Rehab service code	Start date		Cease	date /			
Time 3 - Rehabilitation se	rvice name	Rehab service code	Start date		Cease	date /			
Time 4 - Rehabilitation se	rvice name	Rehab service code	Start date		Cease	date /			
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Page 41 of 76

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10) HOME MODIFICATIONS

If NO, proceed to question 11

Has your home been modified as a consequence of your stroke?

Case Report Form - Cost

e.q. installation of rails, bathroom modifications, installation of ramp(s), kitchen modifications etc

If YES, please indicate the type of modifications, who supplied the modifications and estimate any personal cost to you. SUPPLIERS



National Stroke PATIENT STUDY NUMBER Research Institute

Yes 🗆

Yes 🗖

3 months

3-12 months

ΡΑΤΙ	FNT	INITI	AI S

No 🗌

No 🗆

Unknown 🗌

Unknown

3	336
	52(

Type of modification	1 = Hospital/rehabilitation centre 2 = Patient/family	3 = Veteran's Affairs 4 = Local Council	5 = Housing commision 6 = Charity	7 = Other (specify)
(check box for each type supplied)	Who supplied the modificat	ion? If supplier is "o	other", please specify	
Rail(s) for steps/stairs		6 🗆 7 🔄 🗌	Cost to you	u/family* - \$
□ Ramp(s)		6 □ 6 □ 7 <u> </u> _	Cost to you	u/family* - \$
□ Platform step(s)		6 🗆 7 📙 📕	Cost to you	u/family* - \$
☐ Shower, bath and toilet rail(s)		· □ 6 □ 7	Cost to you	u/family* - \$
Shower(s) modification	□1 □2 □3 □4 □5	;	Cost to you	u/family* - \$
☐ Toilet(s) modification	□1 □2 □3 □4 □5	6 🗆 7 📗 📗	Cost to you	u/family* - \$
Remove/modify door(s) from shower/toilet/bath		6 □ 7	Cost to you	u/family* - \$
Kitchen modifications	□1 □2 □3 □4 □5	6 □ 6 □ 7 	Cost to you	u/family* - \$
Other modification (specify below) Other home modification - 1				
		5 🗆 6 🗆 7 📃 📃	Cost to you	ı/family* - \$
Other home modification - 2				
		6 🗆 6 🗆 7	Cost to you	u/family* - \$

	* If an overall cost is provided, please indicate type of modifications above, and provide the total cost here, INCLUSIVE of any known itemised costs listed above:
	Overall Cost \$
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ave you been given, hired or purchased any special equipment, aids or special food as a consequence of stroke Prompt: These may have been provided by an Occupational Therapist or Physiotherapist. What about a? In No, proceed to question 12 Walking aids Mobility aids Eating aids Single point stick Manual wheelchair Built-up cutlery Three or four point stick Electric wheelchair/scooter Plate guard Walking frame - pick up Car steering wheel knob Non-slip mat Walking frame - gutter (forearm suppt) If yes, number of days used: 3 months 3-12 months 1 1 Lounge and bedroom equipment Bathroom equipment Continence aids Chair platform/blocks raise Over-toilet seat Urine bottle Cushion to relieve pressure Toilet surround Bedpan	3 months Yes 3-12 months Yes	No Unknown No Unknown Kitchen aids Tap handles Chopping board Modified knife Vitamiser/blender Non-slip mat
Wolking aids Mobility aids Eating aids Single point stick Manual wheelchair Built-up cutlery Three or four point stick Electric wheelchair/scooter Plate guard Walking frame - pick up Car steering wheel knob Non-slip mat Walking frame - wheelie Special food e.g. NG/PEG If yes, number of days used: Walking frame - gutter (forearm suppt) fryes, number of days used: 3 months Crutch(es) Bathroom equipment Continence aids Over-toilet seat Urine bottle	3-12 months Yes	Kitchen aids Tap handles Chopping board Modified knife Vitamiser/blender
Walking aids Mobility aids Eating aids Single point stick Manual wheelchair Built-up cutlery Three or four point stick Electric wheelchair/scooter Plate guard Walking frame - pick up Car steering wheel knob Non-slip mat Walking frame - wheelie Special food e.g. NG/PEG If yes, number of days used: Walking frame - gutter (forearm suppt) If yes, number of days used: 3 months Crutch(es) Bathroom equipment Continence aids Chair platform/blocks raise Over-toilet seat Urine bottle		 Tap handles Chopping board Modified knife Vitamiser/blender
□ Single point stick □ Manual wheelchair □ Built-up cutlery □ Three or four point stick □ Electric wheelchair/scooter □ Plate guard □ Walking frame - pick up □ Car steering wheel knob □ Non-slip mat □ Walking frame - gutter (forearm suppt) □ Car steering wheel knob □ Special food e.g. NG/PEG □ Walking frame - gutter (forearm suppt) □ Crutch(es) □ Special food e.g. NG/PEG ■ Counge and bedroom equipment □ Over-toilet seat Continence aids □ Chair platform/blocks raise □ Over-toilet seat □ Urine bottle		 Tap handles Chopping board Modified knife Vitamiser/blender
□ Three or four point stick □ Electric wheelchair/scooter □ Plate guard □ Walking frame - pick up □ Car steering wheel knob □ Non-slip mat □ Walking frame - wheelie □ Special food e.g. NG/PEG □ Walking frame - gutter (forearm suppt) □ Crutch(es) 3 months □ Crutch(es) ■ Bathroom equipment □ Over-toilet seat □ Urine bottle		 Chopping board Modified knife Vitamiser/blender
□ Walking frame - pick up □ Car steering wheel knob □ Non-slip mat □ Walking frame - wheelie □ Special food e.g. NG/PEG □ Walking frame - gutter (forearm suppt) □ Crutch(es) □ Crutch(es) Bathroom equipment □ Chair platform/blocks raise Bathroom equipment □ Over-toilet seat □ Urine bottle		Modified knife Vitamiser/blender
□ Walking frame - wheelie □ Special food e.g. NG/PEG □ Walking frame - gutter (forearm suppt) □ Crutch(es) □ Crutch(es) 3 months □ Chair platform/blocks raise Bathroom equipment □ Over-toilet seat □ Urine bottle		Vitamiser/blender
□ Walking frame - gutter (forearm suppt) □ Special food e.g. NG/PEG □ Crutch(es) If yes, number of days used: 3 months □ 3-12 months 3-12 months □ 0ver-toilet seat		_
□ Crutch(es) 3 months □ Crutch(es) 3 months 3-12 months 1 □ Chair platform/blocks raise □ Over-toilet seat		□ Non-slip mat
3-12 months 3-12 months 3-12 months Continence aids Chair platform/blocks raise Over-toilet seat		
Lounge and bedroom equipment Bathroom equipment Continence aids Chair platform/blocks raise I Over-toilet seat I Urine bottle		
□ Chair platform/blocks raise □ Over-toilet seat □ Urine bottle		
□ Chair platform/blocks raise □ Over-toilet seat □ Urine bottle		
		General aids
□ Cushion to relieve pressure □ Toilet surround □ Bedpan		Long handled aid
		Blood pressure machine
□ Special chair (NOT wheelchair) □ Bathroom and grooming aids □ Commode		Treadmill
Table - bedside/wheelie Shower chair/stool Incontinence sheet (bed pro	tector)	Stationary bike Intercom (portable)
Bed platform/block raise	reà)	Modified tap handles
☐ Bedstick ☐ Hand held shower If yes, number of days used - 3	months	If yes, number supplied
□ Hospital bed (eg - height/tilt adjust) □ Non-slip mat □ Incontinence pads 3-12	months	
☐ Mobile hoist/lifter If yes, number of days used - 3	months	Personal alarm
	months	If yes, number of days suppl 3 months
		3-12 months
If yes, number of days used - 3	months months	

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	Case Report F	Form - Cost		National Stroke Research Institute	PATIENT STUD	Y NUMBER	
12) PRIVATE F	PHYSIOTHERAPY						
Have you paid for pr	rivate physiotherapy sessions afte	er your stroke? (NOT whil	e a hospital inpatient)	3 month	s Yes 🗆	No 🗖	Unknown 🗆
If no, proceed to qu	estion 13			3-12 mo	nths Yes 🗌	No 🗖	Unknown
If yes, number of se	ssions - 3 months						
13) RESPITE C	ARE						
As a consequence o	f your stroke, have you been adm	itted to a respite bed in a	nursing home or hos	oital? 3 months	Yes 🗌	No 🗌	Unknown
If NO, proceed to que	estion 14			3-12 mor	ths Yes 🗖	No 🗖	Unknown
14) EMPLOYME	ENT STATUS/ PAID WOR	(
Were you working u	p to the time of your stroke?	Yes ☐ No ☐ f YES, what was the nature	Unknown 🗌 e of this work? Full t	ime 🗌 Part time 🗋			
	Н	ow many hours did you wo	rk each week?				
Since the stroke, ha	ive you returned to this work?	3 months	Yes 🗌 No 🗆	Unknown 🗖			
		3-12 months	Yes 🗌 No 🗌	Unknown 🗖			
Have you returned to	o normal hours or decreased hou		Normal	Decreased			
How many hours p	per week of work have you perfori	3-12 months ned since the last assess	Normal	Decreased 🗌			
52036	Record average amount per week			ut less than 1hr, record a	as 1		
Record	d average amount per week over the	•					
l	For p	eer review only - http://br V 4.0	njopen.bmj.com/site/a 1 Nov 10 (AUS)	bout/guidelines.xhtml			Page 34

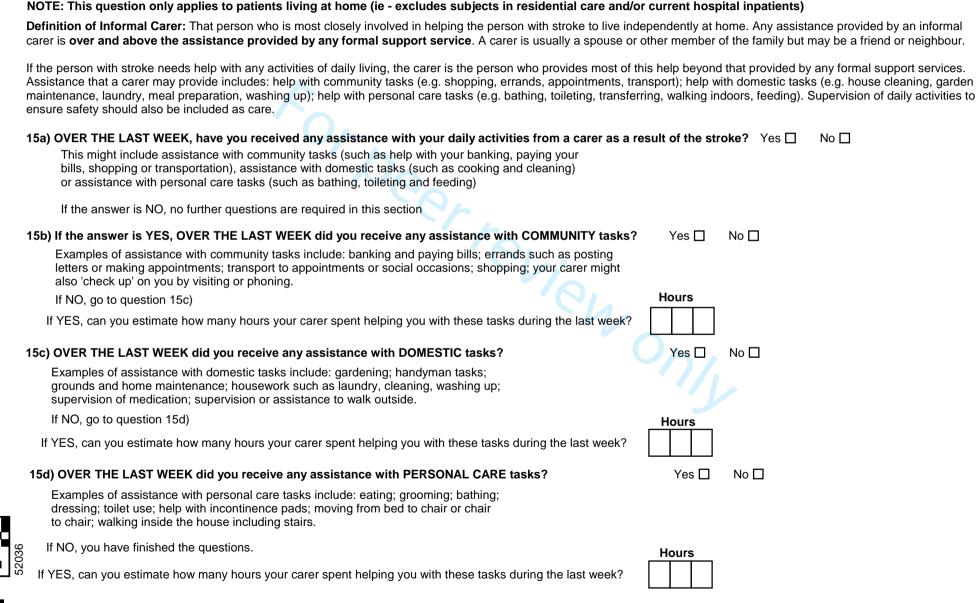


15) INFORMAL CARE - 3 MONTHS



National Stroke PATIENT STUDY NUMBER Research Institute

PATIENT INITIALS





Case Report Form - Cost



National Stroke PATIENT STUDY NUMBER Research Institute

PATIENT INITIALS

	6) INFORMAL CARE - 12 MONTHS	
Ν	OTE: This question only applies to patients living at home (ie - excludes subjects in residential care and	d/or current hospital inpatients)
	efinition of Informal Carer: That person who is most closely involved in helping the person with stroke to live ir arer is over and above the assistance provided by any formal support service. A carer is usually a spouse of the	
A m	the person with stroke needs help with any activities of daily living, the carer is the person who provides most of ssistance that a carer may provide includes: help with community tasks (e.g. shopping, errands, appointments, t aintenance, laundry, meal preparation, washing up); help with personal care tasks (e.g. bathing, toileting, transf nsure safety should also be included as care.	, transport); help with domestic tasks (e.g. house cleaning, garde
16	a) OVER THE LAST WEEK, have you received any assistance with your daily activities from a carer as a This might include assistance with community tasks (such as help with your banking, paying your bills, shopping or transportation), assistance with domestic tasks (such as cooking and cleaning) or assistance with personal care tasks (such as bathing, toileting and feeding)	a result of the stroke? Yes 🔲 No 🗌
	If the answer is NO, no further questions are required in this section	
16	b) If the answer is YES, OVER THE LAST WEEK did you receive any assistance with COMMUNITY tasks?	s? Yes 🗆 No 🗖
	Examples of assistance with community tasks include: banking and paying bills; errands such as posting letters or making appointments; transport to appointments or social occasions; shopping; your carer might also 'check up' on you by visiting or phoning.	
	If NO, go to question 16c)	Hours
	If YES, can you estimate how many hours your carer spent helping you with these tasks during the last week?	</td
16	c) OVER THE LAST WEEK did you receive any assistance with DOMESTIC tasks?	
	Examples of assistance with domestic tasks include: gardening; handyman tasks; grounds and home maintenance; housework such as laundry, cleaning, washing up; supervision of medication; supervision or assistance to walk outside.	
	If NO, go to question 16d)	Hours
	If YES, can you estimate how many hours your carer spent helping you with these tasks during the last week?	?
1	d) OVER THE LAST WEEK did you receive any assistance with PERSONAL CARE tasks?	Yes 🔲 No 🗌
	Examples of assistance with personal care tasks include: eating; grooming; bathing; dressing; toilet use; help with incontinence pads; moving from bed to chair or chair to chair to chair; walking inside the house including stairs.	
036	If NO, you have finished the questions.	Hours
520	If YES, can you estimate how many hours your carer spent helping you with these tasks during the last week?	
	End Case Report Form - Cost For peer review only - http://bmjopen.bmj.com/site/about/c V 4.0 : 1 Nov 10 (AUS)	/guidelines.xhtml Page 36 o

Supplementary document 3: Resource uses, Unit costs and valuation of costs

Resource use items recorded in the cost CRF

Healthcare resource use

The quantity of resources used for the following health care 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 program (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 United Kingdom, Singapore and Malaysia only. N.R

Non-healthcare resource use

The quantity of resources used was recorded for the following non-heath care 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 (i.e. resources used between 0 and 3 months) and 12 (i.e. 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 costs for hospitalisation, rehabilitation, non-health sector costs and productivity costs

Acute stroke hospitalisation costing: Unit costs for acute stroke hospitalisation for all countries at baseline were categorised by stroke severity, using the National Institute of Health Stroke Scale (NIHSS) to group patients into three severity levels: mild (0-7), moderate (8-16) and severe (>16). (1)(2) It was assumed that severity as classified by the NIHSS was consistent with the stroke severity that corresponded to three levels of unit cost for acute hospitalisation. Length of Stay (LoS) together with stroke severity were used to estimate the cost of acute hospitalisation for Australia and New Zealand patients (i.e. the cost of acute hospitalisation was weighted by the LoS). LoS was taken as the difference between the date of hospital discharge and date of hospital admission (plus one day or not) in accordance with country-specific practice. For the other countries, only stroke severity was considered in the assignment of a unit cost to acute stroke hospitalisation due to insufficient health sector data.

Re-hospitalisation and rehabilitation costing: Due to the diversity of causes for patients being readmitted to hospital after the index stroke, the average daily cost of hospitalisation for all disease conditions from individual countries in combination with LoS was used to gauge the cost of readmission for stroke-related causes, while the average cost for an emergency department visit was assigned whenever a patient was hospitalised for one day only. Similarly, the unit cost of rehabilitation hospital admission was taken from the national average cost for all disease conditions. The median cost was used where there was more than one unit cost identified for the same resource item.

Non-health sector costs: Unit costs of non-health sector resource items (e.g. community service, accommodation changes, special aids and equipment) were sourced on a country-specific basis from official websites or published literature where applicable. No unit cost was retrieved for home modification items since the cost of home modifications was generally reported in the Cost CRF.

Productivity cost: Lost productivity was valued based on a human capital approach using average earnings across all occupations up to normal retirement age. The average wage of a

professional carer was adopted to estimate the cost of informal care.

The currency of other countries was converted to AUD using the corresponding exchange rate. The country-specific Consumer Price Index (CPI) from the health sector was employed to adjust costs not valued in the year of 2015.

All the unit costs from participating countries are summarised in Table I.

Resource items	Unit cost (AUD)						
	AU	NZ	UK	SG	MA		
Healthcare							
Acute hospitalisation [*]							
Severe (per episode)	\$19157	\$10867	\$15327	\$4371	\$2066		
Moderate (per episode)	\$9553	\$6104	\$8115	\$2126	\$1572		
Mild (per episode)	\$6279	\$4370	\$4272	\$1493	\$1363		
Stroke-related rehospitalisation (per day)	\$1925	\$320	\$701	\$789	\$230		
Emergency department attendance (per attendance)	\$610	\$325	\$227	\$111	\$68		
Rehabilitation hospital admission [†]							
Severe (per episode)	\$1010 [‡]	\$8032	\$19136 [§]	\$157 [‡]	\$1293		
Moderate (per episode)	\$1010	\$5727	\$19130° \$29788 [§]	\$137	\$1295		
	-	\$5727	\$29788° \$13920 [§]				
Mild (per episode)	-						
Same day (per episode)	\$220	\$758	N/A	\$26	¢17		
Outpatient rehab visit (per/session)	\$239	\$164	\$213	\$36	\$17		
Rehab services at home/nursing	\$239	\$212	\$922	\$36	\$51		
facility (per/session)	¢ (4	¢152	\$1(2)	¢11C	¢0		
Private physiotherapy (per session)	\$64	\$153	\$162	\$116	\$8		
Respite care (per hour)	\$45	\$14	\$26	\$15	\$2		
Individual allied health visit							
Physiotherapy	N/A	N/A	\$243	\$239	\$8		
Occupational therapy	N/A	N/A	\$243	\$36	\$7		
Speech and language therapy	N/A	N/A	\$69	\$36	\$4		
Ambulance transfer	\$508	\$646	\$575	\$265	\$52		
Non-healthcare							
Community services	Not listed here due to the number of items						
Home modifications	Cost was pr	rovided by i	ndividual pa	tients			
Special aids and equipment				l number of ite	ems		
Accommodation changes	Not listed here due to the number of items						
Professional carer (per hour)	\$24	\$14	\$14	\$10	\$2		
Living-in maid (per month)	N/A	N/A	N/A	\$571	\$103		
Average weekly earnings							
Male	\$1137	\$621	\$1152	\$973	\$137		
Female	+	+	\$957	77.0	+ - U /		

 Table I. Unit cost (in Australian dollars) across five countries, 2015 reference year

Unit cost for intervention [#]					
Hospital physiotherapist (per	\$33	\$32	\$30	\$21	\$5
hour)					
Hospital nurse (per hour)	\$30	\$25	\$29	\$21	\$5
AU: Australia; NZ: New Zealand; UK: Ur	ited Kingdom	n; SG: Singapo	ore; MA: Malay	sia;	
Sources of CPI: Australian Bureau of Statistics. Consumer	nniaa indan in	flation coloul	ton Assessed		
from:Http://www.Abs.Gov.Au/websitedbs				ex+inflation+calo	culator, 2017
Office for National Statistics. Inflation and					<u>- alator</u> , 2017
Https://www.Ons.Gov.Uk/economy/inflat					
Department of Statistics Singapore. Consu index-annual. 2017	mer price ind	ex. Accessed f	from: <u>Https://da</u>	ta.Gov.Sg/datase	t/consumer-price
Statistics New Zealand. Consumer price in	idex. accessed	from:			
Http://www.Stats.Govt.Nz/browse_for_sta	ts/economic	indicators/cpi			17
Department of Statistics Malaysia OP. Con					
<u>Https://www.Dosm.Gov.My/v1/index.Php</u> menu_id=bthzthqxn1zqmvf6a2i4rkzondfk		themebycat&c	cat=106&bul_1d	<u>=z19pmutpvz1xb</u>	042mlptt1buellaz
menu_id=bilizinqxii1zqiiiv10azi4ikzondik	<u>qi09</u> . 2017				
* severity was determined by baseline NIH	SS score tea	verity was class	stified by baseli	ne mRS score: *	t is the per
day cost; ^{\$} cost was assigned according to t					
Survey of Household Income was provide					
corresponding to this; [#] hourly wage of ho					
Main sources of unit cost: AU: Independ	ent Hospital P	ricing Author	ity (IHPA), Aus	tralia, National H	Efficient Price
Data (2015-16); National Hospital Cost D					<u>an-public-</u>
hospitals-cost-report-2013-2014-round-18 (https://agedcare.health.gov.au/aged-care-					ureau of
Statistics	anding/aged-	care-subsidies	and-supplement	no), musu allall E	ureau OI
(http://www.abs.gov.au/AUSSTATS/abs@	.nsf/allprima	rymainfeature	s/E9FF9F13B41	17A488CA257F	530014DF30
?opendocument					
NZ: Ministry of Health (<u>http://www.health</u> separations); World Health Organisation (
Version 2.2 (<u>https://www.pharmac.govt.nz</u>					
(Te Ao BJ et al. Are stroke units cost effect					
based study. Int. J. Stroke. 2012;7:623-630					
(http://www.stats.govt.nz/browse for stat work/employment and unemployment/La			Dlup 15 atr oany). District Health	Doord Multi
Employer Agreement, New Zealand Nurse					
meca-2015-2017.pdf);	-			1	
UK: National Health Service (NHS) refer					
(https://www.gov.uk/government/publicat (Davis,S., Holmes,M., Simpson,E., Sutton					
(Davis,S., Holmes,M., Simpson,E., Sutton technology appraisal 122]: A Single Techn					
https://www.nice.org.uk/guidance/ta264/d	ocuments/stro	ke-acute-ischa	aemic-alteplase-	review-of-ta122-	-evidence-
review-group-report2); Personal Social Se					
Services Division, Scotland (<u>http://www.is</u> National Statistics	sdscotland.org	(/); Annual Su	rvey of Hours a	nd Earnings 201:	o, Office for
(https://www.ons.gov.uk/employmentandl	abourmarket/1	peopleinwork/	earningsandwor	kinghours/bullet	ins/annualsur
veyofhoursandearnings/2015provisionalre					
(http://www.payscale.com/research/UK/Jc	b=Care_Worl	ker/Hourly_Ra			
(https://www.healthcareers.nhs.uk/about/c		s-pay-and-ben	efits/agenda-cha	ange-pay-rates);	
SG: Ministry of Health , Hospital Bill Size (https://www.moh.gov.sg/content/moh_we		and financir	19/HosnitalRillS	ize/stroke.html	: Outpatient
Charges, Singapore General Hospital (http://www.mon.gov.sg/content/mon_ww					
charges.aspx); Charges, Ren Ci Hospital (http://www.re	nci.org.sg/pati	ients-guide/char	ges-2/); Hospital	rates and
charges, Bright Vision Hospital (<u>http://ww</u>				inistry of Manpo	ower
(<u>http://stats.mom.gov.sg/Pages/Occupation</u> MA: study by Mohd Nordin et al 2012 (M				entmedical care	for stroke
using Casemix data. BMC Health Services					
(http://www.moh.gov.my/english.php/pag	es/view/160);	Study by Akh	avan Hejazi et a	al 2015(Akhavan	Hejazi SM,
et al. Cost of post-stroke outpatient care in	malaysia. Sir	gapore Med.	J. 2015;56:116-	119); Departmen	t of Statistics
Malaysia (https://www.dosm.gov.my/v1/index.php?	r-column /n Jf	Droveid	MILIILDEVV		BU7700)
(https://www.dosni.gov.my/v1/index.php?	1-colulin/pdf	1 IEV&IU=CZK	<u>ΥΝΚΙΙΟΟΓΥΥΧ.</u>		<u>DALZUY</u>).

Valuation of costs

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 (i.e. excluding non-healthcare costs and productivity cost).

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Supplementary document 4. Missing cost data analyses

Table I. Number of missing data for each cost item

Cost variable	Missing										
	Total	AU		NZ		UK		SG		MA	
0	N=2104	VEM N=522	UC N=532	VEM N=94	UC N=95	VEM N=311	UC N=299	VEM N=64	UC N=64	VEM N=62	UC N=61
Acute hospitalisation	1(0.05%)	1(0.2%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
3 Stroke-related rehospitalisation	51(2.4%)	8(1.5%)	7(1.3%)	0(0%)	0(0%)	17(5.5%)	8(2.7%)	0(0%)	3(4.7%)	7(11.3%)	1(1.6%)
Ambulance transfer	53(2.5%)	8(1.5%)	10(1.9%)	0(0%)	0(0%)	16(5.1%)	7(2.3%)	1(1.6%)	3(4.7%)	7(11.3%)	1(1.6%)
Rehabilitation hospital admission	55(2.6%)	9(1.7%)	9(1.7%)	0(0%)	0(0%)	18(5.8%)	8(2.7%)	0(0%)	3(4.7%)	7(11.3%)	1(1.6%)
7 Outpatient rehabilitation program	47(2.2%)	0(0%)	0(0%)	0(0%)	0(0%)	23(7.4%)	10(3.3%)	0(0%)	3(4.7%)	9(14.5%)	2(3.3%)
8 Rehabilitation provided at home/nursing 9 facility	67(3.2%)	11(2.1%)	10(1.9%)	0(0%)	0(0%)	23(7.4%)	1(3.7%)	0(0%)	3(4.7%)	7(11.3%)	1(1.6%)
• Individual allied health visit [§]	0(0%)	-	-	-	-	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Private physiotherapy	76(3.6%)	12(2.3%)	11(2.1%)	0(0%)	1(1.1%)	27(8.7%)	13(4.4%)	1(1.6%)	3(4.7%)	7(11.3%)	1(1.6%)
Respite care	77(3.7%)	12(2.3%)	11(2.1%)	1(1.1%)	1(1.1%)	27(8.7%)	13(4.4%)	1(1.6%)	3(4.7%)	7(11.3%)	1(1.6%)
Subtotal (medical cost)	94(10.7%)	14(2.7%)	13(2.4%)	1(1%)	1(1.1%)	36(11.6%)	14(4.7%)	1(1.6%)	3(4.7%)	9(14.5%)	2(3.3%)
Accommodation moves	60(2.9%)	15(2.9%)	11(2.1%)	1(1.1%)	1(1.1%)	15(4.8%)	10(3.3%)	0(0%)	2(3.1%)	5(8.1%)	0(0%)
Community services	230(10.9%)	63(12.1%)	87(16.4%)	4(4.3%)	5(5.3%)	32(10.3%)	27(9.0%)	1(1.6%)	3(4.7%)	7(11.3%)	1(1.6%)
Home modifications	13(0.6%)	3(2.6%)	6(1.1%)	0(0%)	1(1.1%)	0(0%)	2(0.7%)	0(0%)	1(1.6%)	0(0%)	0(0%)
Special aids and equipment	48(2.3%)	7(1.3%)	8(1.5%)	1(1.1%)	1(1.1%)	16(5.1%)	14(4.7%)	1(1.6%)	0(0%)	0(0%)	0(0%)
o Informal care	72(3.4%)	11(2.1%)	12(2.3%)	0(0%)	1(1.1%)	26(8.4%)	10(3.3%)	1(1.6%)	3(4.7%)	7(11.3%)	1(1.6%)
Living-in maids [‡]	-	-	-	-	-	-	-	1(1.6%)	3(4.7%)	7(11.3%)	2(3.3%)
Subtotal (non-medical cost)	304(14.5%)	77(14.8)%	97(18.2%)	6(6.4%)	7(7.4%)	54(17.4%)	46(15.4%)	2(3.1%)	5(7.8%)	8(12.9%)	2(3.3%)
Productivity cost	225(10.7%)	50(9.6%)	46(8.7%)	14(14.9%)	10(10.5%)	27(8.7%)	23(7.7%)	17(25.6%)	13(20.3%)	14(22.6%)	11(18.0%
Total cost (exc. productivity cost)	319(15.2%)	80(15.3%)	97(18.2%)	6(6.4%)	7(7.4%)	61(19.6%)	48(16.1%)	2(3.1%)	5(7.8%)	10(16.1%)	3(4.9%)
6 Total cost	512(24.3%)	124(23.8%)	136(25.6%)	20(21.3%)	16(16.8%)	80(25.7%)	68(22.7%)	17(26.6%)	16(25.0%)	22(35.5%)	13(21.3%

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[§]only applicable to UK, Singapore and Malaysia patients; [†]only applicable to Singapore and Malaysia patients

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Resource use items with missing data	Predictor of missingness
Stroke-related rehospitalisation	Age (p=0.001)
Rehabilitation hospital admission	Age (p=0.009), NIHSCORE (p=0.037)
Outpatient rehabilitation program	Age (p=-0.003)
Rehabilitation service provided at home/nursing facility	Age (p=0.014),
Community services used prior to stroke	NIHSCORE (p=0.001)
Community services used at 3 months	Age (p=0.003)
Community services used at 12 months	NIHSCORE (p=0.008)
Aids or special equipment uses at 3 months	Age (p=0.012)
Aids or special equipment uses at 12 months	Age (p=0.035), NIHSCORE (p=0.013)
Private physiotherapy uses at 3 months	Age (p<0.0001)
Private physiotherapy uses at 12 months	Age (p=0.006), NIHSCORE (p=0.034)
Respite care use at 3 months	Age (p<0.0001)
Respite care use at 12 months	Age (p=0.017), NIHSCORE (P=0.018)
Informal care use at 3 months	Age (p=0.003)
Informal care use at 12 months	Age (p<0.0001)

If any of the other variables were able to predict the missingness of a given variable representing resource use, the MAR assumption was deemed to be held true. More specifically, multiple imputations were used to replace the missing values (missing mRS, AQoL-4D data or cost categories) with plausible estimates, and generated 30 datasets. Results were provided as pooled estimates of these sets. Identical analyses were carried out to estimate the incremental costs and benefits between groups on the basis of imputed data following the methods outlined in the statistical analysis section above. As the probability of all the resource use items being missing could be predicted by one or more of the other variables, it is likely that the Missing-at-Random (MAR) assumption could be held true. (https://www.ssc.wisc.edu/sscc/pubs/stata_mi_decide.htm).

Supplementary document 5. Sensitivity analyses

Generally, the difference in QALY gains between VEM and UC groups were fairly consistent across different methods.

Table I. Between-group diff	fferences based on the	Generalised Linear Model
-----------------------------	------------------------	--------------------------

	Adding country dumm	ies	
	mRS	QALYs	Cost
Total medical costs 🧹	0.031(-0.021, 0.083)	-0.013(-0.042, 0.015)	\$704 (-\$1968, \$3376)
Total cost (excl. productivity cost)	0.031(-0.021, 0.083)	-0.013(-0.042, 0.015)	-\$335 (-\$4953, \$4283)
Total cost (incl. productivity cost)	0.031(-0.021, 0.083)	-0.013(-0.042, 0.015)	-\$238 (-\$6012, \$5537)

mRS: modified Rankin Scale; QALYs: Quality-adjusted Life Years

*the p-value was >0.05 for the between-group difference in mRS score, QALYs and cost

	AU	NZ	UK	SG	MA
	(N=1054)	(N=189)	(N=610)	(N=128)	(N=123)
Total medical	\$948	-\$2836	\$2937	-\$81	\$137
costs	(-\$4352, \$6248)	(-\$8403, \$2730)	(-\$3635, \$9509)	(-\$2789, \$2627)	(-\$324, \$599)
Total non-	-\$1318	-\$3959	-\$1387	-\$3164	\$200
medical costs	(-\$3038, \$403)	(-\$7769, -\$150)	(-\$7331, \$4557)	(-\$6834, \$505)	(-\$232, \$631)
Total cost	-\$1735	-\$8981	\$1870	-\$2636	\$479
(incl.	(-\$8482, 5013)	(-\$18380, \$418)	(-\$13955, \$17694)	(-\$9233, \$3961)	(-\$487, \$1446)
productivity)					
Total cost	-\$1185	-\$7610	\$2552	-\$1534	\$416
(excl.	(-\$7184, \$4815)	(-\$15302, \$82)	(-\$11377, \$16481)	(-\$6464, \$3395)	(-\$364, \$1196)
productivity)					
QALY gains	-0.036	0.086	-0.010	0.008	0.003
	(-0.076, 0.003)	(-0.003, 0.176)	(-0.064, 0.044)	(-0.106, 0.123)	(-0.126, 0.132)

Table II. Results of country-specific analysis of costs and benefits

AU: Australia; NZ: New Zealand; UK: United Kingdom; SG: Singapore; MA: Malaysia; QALY: Quality-adjusted Life Year.

*the p-value was >0.05 for the between-group difference in QALYs and cost

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. Likewise, if a societal perspective was taken, VEM was associated with comparable costs (\$1413, 95%CI:-\$4044 to \$6871, including productivity cost; \$1704, 95%CI:-\$3817 to \$7226, excluding productivity cost) and QALY gains (-0.019, 95%CI:-0.044 to 0.005) (Supplementary document 6: Table IV). Even though the point estimate of difference in total costs between groups from a societal perspective varied considerably, the 95% confidence interval derived from base case and multiple imputation analyses were nearly identical (Supplementary document 6: Table IV).

From a health sector perspective, the between-group difference for each participating country yielded consistent conclusions with the base case analysis. VEM was associated with both non-significantly different costs and benefits (i.e. QALY gains at 12 months) compared to the UC, although the point estimate of the cost difference between groups varied from country to country, ranging from -\$2836 (New Zealand) to \$2937 (UK) (Supplementary document 6: Table II).

It was found that VEM was likely to cost less and associated with a greater gain in QALYs in comparison to UC in New Zealand and Singapore., Meanwhile, except for total medical cost, VEM seemed to incur less cost while leading to less gain in QALYs at month 12 months for participants from Australia, whilst in the United Kingdom, VEM was associated with higher

cost and lower QALY gains than UC. Lastly, for patients from Malaysia, VEM contributed to higher cost while greater QALY gains at 12 month follow-up. However, none of the aforementioned between-group differences were statistically significant.

When a societal perspective was assumed, again, the point estimate of difference in costs between groups across countries varied substantially, with the 95% confidence intervals mostly overlapping

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Table III. Between-group differences based on the Generalised Linear Model_ base case analysis vs. multiple imputation analysis

	ITT (not imputed)			ITT (imputed)		
	mRS score	QALYs	Cost (AUD)	mRS	QALYs	Cost (AUD)
Health Sector Perspec	ctive	~		1		
Total medical costs	0.030	-0.013	\$1082	0.042	-0.019	\$940
	(-0.022, 0.082)	(-0.041, 0.016)	(-\$2399, \$4563)	(-0.008, 0.092)	(-0.046, 0.007)	(-\$2584, \$4465)
Societal Perspective			0			
Total cost (excl.	0.030	-0.013	-\$6	0.042	-0.019	\$1704
productivity cost)	(-0.022, 0.082)	(-0.041, 0.016)	(-\$5703, \$5690)	(-0.008, 0.092)	(-0.046, 0.007)	(-\$5423, \$8832)
Total cost (incl.	0.030	-0.013	\$102	0.042	-0.019	\$1413
productivity cost)	(-0.022, 0.082)	(-0.041, 0.016)	(-\$6945, \$7149)	(-0.008, 0.092)	(-0.046, 0.007)	(-\$5940, \$8766)
TT: intention to treatment;	; mRS: modified Rank	in Scale; AUD: Austra	lian dollars	(9)	1	
the p-value was >0.05 for	the between-group dif	ference in mRS score,	QALYs and cost			

	Efficacy (QALYs)	Cost (AUD)	Probability of being cost-effective
Health Sector Perspectiv	/e		1
Total medical costs	-0.019	\$940	25%
	(-0.044, 0.005)	(-\$4622, \$4682)	
Societal Perspective	I		
Total cost (excl.	-0.019	\$1704	20%
productivity cost)	(-0.044, 0.005)	(-\$3817, \$7226)	
Total cost (incl.	-0.019	\$1413	23%
productivity cost)	(-0.044, 0.005)	(-\$4044, \$6871)	

Table IV. Cost-utility analysis based on multiple imputation analysis

QALYs: Quality-adjusted Life Years; AUD: Australian dollar.

*the p-value was >0.05 for the between-group difference in QALYs and cost

Supplementary document 6. Outcomes

Modified Rankin Scale Score	UC group n=1050		VEM grou n=1054	р
	3M	12M	3M	12M
0	96	132	90	137
1	204	231	200	219
2	225	175	190	166
3	218	199	238	186
4	127	95	140	113
5	103	83	92	59
6	72	118	88	139
Total	1045	1033	1038	1019
Missing data	5	17	16	35

Table I. Results of mRS score at 3 and 12 months follow-up

Number of patients falling into each category

Since there was no significant intervention effect together with no accepted willingness-topay (WTP) per unit increase in probability of achieving a better mRS outcome, further estimation of the ICER was considered not meaningful (i.e. no cost-effectiveness plane or cost-effectiveness acceptability curve could be generated).

	VEM		UC		Between grou	p difference
	Total time	Cost (AUD)	Total time	Cost (AUD)	Total time	Cost (AUD)
	(min)		(min)		(min)	
Physiotherapist	243	\$117	95	\$48	147	\$69
	(232, 254)	(\$111, \$123)	(90, 101)	(\$45, \$51)	$(135, 159)^*$	(\$63, \$75)*
Nurse [†]	494	\$225	439	\$202	55	\$23
	(456, 532)	(\$207, \$244)	(404, 474)	(\$185, \$219)	$(4, 106)^*$	(-\$2, \$48)
Total cost	-	\$342	-	\$250	-	\$92
		(\$320, \$364)		(\$231, \$269)		$(\$63, \$121)^*$

Table II. Time and cost associated with delivering VEM and UC (mean, 95%CI)

VEM: very early mobilisation; UC: usual care; CI: confidence interval

*p<0.0001 (adjusted for age, baseline NIHSS and mRS); [†] nurse's time devoted to delivery of VEM/UC was not recorded in the process of data collection, so the physiotherapist time was used as a proxy

Because VEM and UC were supplied by the same group of physiotherapists and nurses, the key difference was that a patient randomised to VEM received early rehabilitation within 24 hours of stroke onset and more out-of-bed mobilisation sessions of early mobilisation.

The total health practitioner (physiotherapist and nurses) time devoted to the delivery of the VEM and UC differed significantly, with the VEM group receiving substantially longer mean service time from both the physiotherapist (VEM: 243 mins, 95%CI: 232 to 254 vs UC: 95 mins, 95%CI: 90 to 101, p<0.0001) and nurse (VEM: 494 mins, 95%CI: 456 to 532 vs UC: 439 mins, 95%CI: 404 to 474, p<0.0001). The resultant difference in costs between groups was significant (\$92, 95%CI: \$63 to \$121, p<0.0001).

20

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SG (N=128)

(1493, 1809)

\$1721 (547)

(111, 111)

(0, 2921)

\$1815 (2759)

\$364 (1090)

\$2756 (7565)

UC

\$1493

\$111

\$1298

\$0

\$0

\$0

\$0

\$0

\$0

(0, 0)

\$0(0)

(0, 0)

(0, 0)

\$5 (42)

(0, 179)

(0, 265)

\$113 (208)

\$333 (1938)

\$1126 (3150)

(0, 36)

\$562 (1478)

(0, 3570)

(1493, 1493)

\$1676 (432)

(111, 111)

\$1679 (3465)

\$2798 (5082)

(0, 265)

\$164 (348)

\$238 (1096)

\$93 (570)

\$432 (1521)

MA (N=123)

(1363, 1572)

\$1482 (212)

\$714 (1608)

UC

\$1363

\$68

\$0

\$0

\$0

\$0

\$0

\$0

(0, 0)

\$1 (9)

(0, 0)

\$1 (8)

\$0

(0, 0)

\$14 (64)

(0,0)\$0.2 (2)

(0, 0)

\$7 (53)

(0, 249)

\$126 (206)

(0, 0)

\$43 (234)

(68, 68)

\$603 (1479)

(1363, 1572)

\$1472 (200)

VEM

\$1363

\$68

\$0

(0, 0)

\$0(0)

\$33

\$0

\$0

\$0

\$0

\$0

(0, 0)

\$0(0)

(0, 0)

\$4 (19)

(0, 0)

\$6 (26)

(0,0)

\$0(0)

(0, 0)

\$97 (719)

(0, 265)

\$174 (286)

(68, 68)

UC

\$6294

\$111

(0, 610)

\$1136

\$0

\$0

N/A

N/A

\$0

\$0

\$0

(0, 0)

\$27 (386)

(0, 0)

(0, 610)

\$578 (1838)

\$132 (1336)

(0, 239)

(0, 1913)

\$1142 (3976)

\$4180 (15203)

(0, 29788)

(2418, 9553)

\$7521 (8916)

\$4551 (16707)

\$18458 (30811)

All Countries

(2279, 9535)

\$7369 (8469)

\$4610 (14518)

VEM

\$6294

\$111

\$0

\$0

\$0

N/A

N/A

\$0

\$0

\$0

(0, 0)

\$27 (259)

(0, 0)\$109 (693)

(0, 611)

\$627 (1920)

(0, 478)

(0, 1913)

\$1246 (3244)

\$4447 (16294)

(0, 1401)

(0, 29788)

\$18197 (31241)

* 5	AU (N=1054)		NZ (N=189)	d over 12 mor	UK (N=610)		SG (N=
) -	VEM	UC	VEM	UC	VEM	UC	VEM
	I.	1			Не	alth care cost (AU	D)
Acute hospi	talisation					·	
³ Median,	\$6294	\$6294	\$6104	\$6104	\$2763	\$3109	\$1493
PIQR	(6294, 9553)	(6294, 9553)	(4370, 6104)	(4370, 6104)	(1382, 6563)	(1727, 6563)	(1493, 1
Mean, SD	\$9883 (9484)	\$10010(10508)	\$6635 (3244)	\$6549 (3555)	\$5714(7876)	\$5885 (7101)	\$1721 (
	ed rehospitalisation						
Median,	\$0	\$0	\$0	\$0	\$227	\$227	\$111
IQR	(0, 3850)	(0, 3850)	(0, 325)	(0, 2243)	(227, 1401)	(227, 227)	(111, 12
Mean, SD	\$6030 (17114)	\$6473 (21590)	\$651 (1371)	\$1507 (2828)	\$4524 (13968)	\$3494(11349)	\$2756 (
	o rehab hospital						
Median,	\$13134	\$13134	\$11262	\$11262	\$0	\$0	\$0
F QR	(0, 36371)	(0, 38391)	(0, 30983)	(0, 26486)	(0, 29788)	(0, 29788)	(0, 292)
Mean, SD	\$25667 (38892)	\$26648(38315)	\$16871(18536)	\$15573(16848)	\$12539(19682)	\$11758 (18390)	\$1815 (
8							
9					Outpati	ent rehab program	(AUD)
2 M edian,	\$0 (0, 2451)	\$0	\$0	\$0	\$0	\$0	\$0
IQR		(0, 1913)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)
Mean, SD	\$2081 (4183)	\$1934 (5316)	\$821 (2236)	\$721 (1991)	\$266 (1026)	\$155 (676)	\$364 (1
Rehab provi	ded at home/nursin \$0	g facility					
Median,			\$1168	\$212	\$922	\$0	\$0
IQR	(0, 717)	(0, 956)	(0, 4299)	(0, 3821)	(0, 11064)	(0, 11064)	(0, 0)
Mean, SD	\$1382 (4069)	\$1551 (4252)	\$3171 (4960)	\$3111 (5754)	\$12085 (28516)	\$11051 (26723)	\$93 (57
	llied health visit						
2 Median,	N/A	N/A	N/A	N/A	\$0	\$0	\$0
2 8 QR					(0,0)	(0,0)	(0,0)
y lean, SD	N/A	N/A	N/A	N/A	\$375 (1144)	\$329 (1291)	\$432 (1
mbulance							
Median,	\$508	\$508	\$0	\$0	\$0	\$0	\$0
<u>I</u> QR	(0, 1015)	(0, 1015)	(0, 646)	(0, 646)	(0, 1150)	(0, 575)	(0, 265)
Mean, SD	\$671 (1057)	\$623 (946)	\$543 (1082)	\$605 (928)	\$790 (3209)	\$701 (3150)	\$164 (3
Private phys							
Median,	\$0	\$0	\$0	\$0	\$0	\$0	\$0
3 5 QR	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)
Solean, SD	\$70 (375)	\$124 (797)	\$245 (1308)	\$4 (36)	\$128 (780)	\$174 (2102)	\$238 (1
Respite care							
Median,	\$0	\$0	\$0	\$0	\$0	\$0	\$0
JQR Mean, SD	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)
Man CD	\$48 (355)	\$20 (182)	\$7 (46)	\$2 (15)	\$9 (95)	\$58 (686)	\$0(0)

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Page 61	of 76
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3	AU (N=1054)		NZ (N=189)		UK (N=610)		SG (N=128)		MA (N=123)		All Countries	
4	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC
5 Sub-total												
6 Median	\$29278	\$29441	\$20621	\$23722	\$18896	\$20843	\$4525	\$4687	\$1713	\$1746	\$19271	\$20411
7 (IQR)	(8218, 63622)	(9811, 62489)	(6068, 46909)	(7316, 40162)	(4030, 48999)	(3682, 47908)	(1604, 8668)	(2724, 10926)	(1431, 2532)	(1431, 2348)		(7238, 63835
o Mean	\$45620 (51458)	\$47453(53715)	\$28898 (25011)		\$34863 (42509)	\$32842 (39517)		\$8358 (8787)	\$2385(1587)			\$36604 (4630
o (SD)						,						
9	l.	1			N	on-health care cos	t	1				I.
10 Accommoda	ation moves											
¹ Median,	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
12 _{QR}	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)
1 M ean, SD	\$2089 (8518)	\$2482 (9323)	\$5975 (19614)	\$9135 (26918)	\$2901 (12958)	\$2532 (11125)	\$72 (578)	\$108 (507)	\$425 (1893)	\$104 (501)	\$2460 (11036)	\$2821 (12212
1 4 ommunity	services											
1 Median,	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
1 QR	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 430)	(0, 174)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)
Mean, SD	\$570 (2681)	\$1091 (8556)	\$238 (950)	\$1022 (4113)	\$22275 (294988)	\$10738 (57306)	\$0 (0)	\$244 (1902)	\$21 (110)	\$0 (0)	\$6870 (160318)	\$3786 (31893
Home modif	fications										· · ·	
Median,	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
19QR	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)
2 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)
2\$pecial aids	and equipment											
2 M edian,	\$0	\$0	\$70	\$103	\$27	\$0	\$0	\$0	\$15	\$36	\$0	\$0
2 5 QR	(0, 332)	(0, 318)	(0, 549)	(0, 357)	(0, 786)	(0, 846)	(0, 240)	(0, 210)	(0, 218)	(0, 186)	(0, 414)	(0, 414)
∂ Mean, SD	\$1986 (7668)	\$2787 (10396)	\$2198 (7993)	\$1798 (7229)	\$1354(3649)	\$1720 (5083)	\$1117 (5843)	\$1079 (5483)	\$153 (252)	\$193 (658)	\$1660 (6426)	\$2141 (8328)
Informal car	e											
Median,	\$24	\$48	\$14	\$0	\$29	\$29	\$0	\$0	\$24	\$9	\$24	\$24
IQR	(0, 503)	(0, 455)	(0, 283)	(0, 149)	(0, 471)	(0, 375)	(0, 114)	(0, 238)	(0, 60)	(0, 50)	(0, 407)	(0, 407)
	\$414 (747)	\$405 (758)	\$236 (536)	\$152 (311)	\$324 (516)	\$324 (645)	\$144 (285)	\$159 (300)	\$43 (57)	\$27 (34)	\$335 (633)	\$322 (660)
2 Living-in ma	aids											
2 Median,	N/A	N/A	N/A	N/A	N/A	N/A	\$0	\$0	\$0	\$0	N/A	N/A
3 0 QR							(0,0)	(0,0)	(0,0)	(0,0)		
3Mean, SD	N/A	N/A	N/A	N/A	N/A	N/A	\$3154 (8146)	\$4268(11338)	\$179 (930)	\$83 (504)	N/A	N/A
32 Sub-total												
33 Median	\$459	\$673	\$381	\$638	\$758	\$471	\$25	\$194	\$74	\$57	\$358	\$438
34 (IGR)	(0, 3334)	(0, 5209)	(0, 3674)	(103, 14551)	(0, 5097)	(0, 4725)	(0, 1293)	(0, 6999)	(0, 285)	(0, 318)	(0, 3334)	(0, 4561)
Mean	\$6104 (15582)	\$6985 (17554)	\$7752 (17751)	\$11981(27676)	\$27892 (306917)	\$15345(61750)	\$4802 (10366)	\$6177 (13942)	\$861 (2272)	\$484 (1113)	\$12043 (164026)	\$9360 (36504
35 (SD)												
36						Productivity cost						
3 Median,	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
3 8 QR	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)
3 9 /Iean, 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)
4 Jotal cost												
41												
41												

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3	AU (N=1054)		NZ (N=189)		UK (N=610)		SG (N=128)		MA (N=123)		All Countries	
4	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC
5 Median	\$33203	\$35143	\$29934	\$32216	\$25374	\$30537	\$6960	\$8810	\$2016	\$1816	\$25675	\$27042
6(IGR)	(9687, 71902)	(12696, 74070)	(8528, 65781)	(15710, 68292)	(4712, 64285)	(4629, 67012)	(1674, 26187)	(3426, 19493)	(1561, 3994)	(1537, 3301)	(6766, 63617)	(7257, 63824)
7Mean (SD)	\$52456(57264)	\$56408(62536)	\$40381(37242)	\$43901(43170)	\$65530(332044)	\$49627(78644)	\$15036(16921)	\$16340(19650)	\$3609(3985)	\$2938(2350)	\$50448(184931)	\$47627(64249)

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8 Where only a low proportion (i.e. 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 9 hospitalisation includes a patient's immediate admission to rehabilitation hospital on discharge from hospital as the rehabilitation service immediately following the acute stroke hospitalisation

interval overlapped to a great extent. Given the concern raised by the large variability in mapped utility for patients within the same mRS category (≤ 2 or ≥ 3) and the fairly consistent results across different models, only the 12 month AQol utility values were employed to estimate the difference in QALYs gains between two treatment groups.

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Supplementary document 7. 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 Countri	es
	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 rehospita	alisation											
% 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 rehabilita	tion hospital [‡]	1		Co.	1	1	1	l	1	l	1	
% 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 rehabilitatio	n program											
% 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								L		
% 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	I			<u> </u>			1		<u> </u>	<u> </u>		1
% 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			<u> </u>			1		<u> </u>	<u> </u>		
% of pts using	N/A	N/A	N/A	N/A	19	15	-	2	20	25	-	-

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Page 65	of	76
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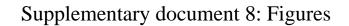
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	AU (N=1054))	NZ (N=189)		UK (N=610)		SG (N=128))	MA (N=123	6)	All Countrie	s
	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC
No. of services	N/A	N/A	N/A	N/A	8(2-12)	8(4-15)	-	2(2-2)	8(3-10)	16(8-31)	-	-
Private physiotherapy												
% of pts using	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	e past year		10							
% 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 of	over 12 months	after stroke										
% of pts using	30	35	32	28	31	28	- 0	3	6	-	27	28
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(12-12
Home modifications under	taken over 12 n	nonths										
% 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 o	over 12 months											
% of pts using	46	47	55	63	58	51	44	45	58	59	51	50
	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)

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	AU (N=1054))	NZ (N=189)		UK (N=610))	SG (N=128)	1	MA (N=123))	All Countrie	25
	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC
% 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 a	t 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 Malaysi	a and Singapore wh	io had a maid prie	or to stroke									
% of patients	a and Singapore wh	no had a maid prie	or to stroke		-	-	19 1(1-1)	16 1(1-1)	5 1(1-1)	10	-	-
% of patients No. of maids	-	-			-	-		-			-	-
% of patients No. of maids Patients from Singapo	-	-			-	-		-			-	-
Patients from Malaysi % of patients No. of maids Patients from Singapor % of patients No. of maids	-	-				-	1(1-1)	1(1-1)	1(1-1)		- - -	-
% of patients No. of maids Patients from Singapo % of patients	- ore and Malaysia wh - -	- - 10 had a maid at 1 -		ving stroke		- - -	1(1-1) 23	1(1-1) 22	1(1-1) 5	7	-	-
% of patients No. of maids Patients from Singapo % of patients No. of maids	- ore and Malaysia wh - -	- - 10 had a maid at 1 -		ving stroke	- - - - 41	- - - - 40	1(1-1) 23	1(1-1) 22	1(1-1) 5	7	-	- - - - 39

ITT: Intention-to-treat; AU: Australia; NZ: New Zealand; UK: United Kingdom; SG: Singapore; MA: Malaysia; LoS: length of stay; pts: patients; No.: number; hrs: hours; mod: modification; -: no such resource use; all numbers were expressed as median and interquartile range (IQR); ⁺ includes any admissions to rehabilitation hospital following the indexed stroke;



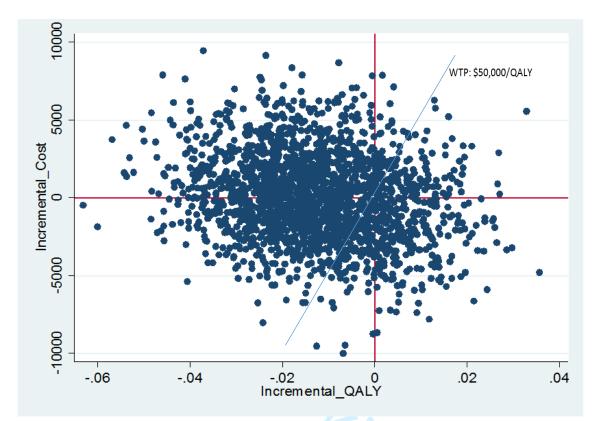
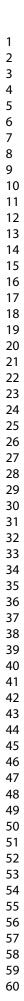


Figure I cost-effectiveness plane_ societal perspective (excl. productivity cost)

*Probability of VEM being cost-effective is 42%; WTP: willingness-to-pay; QALY: quality-adjusted life year



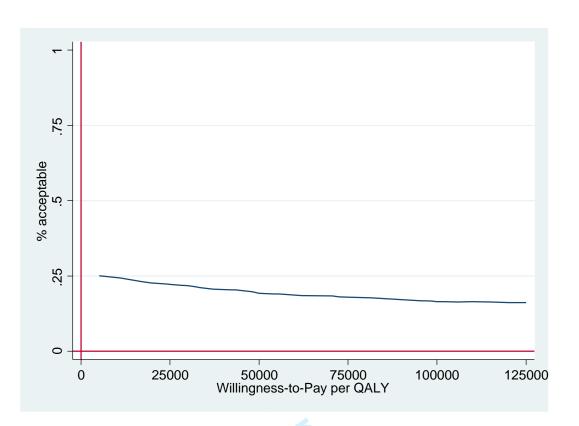
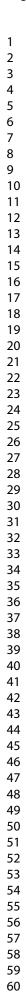


Figure II Cost-effectiveness acceptability curve for medical cost

Note: The probability of VEM being cost-effective decreases with the increasing WTP/QALY threshold because the VEM is associated with less costs



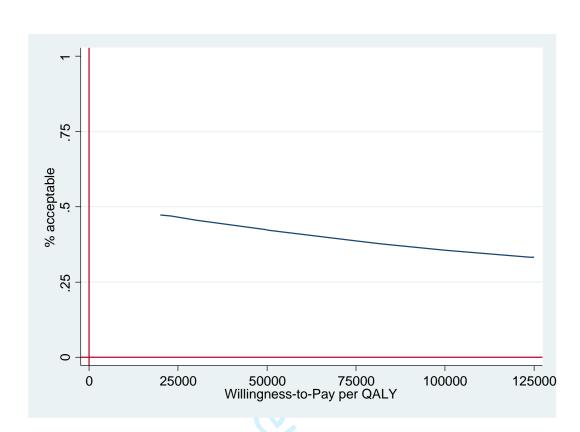
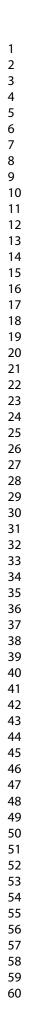


Figure III Cost-effectiveness acceptability curve for total cost excluding productivity cost

Note: The probability of VEM being cost-effective decreases with the increasing WTP/QALY threshold because the VEM is associated with less costs



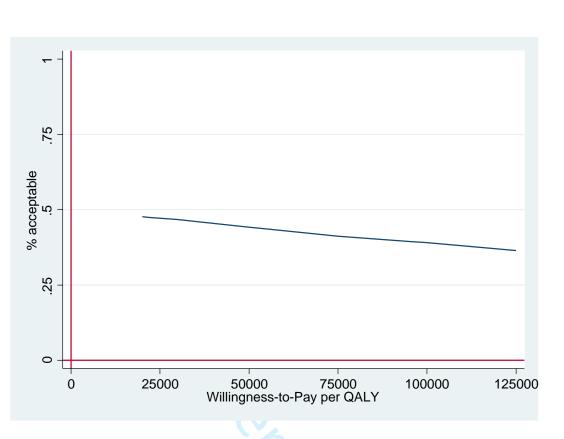


Figure IV Cost-effectiveness acceptability curve for total cost including productivity cost

Note: The probability of VEM being cost-effective decreases with the increasing WTP/QALY threshold because the VEM is associated with less costs

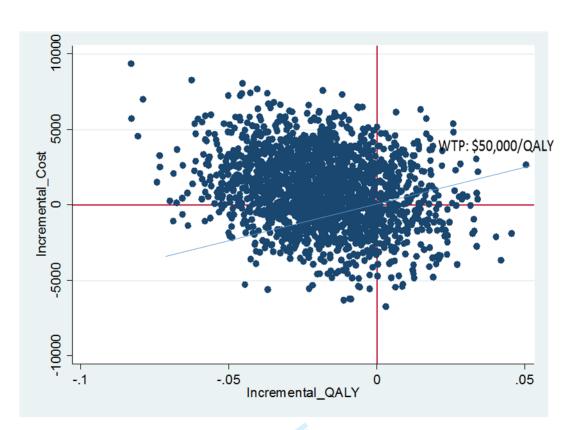


Figure V Cost-effectiveness plane_ health sector perspective (multiple imputation analysis)

WTP: willingness-to-pay; QALY: quality-adjusted life year

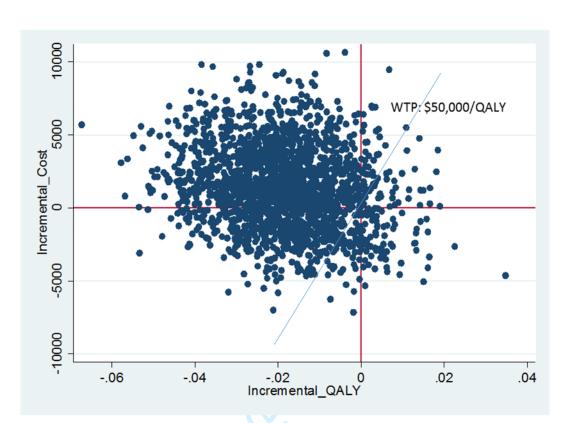
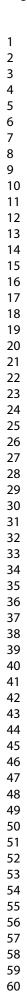


Figure VI Cost-effectiveness plane_ societal perspective including productivity cost (multiple imputation analysis)

WTP: willingness-to-pay; QALY: quality-adjusted life year



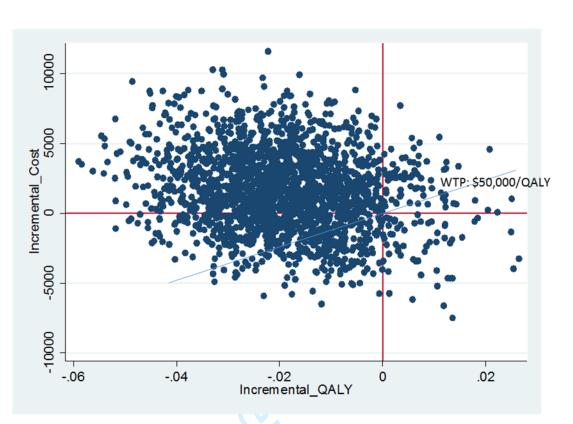


Figure VII Cost-effectiveness plane_ societal perspective excluding productivity cost (multiple imputation analysis)

WTP: willingness-to-pay; QALY: quality-adjusted life year

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1. Claesson L, Gosman-Hedstrom G, Johannesson M, Fagerberg B, Blomstrand C. Resource utilization and costs of stroke unit care integrated in a care continuum: A 1-year controlled, prospective, randomized study in elderly patients: the Goteborg 70+ Stroke Study. Stroke 2000;31(11):2569-77.

2. 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(2):390-6.

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Section/item	Item No		Reported page No/ line No	
Title and abstract		Recommendation		
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	4-5	
Introduction				
Background and objectives	3	Provide an explicit statement of the broader context for the study.	7	
		Present the study question and its relevance for health policy or practice decisions.	8	
Methods				
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	12	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	9	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	9	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	8	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	11	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	11	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	8-9	
Measurement of effectiveness	11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	^{rhy} 11 11 8-9 tudy 12 ies 9 e s 9-1	
	11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.		
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences foroutcomes.	9	
Estimating resources and costs	13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	9-1	
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.		
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	10	
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providinga figure to show model structure is strongly recommended.		
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.		
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	11-1	
Results				
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	N/	
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	14-	
Characterising uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	14	
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.		
haracterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.		
Discussion				
tudy findings, limitations,	22	Summarise key study findings and describe how they support the conclusions reached. Discuss		

Study findings, limitations, 22 Summarise key study findings and describe how they support the conclusions reached. Discuss generalisability, and current For peer reviewing the study findings and the describe how they support the conclusions reached. Discuss

Other		
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, o and reporting of the analysis. Describe other non-monetary sources of support.
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with In the absence of a journal policy, we recommend authors comply with Internation of Medical JournalEditors recommendations.
For consistency, the CHEE	RS statement che	ecklist format is based on the format of the CONSORT statementchecklist

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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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Title Page

Title

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

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Cover title

Economic evaluation of AVERT trial

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Keywords

rectiv stroke; rehabilitation; AVERT; economic evaluation; cost-effectiveness analysis; cost-utility analysis

Word count

Abstract

Objectives While Very Early Mobilisation (VEM) intervention for stroke patients was shown not to be effective at 3 months, 12 -month clinical and economic outcomes remain unknown. It was aimed to assess cost-effectiveness of a VEM intervention within a Phase III randomised controlled trial (RCT).

Design An economic evaluation alongside a RCT

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 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 (0-2 vs 3-6) 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 (ITT) basis and 95% confidence intervals (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 AUD\$102, 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.

Trial registration Australian New Zealand ClinicalTrials Registry, number 00185501. ACTRN12606000185561.

Strength and limitations

- 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.

Introduction

Stroke is one of the biggest killers and a leading cause of disability worldwide.¹² 65% 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.⁴⁵ 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 2,104 patients enrolled from Australia, New Zealand, United Kingdom, Singapore and Malaysia.¹⁰ The evidence from this trial indicated that at three 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 0-2 compared to that in the usual care (UC) group.¹⁰ In the research field of stroke, primary endpoint is usually assessed at month 3 after stroke¹¹⁻¹⁴, 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 (i.e. 12 months) comprehensive measurement of costs relating to stroke care (i.e. 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 (i.e., 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.

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This examination also benefits healthcare funders (i.e. 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 (UC), 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 (CHEERS) 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 (UC) 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-4D (AQoL-4D)¹⁷ were used as the effectiveness measures in the economic evaluation. The AQoL-4D instrument is a multi-

BMJ Open

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 0-2) and "poor" (mRS 3-6) based on patients outcomes at 12-month follow up.¹⁰ The difference in the probability of patients achieving a favourable mRS outcome (mRS 0-2) 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 (i.e. most of patients were not able to respond to these questions at baseline), the mRS score at baseline¹⁰ was used as a surrogate measure of patient utility during the acute phase. The detailed methods of this work are reported elsewhere¹⁹ 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

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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 (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 health care 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 program (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 United Kingdom, Singapore and Malaysia only.

Non-healthcare resource use

The quantity of resources used was recorded for the following non-heath care 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),

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changes to employment (employment status and weekly hours of working both prior to and post-stroke).

Resource use reported at 3 (i.e. resources used between 0 and 3 months) and 12 (i.e. 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 (Supplementary document 3). Unit costs from a country with a similar economic status and healthcare system were used where local countryspecific unit costs were unavailable.

All costs are expressed in Australian dollars (AUD) for the 2015 reference year value and can be converted to United States dollar (USD) using the Purchasing Power Parity rate 1 USD=1.463 AUD²⁰ (December 2015). The currency of other countries was converted to AUD using the corresponding exchange rate. The country-specific Consumer Price Index (CPI) 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 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 interquartile ranges (IQRs) due the skewness of the raw data. Means and standard deviations (SDs) were also reported. Base case analysis of the economic evaluation was performed based on the Intention-to-Treat (ITT) population²¹ 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 mRS¹⁵ 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 (i.e. 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% confidence intervals (CIs) around mean difference in costs and effects for cost-effectiveness analysis. To

BMJ Open

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 (i.e. excluding non-healthcare costs and productivity cost). The differences between groups in terms of costs and benefits (i.e. 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 14.0 statistical package (StataCorp. 2015. Release 14. StataCorp LP.) e e

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 missing²⁶ (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, 2,104 patients (VEM 1,054; UC 1,050) were recruited across 58 sites from Australia (N=1,054, 24 sites), New Zealand (N=189, 1 site), United Kingdom (N=610, 29 sites), Singapore (N=128, 1 site) and Malaysia (N=123, 1 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 randomisation¹⁰. Baseline characteristics were similar between the two treatment groups¹⁰.

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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 Supplementary document 5: Table I.

Resource use and costs

Page 15 of 82

BMJ Open

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 patients experienced rehabilitation hospital admission and more than a quarter of 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 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, whilst 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 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: \$7,238 to \$63,835) than in the VEM group (\$19,271, IQR: \$6,294 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 \$4,561) than in the VEM group (\$358, IQR: \$0 to \$3,334). 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: \$7,257 to \$63,824) compared to the VEM group (\$25,675, IQR: \$6,766 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 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, \$4563) for the total medical cost (Supplementary document 6: Table I) and \$3 (95%CI: -\$5, \$12) for the productivity cost per person at 12 months; the between-group difference in the total non-health care cost was -\$1300 (95%CI: -\$3361, \$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 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 Supplementary document 7: Figures I to V.

Sensitivity analyses

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Inclusion of a country dummy variable in the analysis produced similar results to the base case (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. (Supplementary document 6: Table III and 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% confidence intervals mostly Discussion overlapping (Table 4).

The 12 months within-trial cost-effectiveness analysis showed that VEM was unlikely to be cost-effective than 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 one year study period were comparable from a health sector perspective. The findings from this economic evaluation is also underpinning an adapted version of trial underway to investigate the effectiveness of optimal rehabilitation in patients with mild to moderate stroke (i.e. 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 to 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 health care 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% confidence intervals 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

BMJ Open

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 tended to receive rehabilitation services in an outpatient (i.e. up to 52% of patients received the outpatients rehabilitation program services) rather than inpatient (i.e. only up to 2% patients were admitted to rehabilitation hospital) setting; and patients were less likely to utilise ambulant transfer and apply home modifications, as compared to 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 program. 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 health-related quality of life (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

BMJ Open

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 Whilst 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 to approximate the difference in QALY gains over one 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.

Whilst 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

Page 21 of 82

BMJ Open

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 (i.e. base case of pooling all countries) and disaggregated (i.e. 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. Firstly, the missing data on total costs from a societal perspective was around 24%, and related mainly to the missing information on

BMJ Open

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 (i.e. comparable results in costs and benefits between treatment groups). Secondly, unit costs originating from individual countries were assigned to value resource use. The differences in health care 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 to UC. The sensitivity analyses based on the multiple imputation and subgroup analyses by each country separately yielded fairly consistent results. Overall, the VEM intervention was demonstrated to be comparable with UC in terms of both benefits and costs at one-year, however given its poorer outcomes at 3 months, VEM cannot be recommended to clinicians, patients or policymakers.

Acknowledgements

Page 23 of 82

BMJ Open

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Authors' Contribution

Conception/design, revising and final approval: LG, LS, LC, OW, MM, JC, FE, JB, HD, MMoodie. Methodology: LG, MM, LS, LC, MMoodie, OW. Data analysis: LG, LS, MM, LC. Drafting: LG, MMoodie.

Competing Interests Statement

All authors confirm that there is nothing to declare.

Data Availability Statement

No additional data available

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Tables

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

	AU (N=1054)		NZ (N=189)		UK (N=610	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 rehospita	lisation												
% 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 rehabilitat	ion hospital [‡]			8									
% 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 rehabilitatio	n program				10								
% 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					<u> </u>							
0/ 0 / .	N/A	N/A	N/A	N/A	19	15	-	2	20	25	-	-	
% of pts using	1		N/A	N/A	8(2-12)	8(4-15)	-	2(2-2)	8(3-10)	16(8-31)	-	-	

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% 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(
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(
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-
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(2
Community services used of	over 12 months	after stroke		104								
% of pts using	30	35	32	28	31	28	-	3	6	-	27	28
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(1
Home modifications under	taken over 12 n	nonths										
% 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-
Aids and appliances used o	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-
Working prior to stroke	1		1			1	.]					
% 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(2
Proportion working at 12 r	nonths		1	1	1	<u>I</u>	1	1		1	1	1
% 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(1

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% of patients	-	-	-	-	-	-	19	16	5	10	-	-
No. of maids	-	-	-	-	-	-	1(1-1)	1(1-1)	1(1-1)	1(1-1)	-	-
Patients from Singap	oore and Malaysia w	ho had a maid at	12 months follow	ing stroke	_	-	23	22	5	7		-
1					_		1(1-1)	1(1-1)	1(1-1)	1(1-1)		
No of moids					-	-		1 1(1-1)	1 1(1-1)	1 1(1-1)	-	-
	-	-										
	care at 12 months		,									
No. of maids Receipt of informal of % of patients	care at 12 months	39	37	33	41	40	30	36	42	44	37	39

ITT: Intention-to-treat; AU: Australia; NZ: New Zealand; UK: United Kingdom; SG: Singapore; MA: Malaysia; LOS: length of stay; pts: patients; No.: number; hrs: hours; mod: modification; -: no such resource use; all numbers were expressed as median and interquartile range (IQR); ¹includes any admissions to rehabilitation hospital following the indexed stroke;

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

2 Table 2 C		i esources used	u over 12 mont				~~~~					
В	AU (N=1054)		NZ (N=189)		UK (N=610)		SG (N=128)		MA (N=123)		All Countries	
4	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC
5					He	ealth care cost (Al	UD)					
Acute hospi												
Median,	\$6294	\$6294	\$6104	\$6104	\$2763	\$3109	\$1493	\$1493	\$1363	\$1363	\$6294	\$6294
IQR	(6294, 9553)	(6294, 9553)	(4370, 6104)	(4370, 6104)	(1382, 6563)	(1727, 6563)	(1493, 1809)	(1493, 1493)	(1363, 1572)	(1363, 1572)	(2279, 9535)	(2418, 9553)
⁸ Mean, SD	\$9883 (9484)	\$10010(10508)	\$6635 (3244)	\$6549 (3555)	\$5714(7876)	\$5885 (7101)	\$1721 (547)	\$1676 (432)	\$1482 (212)	\$1472 (200)	\$7369 (8469)	\$7521 (8916)
9 Stroke-relate	ed rehospitalisatio	n										
1 0 Median,	\$0	\$0	\$0	\$0	\$227	\$227	\$111	\$111	\$68	\$68	\$111	\$111
1 1 QR	(0, 3850)	(0, 3850)	(0, 325)	(0, 2243)	(227, 1401)	(227, 227)	(111, 111)	(111, 111)	(68, 68)	(68, 68)	(0, 1401)	(0, 610)
	\$6030 (17114)	\$6473 (21590)	\$651 (1371)	\$1507 (2828)	\$4524 (13968)	\$3494(11349)	\$2756 (7565)	\$1679 (3465)	\$714 (1608)	\$603 (1479)	\$4610 (14518)	\$4551 (16707)
Admission t	o rehab hospital								-			
Median,	\$13134	\$13134	\$11262	\$11262	\$0	\$0	\$0	\$1298	\$0	\$0	\$0	\$1136
ĮĮQR	(0, 36371)	(0, 38391)	(0, 30983)	(0, 26486)	(0, 29788)	(0, 29788)	(0, 2921)	(0, 3570)	(0, 0)	(0, 0)	(0, 29788)	(0, 29788)
Mean, SD	\$25667 (38892)	\$26648(38315)	\$16871(18536)	\$15573(16848)	\$12539(19682)	\$11758 (18390)	\$1815 (2759)	\$2798 (5082)	\$0(0)	\$43 (234)	\$18197 (31241)	\$18458 (30811)
¹ Outpatient r	ehab program											
18 _{Median}	\$0 (0, 2451)	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$33	\$0	\$0	\$0
1 9 QR		(0, 1913)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 36)	(0, 265)	(0, 249)	(0, 478)	(0, 239)
2 M ean, 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 provi	ided at home/nursi	ing facility	•							•		
→Median,	\$0	\$0	\$1168	\$212	\$922	\$0	\$0	\$0	\$0	\$0	\$0	\$0
L ÍQR	(0, 717)	(0, 956)	(0, 4299)	(0, 3821)	(0, 11064)	(0, 11064)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 1913)	(0, 1913)
Mean, SD	\$1382 (4069)	\$1551 (4252)	\$3171 (4960)	\$3111 (5754)	\$12085 (28516)	\$11051 (26723)	\$93 (570)	\$5 (42)	\$97 (719)	\$7 (53)	\$4447 (16294)	\$4180 (15203)
	llied health visit								•			
²⁵ Median,	N/A	N/A	N/A	N/A	\$0	\$0	\$0	\$0	\$0	\$0	N/A	N/A
2 6 QR					(0,0)	(0,0)	(0,0)	(0,179)	(0,0)	(0,0)		
	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
28Ambulance	transfers	•							•			
>% Iedian,	\$508	\$508	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
BOR	(0, 1015)	(0, 1015)	(0, 646)	(0, 646)	(0, 1150)	(0, 575)	(0, 265)	(0, 265)	(0, 0)	(0, 0)	(0, 611)	(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 phys	siotherapy		•							•		
Median,	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
^B ³ QR	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)
	\$70 (375)	\$124 (797)	\$245 (1308)	\$4 (36)	\$128 (780)	\$174 (2102)	\$238 (1096)	\$333 (1938)	\$4 (19)	\$1 (9)	\$109 (693)	\$132 (1336)
B Respite care								u	•			
B6Median,	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
B [†] QR	(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	\$48 (355)	\$20 (182)	\$7 (46)	\$2 (15)	\$9 (95)	\$58 (686)	\$0 (0)	\$0 (0)	\$0 (0)	\$1 (8)	\$27 (259)	\$27 (386)
39 39	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
40	1	1				31		1				·]
41						21						

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Page 32 of	82
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1												
5 Sub-total												
Median	\$29278	\$29441	\$20621	\$23722	\$18896	\$20843	\$4525	\$4687	\$1713	\$1746	\$19271	\$20411
(IQR)	(8218, 63622)	(9811, 62489)	(6068, 46909)	(7316, 40162)	(4030, 48999)	(3682, 47908)	(1604, 8668)	(2724, 10926)	(1431, 2532)	(1431, 2348)	(6294, 52637)	(7238, 63835)
d Mean	\$45620 (51458)	\$47453(53715)	\$28898 (25011)	\$27986(22676)	\$34863 (42509)	\$32842 (39517)	\$7681 (8828)	\$8358 (8787)	\$2385(1587)	\$2269(1574)	\$36351 (45620)	\$36604 (46309)
5 (SD)	. ,	, , , , , , , , , , , , , , , , , , ,				, í						
б		`			N	on-health care cos	st	·				
7 Accommoda	ation moves											
8 Median,	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
9 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)
1 Mean, SD	\$2089 (8518)	\$2482 (9323)	\$5975 (19614)	\$9135 (26918)	\$2901 (12958)	\$2532 (11125)	\$72 (578)	\$108 (507)	\$425 (1893)	\$104 (501)	\$2460 (11036)	\$2821 (12212)
Community												
Median,	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
¹ f QR	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 430)	(0, 174)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)
Mean, SD	\$570 (2681)	\$1091 (8556)	\$238 (950)	\$1022 (4113)	\$22275(294988)	\$10738 (57306)	\$0 (0)	\$244 (1902)	\$21 (110)	\$0 (0)	\$6870 (160318)	\$3786 (31893)
Home modi						· · · · · · · · · · · · · · · · · · ·		L .		1 .	I .	
15Median,	\$0 (0, 0)	\$0 (0)	\$0 (0)	\$0	\$0	\$0 (0)	\$0	\$0	\$0	\$0	\$0	\$0 (0, 0)
160R	(0, 0)	(0,0)	(0,0)	(0,0)	(0, 0)	(0,0)	(0, 0)	(0, 0)	(0,0)	(0, 0)	(0, 0)	(0,0)
1 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)
10-	and equipment		*- ^	\$102		*	<u></u>				
1 Median,	\$0 (0, 222)	\$0 (0, 218)	\$70	\$103	\$27	\$0	\$0 (0, 240)	\$0	\$15	\$36	\$0	\$0 (0, 41.4)
1QR	(0, 332)	(0, 318)	(0, 549)	(0, 357)	(0, 786)	(0, 846)	(0, 240)	(0, 210)	(0, 218)	(0, 186)	(0, 414)	(0, 414)
Mean, SD	\$1986 (7668)	\$2787 (10396)	\$2198 (7993)	\$1798 (7229)	\$1354(3649)	\$1720 (5083)	\$1117 (5843)	\$1079 (5483)	\$153 (252)	\$193 (658)	\$1660 (6426)	\$2141 (8328)
² Informal car		¢40	φ14	\$ 0	\$2 0	\$20	AAAAAAAAAAAAA				\$24	\$24
2 2 Median, 2 3 QR	\$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)
24Mean, SD	(0, 303) \$414 (747)	(0, 433) \$405 (758)	\$236 (536)	\$152 (311)	\$324 (516)	\$324 (645)	(0, 114) \$144 (285)	\$159 (300)	\$43 (57)	\$27 (34)	\$335 (633)	\$322 (660)
24vicali, 3D 25 Jiving-in m		\$403 (738)	\$250 (550)	\$152 (511)	\$524 (510)	\$324 (043)	\$144 (283)	\$139 (300)	\$45 (57)	\$27 (34)	\$333 (033)	\$322 (000)
	N/A	N/A	N/A	N/A	N/A	N/A	\$0	\$0	\$0	\$0	N/A	N/A
2 ∂ ∕ledian, 1 JQR	IN/A	IN/A	IN/A	N/A	IN/A	IN/A	\$0 (0,0)	(0,0)	(0,0)	(0,0)	IN/A	IN/A
27 Mean SD	N/A	N/A	N/A	N/A	N/A	N/A	\$3154 (8146)	\$4268(11338)	\$179 (930)	\$83 (504)	N/A	N/A
Mean, SD	10/11	10/11	14/14	11/21	10/21	14/24	\$5151 (0110)	\$1200(11550)	\$175 (550)	\$05 (50 l)	10/21	10/11
29 Median	\$459	\$673	\$381	\$638	\$758	\$471	\$25	\$194	\$74	\$57	\$358	\$438
B0 (IGR)	(0, 3334)	(0, 5209)	(0, 3674)	(103, 14551)	(0, 5097)	(0, 4725)	(0, 1293)	(0, 6999)	(0, 285)	(0, 318)	(0, 3334)	(0, 4561)
B1 Mean	\$6104 (15582)	\$6985 (17554)	\$7752 (17751)	\$11981(27676)	\$27892(306917)	\$15345(61750)	\$4802 (10366)	\$6177 (13942)	\$861 (2272)	\$484 (1113)	\$12043 (164026)	\$9360 (36504)
32 (SD)												
33						Productivity cost						
B ₄ ∕ledian,	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
J QR	(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	\$33203	\$35143	\$29934	\$32216	\$25374	\$30537	\$6960	\$8810	\$2016	\$1816	\$25675	\$27042
^{B8} (IGR)	(9687, 71902)	(12696, 74070)	(8528, 65781)	(15710, 68292)	(4712, 64285)	(4629, 67012)	(1674, 26187)	(3426, 19493)	(1561, 3994)	(1537, 3301)		(7257, 63824)
BMean (SD)	\$52456(57264)	\$56408(62536)	\$40381(37242)	\$43901(43170)	\$65530(332044)	\$49627(78644)	\$15036(16921)	\$16340(19650)	\$3609(3985)	\$2938(2350)	\$50448(184931)	\$47627(64249)
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1 Where only a low proportion (i.e. 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
	ation hospital on discharge from hospital as the rehabilitation service immediately following the acute stroke hospitalisation is not
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Table 3. Baseline cost-utility analysis_ITT

	QALYs	Per capita mean cost (AUD)					
Health care perspective							
Total medical costs	-0.013	\$1082					
	(-0.041, 0.016)	(-\$2520 <i>,</i> \$4685)					
Societal perspective							
Total medical and non-medical	-0.013	-\$6					
costs (excl. productivity cost)	(-0.041, 0.016)	(-\$5476 <i>,</i> \$5463)					
Total medical and non-medical	-0.013	\$102					
costs (incl. productivity cost)	(-0.041, 0.016)	(-\$6907, \$7111)					
	(0.0 11, 0.010)	(,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,					

ITT: Intention-to-treat; QALYs: Quality-adjusted Life Years; AUD: Australian dollar; excl: excluding; incl: including

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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	\$948	-\$2836	\$2937	-\$81	\$137
costs	(-\$4352, \$6248)	(-\$8403, \$2730)	(-\$3635, \$9509)	(-\$2789, \$2627)	(-\$324, \$599)
Total non-	-\$1318	-\$3959	-\$1387	-\$3164	\$200
medical costs	(-\$3038, \$403)	(-\$7769, -\$150)	(-\$7331, \$4557)	(-\$6834, \$505)	(-\$232, \$631)
Total cost	-\$1735	-\$8981	\$1870	-\$2636	\$479
(incl.	(-\$8482, 5013)	(-\$18380, \$418)	(-\$13955, \$17694)	(-\$9233, \$3961)	(-\$487, \$1446)
productivity)					
Total cost	-\$1185	-\$7610	\$2552	-\$1534	\$416
(excl.	(-\$7184, \$4815)	(-\$15302, \$82)	(-\$11377, \$16481)	(-\$6464, \$3395)	(-\$364, \$1196)
productivity)					
QALY gains	-0.036	0.086	-0.010	0.008	0.003
~ 0	(-0.076, 0.003)	(-0.003, 0.176)	(-0.064, 0.044)	(-0.106, 0.123)	(-0.126, 0.132)

AU: Australia; NZ: New Zealand; UK: United Kingdom; SG: Singapore; MA: Malaysia; QALY: Quality-adjusted Life Year.

*the p-value was >0.05 for the between-group difference in QALYs and cost

JSG (-0.003, 0... J Kingdom; SG; (up difference in QAL

Supplementary document 1: Mapping baseline mRS score to utility of AQoL-4D

Methods

Generalized additive model (GAM) with spline smother was used to map AQoL from premorbid mRS, stroke severity, and/ or age group. The performance of the models was evaluated using mean absolute, mean squared errors (MAE and MSE) and R2. 10-fold cross- validation was implemented for model validation. The mapped baseline utility of AQoL-4D was used in the following models.

The analyses are structured as follows:

Model 1:

a) A complete case model with the utility value at 12 months as an output, group as an input, and pre- morbid mRS as a covariate;

b) A complete case model with the utility value at 12 months as an output, group as an input, and pre- morbid mRS + stroke severity as covariates;

c) A complete case model with the utility value at 12 months as an output, group as an input, and pre-morbid mRS + stroke severity + age group as covariates;

d) Sensitivity analyses for the unadjusted model using pattern-mixture models that confirm that there is no statistically significant difference between the groups for the plausible range of changes of a parameter that describes the departure from the assumed "missing-at-random" pattern.

Model 2:

a) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output and group as an input;

b) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output and group as an input + stroke severity as a covariate;

c) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output and group as an input + stroke severity and age group as covariates;

d) Sensitivity analyses for the unadjusted model using pattern-mixture models that confirm that there is no statistically significant difference between the groups for the plausible range of changes of a parameter that describes the departure from the assumed "missing-at-random" pattern.

Model 3:

a) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output, group as an input, and baseline mapped utility value as a covariate;

b) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output, group as an input, and baseline mapped utility value + stroke severity as covariates;

c) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output, group as an input, and baseline mapped utility value + stroke severity + age group as covariates;

d) Sensitivity analyses for the unadjusted model using pattern-mixture models that confirm that there is no statistically significant difference between the groups for the plausible range of changes of a parameter that describes the departure from the assumed "missing-at-random" pattern.

Model 4:

a) A complete case model with the utility value at 12 months as an output, group as an input, and baseline mapped utility value as a covariate;

b) A complete case model with the utility value at 12 months as an output, group as an input, and baseline mapped utility value + stroke severity as covariates;

c) A complete case model with the utility value at 12 months as an output, group as an input, and baseline mapped utility value + stroke severity + age group as covariates;

d) Sensitivity analyses for the unadjusted model using pattern-mixture models that confirm that there is no statistically significant difference between the groups for the plausible range of changes of a parameter that describes the departure from the assumed "missing-at-random" pattern.

Results

Table I. Difference in utility values between treatment groups by different models

	a	b	c	d	
				1	2
Model 1	-0.011	-0.015	-0.016	-0.026	0.006
	(-0.042, 0.020)	(-0.042, 0.011)	(-0.042,0.010)	(-0.062,	(-0.030,
				0.009)	0.041)
Model 2	-0.001	-0.007	-0.008	-0.007	0.005
	(-0.046, 0.044)	(-0.047, 0.034)	(-0.048, 0.031)	(-0.062,	(-0.050,
				0.048)	0.060)
Model 3 [*]	-0.008	-0.014	-0.015	-0.014	0.002
	(-0.043, 0.026)	(-0.043, 0.016)	(-0.043, 0.014)	(-0.052,	(-0.050,
				0.033)	0.045)
Model 4	-0.008	-0.014	-0.015	-0.026	0.006
	(-0.043, 0.026)	(-0.043, 0.016)	(-0.043, 0.014)	(-0.062,	(-0.030,
				0.010)	0.042)

*models 2 and 3 used the mapped baseline AQol utility to estimate the QALY gains over 12 month for each patient.

utility value to calculate the difference in QALYs between treatment groups (results from models 2 and 3) yielded similar results to the primary analysis (-0.013, 95%CI [-0.043, 0.018]), and the 95% confidence

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Supplementary document 2: Cost Case Report Form (CRF)

The Cost CRF was originally developed via pathway analysis during Phase II of AVERT to identify resource items associated with the trial11. Since the Phase II of AVERT trial was a national project and resource utilisation tools were tailored to the Australian setting, the form was further modified to accommodate international differences in the acute service delivery, rehabilitation and post-acute care. An extensive review of country-specific literature and consultation with international AVERT project team members based in each country were ie Cosi ... undertaken to tailor the Cost CRF tool to each participating country.

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Case Report Form - Cost

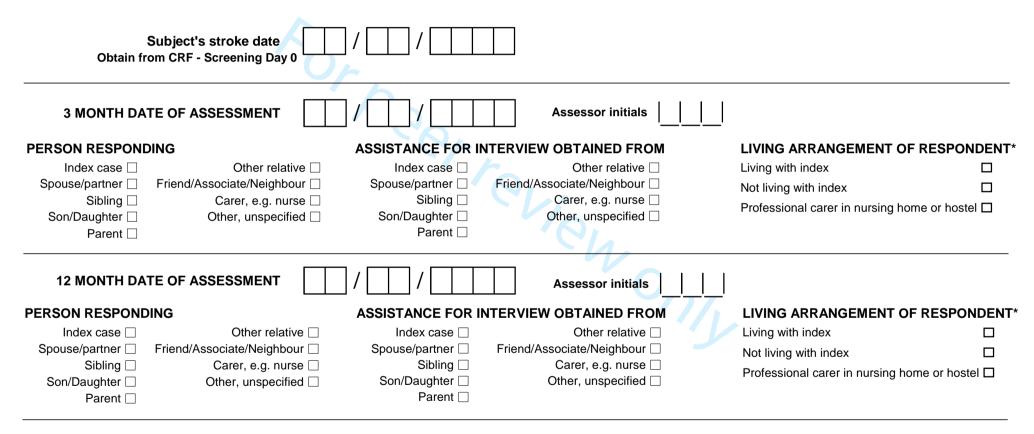


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NOTE: this one form is to be completed AND faxed following BOTH the 3 and 12 month interviews. When CRF Cost complete at 3 months AND at 12 months, fax all pages 25-36 to the Data Fax.

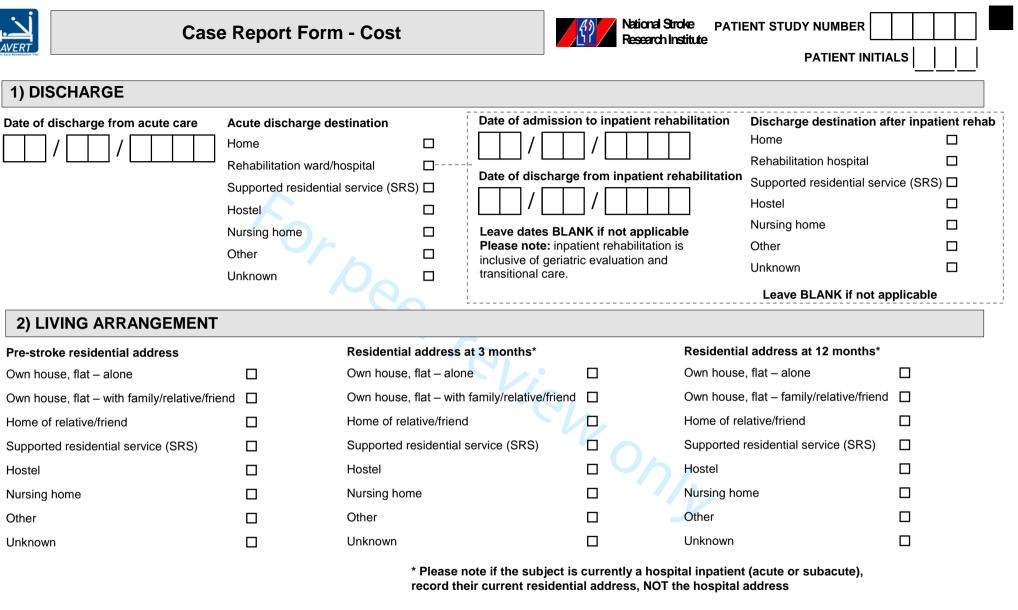
Instructions to the person responding: These questions are about health care provided as a consequence of the stroke which occurred on (give date of stroke) or as a result of any further stroke. I will be asking about health care such as visits to hospital, rehabilitation, therapy at home, equipment and work. To help us work out the cost of stroke to the community, and to you and your family, I will be asking about how often services were provided and their cost.



* Please note: this is the 'normal' living arrangement of the respondent with respect to the subject, even if the subject is currently in hospital

Page 41 of 82

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3) CHANGE IN LIVING ARRANGE	MENTS					
As a consequence of your stroke, have you ne	eeded to change your p	lace of residence?	3 months	Yes 🗌	No 🔲 🛛	Jnknown 🗖
If NO, proceed to question 4. * Please note: if subject has been a hospital	3-12 months	Yes 🗌	No 🔲 🛛	Jnknown 🗖		
DATE OF MOVE	LOCATION					
1) / / /	Home of relative/friend SRS Hostel Nursing home					
2) / /	Own home or unit Home of relative/friend SRS Hostel Nursing home					
3) / /	Hostel Nursing home					
4) / /	Home of relative/friend SRS Hostel					
4) AMBULANCE TRANSFERS: EN		ION-EMERGENCY				
As a consequence of your stroke, have you re If NO, please proceed to question 5	equired ambulance tran	sport after your acute admission to hospital?	* 3 months	s Yes 🗌	No 🗖	Unknown 🗖
			3-12 mor	ths Yes 🗌	No 🗖	Unknown 🗌
Count number of ambulance trips (recruitment to 3 months) * Include post-acute transfers (eg - acute Count number of ambulance trips (from 3 to 12 months)						

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5) HOSPITALISATION OR EMERGENCY DEP	PARTMENT AT	TENDANCES			
5a) Have you been readmitted to hospital or attended the e or for any stroke related problems?	mergency departm		3 months Yes		
(ONLY include information for admissions and attendance stroke-related problems and CRF completion manual for fu		d problems (see below for summary list of	3-12 months Yes	No 🗖	Unknown 🗖
If NO, proceed to question 6					
5b) If YES, Start with the earliest admission or attendance. If p dates BLANK (complete dates at 12 month assessment)	atient NOT discharg	ged at 3 month assessment, leave discharge			If patient not discharged a
Admission or Attendance 1 - Hospital name	Hospital code	Date admitted	Date discharged		12 month assessment cross box.
Admission or Attendance 2 - Hospital name	Hospital code	Date admitted	Date discharged		
Admission or Attendance 3 - Hospital name	Hospital code	Date admitted	Date discharged		
Admission or Attendance 4 - Hospital name	Hospital code	Date admitted	Date discharged		
Admission or Attendance 5 - Hospital name	Hospital code	Date admitted	Date discharged		
Stroke related problems include: 1. Recurrent stroke, 2. TIA or 9. Fractures, 10. DVT, 11. Pulmonary Embolism, 12. Complication enema or other procedure to investigate GI haemorrhage, 16. Comprocedural management of of an atrial septal defect or patent for or cognitive impairment, 23. Constipation - investigation or treatment	ons of stroke treatmen erebral angiography, 1 ramen ovale, 20. Surg	t or stroke prevention, 13. Haemorrhage, 14. Nutritional 7. Carotid endarectomy, 18. Carotid (or other cerebral ve ical or electrophysiological procedure to treat AF, 21. Ina	problem, 15. Gastroscopy/col- essel) angioplasty and/or sten ability to manage at home, 22.	onoscopy/bar ting 19. Surge	ium ery or





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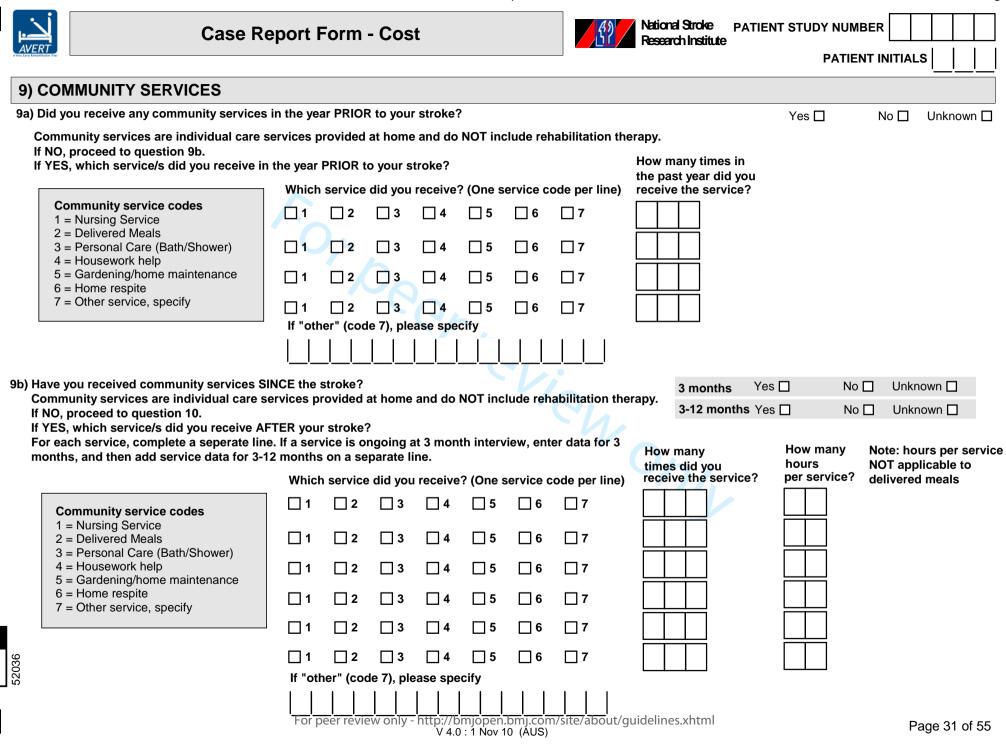
	Case Report F	orm - Cost	<u></u> 51	Research Institute	PA		;
6) INPATIENT F	REHABILITATION ADMISSI	ON					<u>''</u>
-	give date of stroke), were you adm		Hospital or other hospital	3 months	Yes 🗖	No 🔲 Un	known 🗖
where you received a evaluation' and 'transit	ehabilitation treatment? Please incl	ude admissions with the	care type 'rehabilitation', 'ge	riatric 3-12 months	Yes 🗖	No 🔲 🛛 Un	known 🗖
If NO, proceed to que If YES, complete inpa		scharge dates BLANK (c	omplete dates at 12 month a				If patien discharg <u>12 mont</u>
Admission 1- I	Rehabilitation hospital name	Rehab hospit code	al Date admitted		Date dischar	qed	assessn
	0				/ / [cross bo
Admission 2-	Rehabilitation hospital name	Rehab hospit code	al Date admitted		Date dischar	ged	
					/ / [
Admission 3-	Rehabilitation hospital name	Rehab hospit	Date admitted		Date dischar	ged	
					/ 🗍 / [
7) OUTPATIEN	IT REHABILITATION PROG	BRAM					
	re you attending an outpatient reha		consequence of your stro	ke? 3 months	Yes 🗌	No 🗖	Unknown
An outpatient rehabi	apy, occupational therapy, speech itation program is any rehabilitation p or community facility.	therapy, etc rogram where the patien	attends a facility. The progr	ram can be 3-12 mor	ths Yes 🗌	No 🗖	Unknown
If NO, proceed to qu	lestion 8.						If pa
	patient rehabilitation details, starting f irged at 3 month assessment, leave d			(complete dates at 12 mo	nth assessment	Total	disc
·		Rehab facility	-			of DAYS	<u>12 m</u> asse
Admission 1 - O	itpatient rehabilitation name	code	Date admitted	Date dis	scharged		d _{cros}
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Admission 2 - O	utpatient rehabilitation name	Rehab facility code	Date admitted	Date dis	scharged		
]/ /]/		
Admission 3 - Ou	tpatient rehabilitation name	Rehab facility code	Date admitted	Date dis	scharged		
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Page 45 of 82

44 45

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8) REHABIL	ITATION SERVICES PRO	VIDED AT HOME OR IN A NURSING HO	ME	
		o you at home or a nursing home siotherapy, occupational therapy, speech	3 months Yes No	
) sessions. If patient NOT dis	rehabilitation details, starting from	the first visit since your stroke. Count number of eave discharge dates and number of sessions BLANK	3-12 months Yes □ No □	Unknown
Time 1 - Rehabilitat	ion service name	Rehab service code Start date		al <u>12 month</u> mber of <u>3550005</u> SSIONS cross box.
7 3 5 5 6 7 7 7 7 7 7 7 7 7 7 7 7 7	ion service name	Rehab service code Start date Image: Image of the service code Image of the service code	Cease date	
2 3 Time 3 - Rehabilitat 4	ion service name	Rehab service code Start date Image: Start date Image: Start date	Cease date	
5 7 Time 4 - Rehabilitat 3 9	ion service name	Rehab service code Start date Image: Start date Image: Start date	Cease date	
1 2 3 4		For peer review only - http://bmjopen.bmj.com/site/ab V 4.0 : 1 Nov 10 (AUS)	oout/guidelines.xhtml	Page 30 of 55



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10) HOME MODIFICATIONS

Has your home been modified as a consequence of your stroke?

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e.g. installation of rails, bathroom modifications, installation of ramp(s), kitchen modifications etc



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Yes 🗆

3 months

PATI	FNT	INITI	AI S

No 🗆

Unknown 🗌

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If NO, proceed to question 11 If YES, please indicate the type of modification	s, who supplied the modifications and estin	mate any personal cost to you	3-12 months	Yes 🗌 No 🗌	Unknown 🗌
Type of modification	SUPPLIERS 1 = Hospital/rehabilitation centre 2 = Patient/family	3 = Veteran's Affairs 4 = Local Council	5 = Housing commis 6 = Charity	sion 7 = Ot	her (specify)
(check box for each type supplied)	Who supplied the modificat	ion? If supplier is "o	ther", please specify		
☐ Rail(s) for steps/stairs				Cost to you/family* - \$	
□ Ramp(s)		6 [] 7 [] [] []		Cost to you/family* - \$	
☐ Platform step(s)		6 0 7 0 0		Cost to you/family* - \$	
\Box Shower, bath and toilet rail(s)		□6 □7		Cost to you/family* - \$	
☐ Shower(s) modification		□ 6 □ 7 <u> </u>		Cost to you/family* - \$	
☐ Toilet(s) modification	□1 □2 □3 □4 □5	6 0 7 1 1 1		Cost to you/family* - \$	
Remove/modify door(s) from shower/toilet/bath	□1 □2 □3 □4 □5	□ 6 □ 7 		Cost to you/family* - \$	
☐ Kitchen modifications	□1 □2 □3 □4 □5	6 0 7 0 0		Cost to you/family* - \$	
Other modification (specify below) Other home modification - 1					
		5 🗆 6 🗆 7 _ _ _		Cost to you/family* - \$	
Other home modification - 2		6 [] 7 [] [] []		Cost to you/family* - \$	
If total costs includes any aids, describe	e in brief below (see also list of aids on p			all cost is provided, ple difications above, and p	

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itemised costs listed above:

total cost here, INCLUSIVE of any known

Overall Cost \$

Page 32 of 55







P Balaffatter The					PATIENT INITIALS
11) SPECIAL EQUIPMENT AND	AIDS				
ave you been given, hired or purchased ar	ny special equipment, aids or special	food as a consequence of stroke?	3 months	Yes 🗌	No 🗌 Unknown 🗌
Prompt: These may have been provided by ar f NO, proceed to question 12	n Occupational Therapist or Physiothera	apist. What about a?	3-12 months	Yes 🗌	No 🗌 Unknown 🗌
Walking aids	Mobility aids	Eating aids			Kitchen aids
□ Single point stick	Manual wheelchair	Built-up cutlery			Tap handles
☐ Three or four point stick	Electric wheelchair/scooter	Plate guard			Chopping board
☐ Walking frame - pick up	Car steering wheel knob	☐ Non-slip mat			Modified knife
Walking frame - wheelie		Special food e.g. NG/PEG			Uitamiser/blender
Walking frame - gutter (forearm suppt)		If yes, number of days used:			□ Non-slip mat
		3-12 months			General aids
Lounge and bedroom equipment Chair platform/blocks raise	Bathroom equipment	Continence aids			Long handled aid
Cushion to relieve pressure	☐ Toilet surround	□ Bedpan			Blood pressure machine
Special chair (NOT wheelchair)					Treadmill
Table - bedside/wheelie	Bathroom and grooming aids Shower shoir/steel	☐ Incontinence sheet (bed protect	ctor)		Stationary bike
Bed platform/block raise	Shower chair/stool	☐ Incontinence sheet (kylie/bluey			☐ Intercom (portable)
	Over bath seat	If yes, number of days used - 3 mo	·		Modified tap handles If yes, number supplied
	Hand held shower	☐ Incontinence pads 3-12 mc	┝╍┿╼┽╼┥		
☐ Hospital bed (eg - height/tilt adjust)	☐ Non-slip mat				Personal alarm
☐ Mobile hoist/lifter		If yes, number of days used - 3 mo			If yes, number of days supp
Any other aids/equipment, specify		Catheter 3-12 mo			3 months
		If yes, number of days used - 3 mo	onths		3-12 months
		3-12 ma	onths		

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Page 49 of 82

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Case Report Form - Cost



PATIENT INITIALS

stroke) or as a result	When CRF Cost con person responding: These quest of any further stroke. I will be as	mplete at 3 months AND a stions are about health ca king about health care su		e Data Fax. stroke which occurred on (give date of therapy at home, equipment and work. To
Obtain fi	Subject's stroke date			
3 MONTH DA			Assessor initials	
PERSON RESPON	DING	ASSISTANCE FOR I	NTERVIEW OBTAINED FROM	LIVING ARRANGEMENT OF RESPONDEN
Index case	Other relative	Index case 🗌	Other relative	Living with index
Spouse/partner 🗌	Friend/Associate/Neighbour	Spouse/partner 🗌 🗸	Friend/Associate/Neighbour	Not living with index
Sibling 🗌	Carer, e.g. nurse 🗌	Sibling 🗌	Carer, e.g. nurse 🗌	Professional carer in nursing home or hostel
Son/Daughter 🗌 Parent 🗌	Other, unspecified 🗌	Son/Daughter 🗌 Parent 🗌	Other, unspecified	
12 MONTH DA			Assessor initials	<u> </u>
PERSON RESPON	DING	ASSISTANCE FOR I		LIVING ARRANGEMENT OF RESPONDEN
Index case	Other relative	Index case	Other relative	Living with index
Spouse/partner	Friend/Associate/Neighbour	Spouse/partner	Friend/Associate/Neighbour	Not living with index
Sibling	Carer, e.g. nurse 🗌	Sibling 🗌	Carer, e.g. nurse 🗌	Professional carer in nursing home or hostel
Son/Daughter 🗌 Parent 🗌	Other, unspecified 🗌	Son/Daughter 🗌 Parent 🗌	Other, unspecified \Box	
				* Please note: this is the 'normal' living arrangement of the respondent with respect to the subject, even if the subject is currently in hospital



Case Report Form - Cost



National Stroke PATIENT STUDY NUMBER Research Institute

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1) DISCHARGE							
Date of discharge from acute care	Acute discharge des	stination	Date of admissior	to inpatient rehal	oilitation	Discharge destination af	ter inpatient reha
	Home]/ []] [Home	
	Rehabilitation ward/h	ospital 🛛 🗖				Rehabilitation hospital	
	Supported residential	l service (SRS) 🗖	Date of discharge from inpatient rehabilitation		abilitation	Supported residential servi	ice (SRS) 🗖
	Hostel					Hostel	
	Nursing home		Leave dates BLA	NK if not applicabl	е	Nursing home	
	Other		Please note: inpat inclusive of geriatri	ient rehabilitation is		Other	
	Unknown		transitional care.	c evaluation and		Unknown	
						Leave BLANK if not ap	plicable
2) LIVING ARRANGEMENT							
Pre-stroke residential address		Residential address a	t 3 months*		Residentia	I address at 12 months*	
Own house, flat – alone		Own house, flat – alone	9		Own house	, flat – alone	
Own house, flat – with family/relative/frien	nd 🗖	Own house, flat – with	family/relative/friend		Own house	, flat – family/relative/friend	
Home of relative/friend		Home of relative/friend			Home of re	ative/friend	
Supported residential service (SRS)		Supported residential s	ervice (SRS)		Supported	esidential service (SRS)	
Hostel		Hostel			Hostel		
Nursing home		Nursing home			Nursing hor	ne	
Other		Other			Other		
Unknown		Unknown			Unknown		
			ote if the subject is ir current residentia			(acute or subacute), address	



Page 51 of 82

 BMJ Open



Case Report Form - Cost



National Stroke PATIENT STUDY NUMBER Research Institute

PATIENT INITIALS

3) CHANGE IN LIVING ARRANGE	MENTS					
As a consequence of your stroke, have you n If NO, proceed to question 4.	eeded to change your plac	e of residence?	3 months	Yes 🗌	No 🗖	Unknown 🗖
* Please note: if subject has been a hospital	inpatient this is NOT a cha	nge of residence	3-12 months	Yes 🗌	No 🗖	Unknown 🗖
DATE OF MOVE	LOCATION					
1) / / /	Own home or unitImage: Constraint of the second					
2) / /	Own home or unit Image: Constraint of the second					
3)	Own home or unit Image: Constraint of the constraint o					
4) / /	Own home or unitHome of relative/friendSRSHostelNursing homeOther					
4) AMBULANCE TRANSFERS: EI	MERGENCY AND NO	N-EMERGENCY				
As a consequence of your stroke, have you If NO, please proceed to question 5	required ambulance transp	ort after your acute admission to hospital?	* 3 month	s Yes □	No 🗆] Unknown 🗌
			3-12 mo	nths Yes 🗌	No 🗆] Unknown 🗌
Count number of ambulance trips (recruin		* Include post-acute transfers (eg - acut	e to rehab)			





National Stroke PATIENT STUDY NUMBER Research Institute

 	 ~	

dependences and a service set of an other strates					
Have you been readmitted to hospital or attended the emergency department as a consequence of another stroke 3 months Yes No for any stroke related problems? 3-12 months Yes No					
	3-12 months Yes L NO L	Unknown [
discharged at 3 month assessment, leave discharge		If patient no discharged			
Date admitted	Date discharged	12 month assessmen cross box.			
Date admitted	Date discharged				
Date admitted	Date discharged				
Date admitted	Date discharged				
al Date admitted	Date discharged				
ıri i D⊤ tta tta tta	tal Date admitted	by the related problems (see below for summary list of prification) T discharged at 3 month assessment, leave discharged tal Date admitted Date admitted Date admitted Date discharged tal Date admitted Date admitted Date discharged tal Date admitted Date discharged			

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Page 53 of 82

6)	INPATIENT REHABILITATION ADMISSIO	N									
-	your stroke on (give date of stroke), were you admit		Rehabilitatio	n Hospita	l or other	hospital		3 months		Yes 🗖	
	re you received rehabilitation treatment? Please inclu			=		-	tric	3-12 mor		Yes 🗆	
	uation' and 'transitional care' , proceed to question 7.							5-12 1101	1113		
If YE	S, complete inpatient rehabilitation admission details, st	0									
If pat	tient NOT discharged at 3 month assessment, leave disc	-	tes BLANK (c A ehab hospi	-	lates at 12	month ass	essment)				
	Admission 1- Rehabilitation hospital name		ode		Date a	dmitted			D	ate disc	harg
					/	/			/		/ [
			ehab hospi	tal	Deter						
	Admission 2- Rehabilitation hospital name		ode		Date a	dmitted				ate disc	narg
		L			/				/		/ _
	Admission 3- Rehabilitation hospital name		ehab hospi ode	tal	Date a	dmitted			D	ate disc	harg
]/[\neg /		/ [
	OUTPATIENT REHABILITATION PROG										
Die	d you attend or are you attending an outpatient rehal	bilitation			uence of y	our stroke	?	3 mc	onths	Yes [
Dic e.g An	d you attend or are you attending an outpatient rehal . with physiotherapy, occupational therapy, speech to outpatient rehabilitation program is any rehabilitation pro	bilitation therapy, e	etc	-	-					Yes [ns Yes [
Dia e.g An loca	d you attend or are you attending an outpatient rehal . with physiotherapy, occupational therapy, speech t	bilitation therapy, e	etc	-	-						
Dic e.g An loca If N If Y	d you attend or are you attending an outpatient rehal . with physiotherapy, occupational therapy, speech to outpatient rehabilitation program is any rehabilitation pro- ated at a hospital or community facility. IO, proceed to question 8. ES, complete outpatient rehabilitation details, starting fr	bilitation therapy, e rogram wh	ere the patier	it attends rehabilita	a facility. T tion visit.	he progran	n can be	3-12	month	ns Yes[]
Dia e.g An loca If N If Y	d you attend or are you attending an outpatient rehal . with physiotherapy, occupational therapy, speech t outpatient rehabilitation program is any rehabilitation pro ated at a hospital or community facility. IO, proceed to question 8. ES, complete outpatient rehabilitation details, starting fra atient NOT discharged at 3 month assessment, leave dis	bilitation therapy, e ogram wh rom your fi ischarge d Reḥał	ere the patier	t attends rehabilita ber of da	a facility. T tion visit. ys attended	The program	n can be	3-12 dates at 12	month	n s Yes [n assessr]
Dia e.g An loca If N If Y	d you attend or are you attending an outpatient rehal . with physiotherapy, occupational therapy, speech to outpatient rehabilitation program is any rehabilitation pro- ated at a hospital or community facility. IO, proceed to question 8. ES, complete outpatient rehabilitation details, starting fr	bilitation therapy, e ogram wh rom your fi ischarge d	ere the patier irst outpatient lates and num	t attends rehabilita ber of da	a facility. T tion visit.	The program	n can be	3-12 dates at 12	month	ns Yes[]
Dia e.g An loca If N If Y	d you attend or are you attending an outpatient rehal . with physiotherapy, occupational therapy, speech t outpatient rehabilitation program is any rehabilitation pro ated at a hospital or community facility. IO, proceed to question 8. ES, complete outpatient rehabilitation details, starting fra atient NOT discharged at 3 month assessment, leave dis	bilitation therapy, e ogram wh rom your fi ischarge d Reḥał	ere the patier irst outpatient lates and num	t attends rehabilita ber of da	a facility. T tion visit. ys attended	The program	n can be	3-12 dates at 12	month	n s Yes [n assessr]
Did e.g An loc: If N If Y	d you attend or are you attending an outpatient rehal with physiotherapy, occupational therapy, speech to outpatient rehabilitation program is any rehabilitation pro- ated at a hospital or community facility. IO, proceed to question 8. ES, complete outpatient rehabilitation details, starting fra- atient NOT discharged at 3 month assessment, leave dis- Admission 1 - Outpatient rehabilitation name	bilitation therapy, e ogram wh rom your fi ischarge d Rehat code	ere the patier irst outpatient lates and num	rehabilita ber of da Date	a facility. T tion visit. ys attended admitte	The program	n can be	3-12 dates at 12 Date	month 2 month e disc	ns Yes [n assessr harged]
Did e.g An loc: If N If Y	d you attend or are you attending an outpatient rehal . with physiotherapy, occupational therapy, speech t outpatient rehabilitation program is any rehabilitation pro ated at a hospital or community facility. IO, proceed to question 8. ES, complete outpatient rehabilitation details, starting fra atient NOT discharged at 3 month assessment, leave dis	bilitation therapy, e ogram wh rom your fi ischarge d Rehat code	ere the patient irst outpatient lates and num o facility	rehabilita ber of da Date	a facility. T tion visit. ys attended	The program	n can be	3-12 dates at 12 Date	month 2 month e disc	n s Yes [n assessr	
Did e.g An loc: If N If Y	d you attend or are you attending an outpatient rehal with physiotherapy, occupational therapy, speech to outpatient rehabilitation program is any rehabilitation pro- ated at a hospital or community facility. IO, proceed to question 8. ES, complete outpatient rehabilitation details, starting fra- atient NOT discharged at 3 month assessment, leave dis- Admission 1 - Outpatient rehabilitation name	bilitation therapy, e ogram wh rom your fi ischarge d Rehat code	ere the patient irst outpatient lates and num o facility	rehabilita ber of da Date	a facility. T tion visit. ys attended admitte	The program	n can be	3-12 dates at 12 Date	month 2 month e disc	ns Yes [n assessr harged	
Dia e.g An loca If N If Y	d you attend or are you attending an outpatient rehal with physiotherapy, occupational therapy, speech to outpatient rehabilitation program is any rehabilitation pro- ated at a hospital or community facility. IO, proceed to question 8. ES, complete outpatient rehabilitation details, starting fra- atient NOT discharged at 3 month assessment, leave disc Admission 1 - Outpatient rehabilitation name Admission 2 - Outpatient rehabilitation name	bilitation therapy, e rogram wh rom your fi ischarge d Rehat code Rehat code	ere the patient irst outpatient lates and num o facility	rehabilita ber of da Date	a facility. T tion visit. ys attended admitted admitted admitted	The program	n can be	3-12 dates at 12 Date Date	month 2 month e disc i disc	ns Yes [n assessr harged / harged /	
Dic e.g An loc: If N If Y If p:	d you attend or are you attending an outpatient rehal with physiotherapy, occupational therapy, speech to outpatient rehabilitation program is any rehabilitation pro- ated at a hospital or community facility. IO, proceed to question 8. ES, complete outpatient rehabilitation details, starting fra- atient NOT discharged at 3 month assessment, leave dis- Admission 1 - Outpatient rehabilitation name	bilitation therapy, e rogram wh rom your fi ischarge d Rehat code Rehat	ere the patien irst outpatient lates and num o facility	rehabilita ber of da Date	a facility. T tion visit. ys attended admitte	The program	n can be	3-12 dates at 12 Date Date	month 2 month e disc i disc	ns Yes [n assessr harged	

Page 29 of 55

PATIENT INITIALS

No 🗖

No 🗖

No 🗖

No 🗌

Total

number

of DAYS attended

Unknown 🗖

Unknown 🗖

If patient not discharged at 12 month assessment,

cross box.

Unknown 🗖

Unknown 🗖

If patient not discharged at

assessment,

cross box.

<u>12 month</u>



 Case Report Form - Cost



National Stroke PATIENT STUDY NUMBER Research Institute

(complete dates at 12 month assessment) Total Rehab service Start date Cease date Cease date SESSIONS						<u></u>
as a consequence of your stroke? e.g. with physiotherapy, occupational therapy, speech If NO, proceed to question 9. If YES, complete rehabilitation details, starting from the first visit since your stroke. Count number of sessions. If patient NOT discharged at 3 month assessment, leave discharge dates and number of sessions BLANK (complete dates at 12 month assessment) me 1 - Rehabilitation service name Rehab service Start date Cease date Mehab service Start date Cease date	VIDED AT HOME	OR IN A NURSING HO	OME			
If NO, proceed to question 9. 3-12 months Yes No Unknown If YES, complete rehabilitation details, starting from the first visit since your stroke. Count number of sessions BLANK (complete dates at 12 month assessment) If patient discharge dates and number of sessions BLANK (complete dates at 12 month assessment) If patient discharge dates and number of sessions BLANK (complete dates at 12 month assessment) If patient discharge dates and number of sessions BLANK (complete dates at 12 month assessment) If patient discharge dates and number of sessions BLANK (complete dates at 12 month assessment) If patient discharge dates and number of sessions BLANK (complete dates at 12 month assessment) If patient discharge dates and number of sessions BLANK (complete dates at 12 month assessment) If patient discharge dates and number of sessions BLANK (complete dates at 12 month assessment) If patient discharge dates at 12 month assessment) me 1 - Rehabilitation service name Rehab service Start date Cease date If patient discharge dates at 0 month assessment) me 3 - Rehabilitation service name Rehab service Start date Cease date Image: date date date date date date date date			3 mo	nths Yes 🗌	No 🗌 Unknowr	
If patient NOT discharged at 3 month assessment, leave discharge dates and number of sessions BLANK (complete dates at 12 month assessment) me 1 - Rehabilitation service name Rehab service Rehab service Code Start date Cease date Image: Code Rehab service Start date Cease date Rehab service Start date Cease date Image: Code Rehab service Start date Cease date Image: Code Rehab service Start date Cease date Image: Code Rehab service Start date Cease date Image: Code Rehab service Start date Cease date Image: Code Rehab service Start date Cease date Image: Code Rehab service Start date Cease date Image: Code Rehab service Code Start date Cease date Rehab service Code Start date Cease date Rehab service Code Start date <td></td> <td></td> <td>3-12 r</td> <td>nonths Yes 🗌</td> <td>No 🗌 Unknown</td> <td></td>			3-12 r	nonths Yes 🗌	No 🗌 Unknown	
ne 1 - Rehabilitation service name Rehab service code Start date Cease date SESSIONS Cease date Cease dat	eave discharge dates an	d number of sessions BLANK			Total	If patient discharge
me 2 - Rehabilitation service name code Start date Cease date me 3 - Rehabilitation service name Rehab service code Start date Cease date me 4 - Rehabilitation service name Rehab service code Start date Cease date me 4 - Rehabilitation service name Rehab service code Start date Cease date		Start date		Cease date	number of	<u>12 month</u> assessme cross box
me 2 - Rehabilitation service name code Start date Cease date me 3 - Rehabilitation service name Rehab service Start date Cease date me 4 - Rehabilitation service name Rehab service Start date Cease date me 4 - Rehabilitation service name Rehab service Start date Cease date						
ne 3 - Rehabilitation service name code Start date Cease date ne 4 - Rehabilitation service name Rehab service code Start date Cease date		Start date	,	Cease date		
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ne 4 - Rehabilitation service name code Start date Cease date	Rehab service code	Start date		Cease date		
ne 4 - Rehabilitation service name code Start date Cease date]/ /]//[
		Start date		Cease date		
]//				
	1	o you at home or a nursiotherapy, occupation the first visit since your seave discharge dates an Rehab service code Rehab service Rehab service Code Rehab service Code	o you at home or a nursing home siotherapy, occupational therapy, speech the first visit since your stroke. Count number of eave discharge dates and number of sessions BLANK Rehab service code Start date Rehab service Start date Rehab service Start date Rehab service Start date Rehab service Start date	o you at home or a nursing home 3 modesiotherapy, occupational therapy, speech 3-12 r the first visit since your stroke. Count number of eave discharge dates and number of sessions BLANK Rehab service code Start date Rehab service code Start date Image: Code Image: Code Start date Image: Code Image: Code	a months Yes siotherapy, occupational therapy, speech 3-12 months the first visit since your stroke. Count number of eave discharge dates and number of sessions BLANK Rehab service Cease date Cease date Rehab service Start date Cease date Rehab service Start date Cease date Rehab service Start date Cease date Cease date Cease date Code Start date Cease date Cease date Code Start date Cease date Code Start date Cease date Cease date Code Start date Cease date Code Start date Cease date Cease date Code Start date Cease date Code Cease date Code Code Code Code Code Code Code Code Code <td>OVIDED AT HOME OR IN A NURSING HOME o you at home or a nursing home siotherapy, occupational therapy, speech 3 months Yes No Unknown 3-12 months Yes No Unknown Secode Start date Cease date Image: Secode 3-12 months Yes Yes Yes Image: Secode Image: Secode</td>	OVIDED AT HOME OR IN A NURSING HOME o you at home or a nursing home siotherapy, occupational therapy, speech 3 months Yes No Unknown 3-12 months Yes No Unknown Secode Start date Cease date Image: Secode 3-12 months Yes Yes Yes Image: Secode Image: Secode

Page 55 of 82

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		eport Forn	ו - Cos	t		52	National Stroke PATIE Research Institute	ENT STUDY NUN PATIE	
9) COMMUNITY SER	VICES								'.
9a) Did you receive any com	nmunity services	in the year PRI	OR to your	stroke?				Yes 🗌	No 🔲 Unkn
Community services are	individual care s	services provide	ed at home	and do NOT	include re	habilitation th	nerapy.		
If NO, proceed to question							How many times in		
If YES, which service/s d	lia you receive in	-	-				the past year did you		
0		Which servio	e did you	receive? (On	e service o	code per line)	receive the service?		
Community service c 1 = Nursing Service	codes		3		5 🗌 6	7 []			
2 = Delivered Meals					- □.	— -			
3 = Personal Care (Ba 4 = Housework help	itn/Snower)		□ 3		5 []6	7 []			
5 = Gardening/home m	naintenance		3	□4 □	5 🗌 6	□ 7			
6 = Home respite 7 = Other service, spec	cify				5 🗌 6				
		lf "other" (c	_						
			_						
9b) Have you received comm	nunity services S	INCE the stroke	?				3 months Ye	es 🔲 🛛 No	o 🔲 🛛 Unknown 🗖
Community services are		ervices provide	d at home	and do NOT	include rel	habilitation the			o 🔲 Unknown 🗖
If NO, proceed to questio		FTFR your strok	e?						
IT YES, Which service/s d	io vou receive Al								
If YES, which service/s di For each service, comple	ete a seperate line	e. If a service is	ongoing a		erview, en	ter data for 3		How many	Note: hours no
	ete a seperate line	e. If a service is	ongoing a		erview, en	ter data for 3	How many times did you	How many hours	
For each service, comple	ete a seperate line	e. If a service is 12 months on a	ongoing a separate li	ne.		ter data for 3 code per line)	times did you		NOT applicable
For each service, comple months, and then add se	ete a seperate line ervice data for 3-1	e. If a service is 12 months on a	ongoing a separate li ce did you	ne.	ne service		times did you	hours	NOT applicable
For each service, comple	ete a seperate line ervice data for 3-1	e. If a service is 12 months on a Which servi	ongoing a separate li ce did you : 3	ne. receive? (Or	ne service 5 🗌 6	code per line)	times did you	hours	NOT applicable
For each service, comple months, and then add se Community service of 1 = Nursing Service 2 = Delivered Meals	ete a seperate line ervice data for 3-1 codes	e. If a service is 12 months on a Which servi	ongoing a separate li ce did you : 3	ne. receive? (Or	ne service 5 🗌 6	code per line)	times did you	hours	NOT applicable
For each service, comple months, and then add se Community service of 1 = Nursing Service 2 = Delivered Meals 3 = Personal Care (Ba	ete a seperate line ervice data for 3-1 codes	e. If a service is 12 months on a Which servi	ongoing a separate li ce did you 2	ne. receive? (Or 4 4 4 4	ne service 5	code per line) 7 7 7	times did you	hours	NOT applicable
For each service, comple months, and then add se Community service of 1 = Nursing Service 2 = Delivered Meals 3 = Personal Care (Ba 4 = Housework help 5 = Gardening/home r	ete a seperate line ervice data for 3-1 codes ath/Shower)	e. If a service is 12 months on a Which servi 1 2 1 2 1 2 1 2	ongoing a separate li ce did you 2 3 2 3 2 3 2 3	ne. receive? (Or 4 4 4 4 4 4 4 4 4 4	ne service 5	code per line) 7 7 7 7 7	times did you	hours	NOT applicable
For each service, complements, and then add service, and then add service at a serv	ete a seperate line ervice data for 3-1 codes ath/Shower) maintenance	e. If a service is 12 months on a Which servi	ongoing a separate li ce did you 2 3 2 3 2 3 2 3	ne. receive? (Or 4 4 4 4	ne service 5	code per line) 7 7 7	times did you	hours	NOT applicable
For each service, comple months, and then add se Community service of 1 = Nursing Service 2 = Delivered Meals 3 = Personal Care (Ba 4 = Housework help 5 = Gardening/home r	ete a seperate line ervice data for 3-1 codes ath/Shower) maintenance	e. If a service is 12 months on a Which servi 1 1 2 1 2 1 2 1 2	ongoing a separate li ce did you 2 3 2 3 2 3 2 3 2 3	ne. receive? (Or 4 4 4 4 4 4 4 4 4 4	ne service 5	code per line) 7 7 7 7 7 7 7	times did you	hours	NOT applicable
For each service, complements, and then add service, and then add service at a serv	ete a seperate line ervice data for 3-1 codes ath/Shower) maintenance	e. If a service is 12 months on a Which servi 1 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1	ongoing a separate li ce did you 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3	ne. receive? (Or 4 4 4 4 4 4 4 4 4	ne service 5	code per line) 7 7 7 7 7 7 7 7 7	times did you	hours	Note: hours per NOT applicable delivered meals
For each service, complements, and then add service, and then add service at a serv	ete a seperate line ervice data for 3-1 codes ath/Shower) maintenance	e. If a service is 12 months on a Which servi 1 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1	ongoing a separate li ce did you ? 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3	ne. receive? (Or 4 4 4 4 4 4 4 4 4 4 4 4 4	ne service 5	code per line) 7 7 7 7 7 7 7 7 7	times did you	hours	NOT applicable
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For each service, complements, and then add service, and then add service at a serv	ete a seperate line ervice data for 3-1 codes ath/Shower) maintenance	e. If a service is 12 months on a Which servi 1 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1	ongoing a separate li ce did you 2 3 3 2 3 3 2 3 3 2 3 3 2 3 3 3 3 3 3	ne. receive? (Or 4 4 4 4 4 4 4 4 4 4 4 4 4	ne service 1 5	code per line) 7 7 7 7 7 7 7 7 7 7 7 7 7 7	times did you	hours	NOT applicable
For each service, complements, and then add service, and then add service at a serv	ete a seperate line ervice data for 3-1 codes ath/Shower) maintenance	e. If a service is 12 months on a Which servi 1 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1	ongoing a separate li ce did you 2 3 3 2 3 3 2 3 3 2 3 3 2 3 3 3 3 3 3	ne. receive? (Or 4 4 4 4 4 4 4 4 4 4 4 4 4	ne service (5	code per line) 7 7 7 7 7 7 7 7 7 7 7 7 7 7	times did you receive the service?	hours	NOT applicabl delivered mea



Has e.g.

1 2

3

4 5



PATIENT STUDY NUMBER

PATIENT	INITIALS

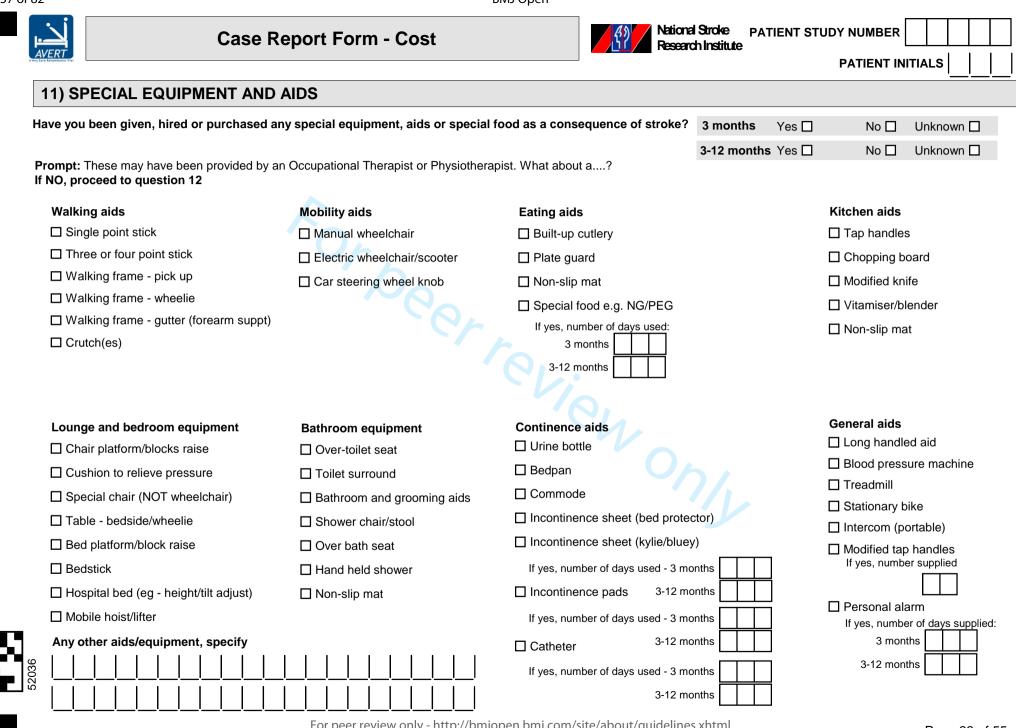
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46

Has your home been modified as a conseque e.g. installation of rails, bathroom modification	3 months	Yes 🗌 🛛 No 🗌	Unknown 🗌		
If NO, proceed to question 11	3-12 months	Yes 🗌 🛛 No 🗌	Unknown 🗌		
If YES, please indicate the type of modifications,	, who supplied the modifications and esti	mate any personal cost to you.			
Type of modification	SUPPLIERS 1 = Hospital/rehabilitation centre 2 = Patient/family	3 = Veteran's Affairs 4 = Local Council	5 = Housing commis 6 = Charity	sion 7 = O	ther (specify)
(check box for each type supplied)	Who supplied the modificat	tion? If supplier is "o	other", please specify		
Rail(s) for steps/stairs		5 🗆 6 🗆 7 📃 📃		Cost to you/family* - \$	
☐ Ramp(s)		5 🗆 6 🗆 7 📗 📗		Cost to you/family* - \$	
□ Platform step(s)		5 [] 6 [] 7 [] [] []		Cost to you/family* - \$	
\Box Shower, bath and toilet rail(s)		5 🗆 6 🗆 7 📘 📘		Cost to you/family* - \$	
☐ Shower(s) modification		5 🗆 6 🗆 7 📙 📙		Cost to you/family* - \$	
☐ Toilet(s) modification		5 🗆 6 🗆 7 📘 📘		Cost to you/family* - \$	
Remove/modify door(s) from shower/toilet/bath		5 🗆 6 🗆 7 📗 📗		Cost to you/family* - \$	
Kitchen modifications		5 🗆 6 🗆 7 📗 📗		Cost to you/family* - \$	
Other modification (specify below) Other home modification - 1					
		5 🗆 6 🗆 7 📘 📕		Cost to you/family* - \$	
Other home modification - 2		5 🗆 6 🗆 7 📗		Cost to you/family* - \$	
If total costs includes any aids, describe i	n brief below (see also list of aids on	page 33):	type of mo total cost	rall cost is provided, ple odifications above, and p here, INCLUSIVE of any osts listed above:	provide the
				Overall Cost \$	

Page 57 of 82

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3-12 months

No \square

If YES, what was the nature of this work?

How many hours did you work each week?

3 months

3 months

3-12 months

3-12 months

Unknown 🗌

Yes 🗖

Yes 🗖

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12) PRIVATE PHYSIOTHERAPY

3-12 months

14) EMPLOYMENT STATUS/ PAID WORK

Were you working up to the time of your stroke?

Since the stroke, have you returned to this work?

Have you returned to normal hours or decreased hours?

If yes, how many days of respite have you received since your stroke? 3 months

How many hours per week of work have you performed since the last assessment?

Record average amount per week over the period 3 to 12 months

Record average amount per week over the 3 month period

If no, proceed to question 13

13) RESPITE CARE

If NO, proceed to question 14

If yes, number of sessions - 3 months

Have you paid for private physiotherapy sessions after your stroke? (NOT while a hospital inpatient)

As a consequence of your stroke, have you been admitted to a respite bed in a nursing home or hospital?

Yes 🗆



Full time

No 🗖

No 🗖

Normal

Normal

National Stroke PATIENT STUDY NUMBER Research Institute

Yes 🗖

Yes 🗌

3 months

3 months

Part time

Unknown 🗖

Unknown 🗌

Decreased

Decreased

If more than 0 but less than 1hr, record as 1

3-12 months Yes □

3-12 months Yes

PATIENT INITIALS

No 🗆

No \square

No 🗌

No \square

Unknown

Unknown

Unknown

Unknown

Page 34 of 55

Page 58 of 82

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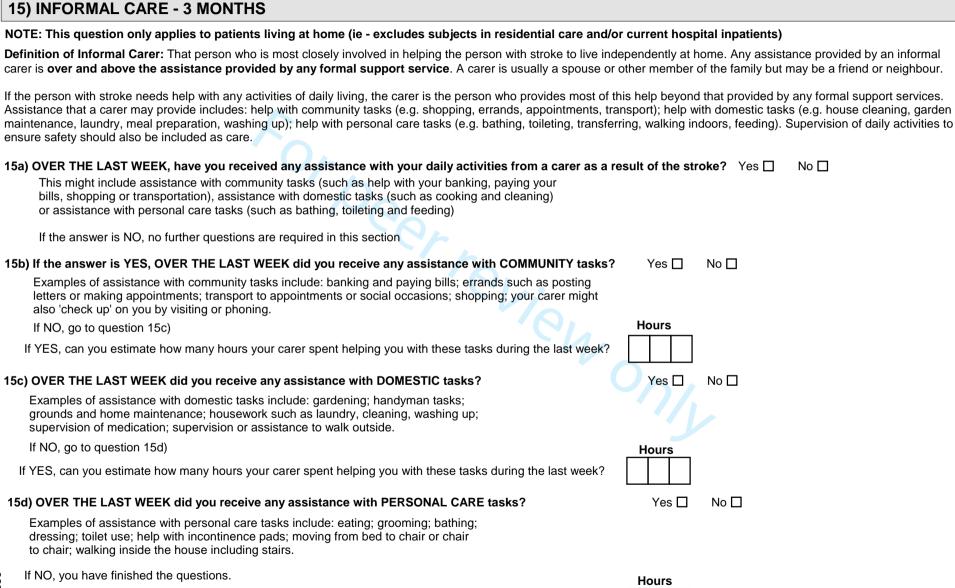
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Case Report Form - Cost



National Stroke PATIENT STUDY NUMBER Research Institute



If YES, can you estimate how many hours your carer spent helping you with these tasks during the last week?

He	ours	rs			





National Stroke PATIENT STUDY NUMBER Research Institute

PATIENT INITIALS

45 46

16) INFORMAL CARE - 12 MONTHS NOTE: This question only applies to patients living at home (ie - excludes subjects in residential care and/or current hospital inpatients) Definition of Informal Carer: That person who is most closely involved in helping the person with stroke to live independently at home. Any assistance provided by an informal carer is over and above the assistance provided by any formal support service. A carer is usually a spouse or other member of the family but may be a friend or neighbour. If the person with stroke needs help with any activities of daily living, the carer is the person who provides most of this help beyond that provided by any formal support services. Assistance that a carer may provide includes: help with community tasks (e.g. shopping, errands, appointments, transport); help with domestic tasks (e.g. house cleaning, garden maintenance, laundry, meal preparation, washing up); help with personal care tasks (e.g. bathing, toileting, transferring, walking indoors, feeding). Supervision of daily activities to ensure safety should also be included as care. 16a) OVER THE LAST WEEK, have you received any assistance with your daily activities from a carer as a result of the stroke? Yes No \square This might include assistance with community tasks (such as help with your banking, paying your bills, shopping or transportation), assistance with domestic tasks (such as cooking and cleaning) or assistance with personal care tasks (such as bathing, toileting and feeding) If the answer is NO, no further questions are required in this section 16b) If the answer is YES, OVER THE LAST WEEK did you receive any assistance with COMMUNITY tasks? Yes 🗆 No 🗖 Examples of assistance with community tasks include: banking and paying bills; errands such as posting letters or making appointments: transport to appointments or social occasions; shopping; your carer might also 'check up' on you by visiting or phoning. If NO, go to guestion 16c) Hours If YES, can you estimate how many hours your carer spent helping you with these tasks during the last week? 16c) OVER THE LAST WEEK did you receive any assistance with DOMESTIC tasks? Yes 🛛 No 🗆 Examples of assistance with domestic tasks include: gardening; handyman tasks; grounds and home maintenance; housework such as laundry, cleaning, washing up; supervision of medication: supervision or assistance to walk outside. If NO, go to question 16d) Hours If YES, can you estimate how many hours your carer spent helping you with these tasks during the last week? 16d) OVER THE LAST WEEK did you receive any assistance with PERSONAL CARE tasks? Yes 🗆 No 🗆 Examples of assistance with personal care tasks include: eating; grooming; bathing; dressing; toilet use; help with incontinence pads; moving from bed to chair or chair to chair; walking inside the house including stairs. If NO, you have finished the questions.

If YES, can you estimate how many hours your carer spent helping you with these tasks during the last week?

Hours									

End Case Report Form - Cost For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml V 4.0 : 1 Nov 10 (AUS)

Supplementary document 3: Unit costs and valuation of costs

Unit costs for hospitalisation, rehabilitation, non-health sector costs and productivity costs

Acute stroke hospitalisation costing: Unit costs for acute stroke hospitalisation for all countries at baseline were categorised by stroke severity, using the National Institute of Health Stroke Scale (NIHSS) to group patients into three severity levels: mild (0-7), moderate (8-16) and severe (>16). (1)(2) It was assumed that severity as classified by the NIHSS was consistent with the stroke severity that corresponded to three levels of unit cost for acute hospitalisation. Length of Stay (LoS) together with stroke severity were used to estimate the cost of acute hospitalisation for Australia and New Zealand patients (i.e. the cost of acute hospitalisation was weighted by the LoS). LoS was taken as the difference between the date of hospital discharge and date of hospital admission (plus one day or not) in accordance with country-specific practice. For the other countries, only stroke severity was considered in the assignment of a unit cost to acute stroke hospitalisation due to insufficient health sector data.

Re-hospitalisation and rehabilitation costing: Due to the diversity of causes for patients being readmitted to hospital after the index stroke, the average daily cost of hospitalisation for all disease conditions from individual countries in combination with LoS was used to gauge the cost of readmission for stroke-related causes, while the average cost for an emergency department visit was assigned whenever a patient was hospitalised for one day only. Similarly, the unit cost of rehabilitation hospital admission was taken from the national average cost for all disease conditions. The median cost was used where there was more than one unit cost identified for the same resource item.

Non-health sector costs: Unit costs of non-health sector resource items (e.g. community service, accommodation changes, special aids and equipment) were sourced on a country- specific basis from official websites or published literature where applicable. No unit cost was retrieved for home modification items since the cost of home modifications was generally reported in the Cost CRF.

Productivity cost: Lost productivity was valued based on a human capital approach using average earnings across all occupations up to normal retirement age. The average wage of a

professional carer was adopted to estimate the cost of informal care.

The currency of other countries was converted to AUD using the corresponding exchange rate. The country-specific Consumer Price Index (CPI) from the health sector was employed to adjust costs not valued in the year of 2015.

All the unit costs from participating countries are summarised in Table I.

Resource items	Unit cost (AUD)								
	AU	NZ	UK	SG	MA				
Healthcare									
Acute hospitalisation [*]									
Severe (per episode)	\$19157	\$10867	\$15327	\$4371	\$2066				
Moderate (per episode)	\$9553	\$6104	\$8115	\$2126	\$1572				
Mild (per episode)	\$6279	\$4370	\$4272	\$1493	\$1363				
Stroke-related rehospitalisation (per day)	\$1925	\$320	\$701	\$789	\$230				
Emergency department attendance (per attendance)	\$610	\$325	\$227	\$111	\$68				
Rehabilitation hospital admission [†]									
Severe (per episode)	\$1010 [‡]	\$8032	\$19136 [§]	\$157 [‡]	\$1293				
Moderate (per episode)		\$5727	\$29788 [§]						
Mild (per episode)		\$5727	\$13920 [§]						
Same day (per episode)		\$758	N/A						
Outpatient rehab visit (per/session)	\$239	\$164	\$213	\$36	\$17				
Rehab services at home/nursing	\$239	\$212	\$922	\$36	\$51				
facility (per/session)									
Private physiotherapy (per session)	\$64	\$153	\$162	\$116	\$8				
Respite care (per hour)	\$45	\$14	\$26	\$15	\$2				
Individual allied health visit									
Physiotherapy	N/A	N/A	\$243	\$239	\$8				
Occupational therapy	N/A	N/A	\$243	\$36	\$7				
Speech and language therapy	N/A	N/A	\$69	\$36	\$4				
Ambulance transfer	\$508	\$646	\$575	\$265	\$52				
Non-healthcare									
Community services	Not listed h	ere due to t	he number of	f items					
Home modifications	Cost was provided by individual patients								
Special aids and equipment	Not listed here due to the substantial number of items								
Accommodation changes	Not listed here due to the number of items								
Professional carer (per hour)	\$24	\$14	\$14	\$10	\$2				
Living-in maid (per month)	N/A	N/A	N/A	\$571	\$103				
Average weekly earnings									
Male	\$1137	\$621	\$1152	\$973	\$137				
Female	1		\$957 [°]						

 Table I. Unit cost (in Australian dollars) across five countries, 2015 reference year

Hospital physiotherapist (per	\$33	\$32	\$30	\$21	\$5
hour) Hospital nurse (per hour)	\$30	\$25	\$29	\$21	\$5
AU: Australia; NZ: New Zealand; UK: Uni					Ψ5
Sources of CPI:		a			
Australian Bureau of Statistics. Consumer p from: <u>Http://www.Abs.Gov.Au/websitedbs/</u>				x+inflation+calc	culator 2017
Office for National Statistics. Inflation and	price indices.	Accessed fro			<u></u> ,
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* severity was determined by baseline NIHS day cost; [§] cost was assigned according to th					
Survey of Household Income was provided					
corresponding to this; [#] hourly wage of hosp	pital physioth	erapist and nu	urse were assign	ed; N/A: not app	licable.
Main sources of unit cost: AU: Independent					
Data (2015-16); National Hospital Cost Dat hospitals-cost-report-2013-2014-round-18);	Department	of Health, Re	vised residential	care subsidies	an-public-
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(Te Ao BJ et al. Are stroke units cost effect					
based study. Int. J. Stroke. 2012;7:623-630)					
(http://www.stats.govt.nz/browse_for_stats/ work/employment and unemployment/Lab			PJun15atr.aspx)	District Health	Board. Multi
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(Davis,S., Holmes,M., Simpson,E., Sutton,A					
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Valuation of costs

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 (i.e. excluding non- healthcare costs and productivity cost).

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Page 65 of 82

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Supplementary document 4. Missing cost data analyses

Table I. Number of missing data for each cost item

Cost variable	Missing										
	Total AU		NZ			UK		SG		MA	
0	N=2104	VEM N=522	UC N=532	VEM N=94	UC N=95	VEM N=311	UC N=299	VEM N=64	UC N=64	VEM N=62	UC N=61
Acute hospitalisation	1(0.05%)	1(0.2%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
3 Stroke-related rehospitalisation	51(2.4%)	8(1.5%)	7(1.3%)	0(0%)	0(0%)	17(5.5%)	8(2.7%)	0(0%)	3(4.7%)	7(11.3%)	1(1.6%)
Ambulance transfer	53(2.5%)	8(1.5%)	10(1.9%)	0(0%)	0(0%)	16(5.1%)	7(2.3%)	1(1.6%)	3(4.7%)	7(11.3%)	1(1.6%)
Rehabilitation hospital admission	55(2.6%)	9(1.7%)	9(1.7%)	0(0%)	0(0%)	18(5.8%)	8(2.7%)	0(0%)	3(4.7%)	7(11.3%)	1(1.6%)
7 Outpatient rehabilitation program	47(2.2%)	0(0%)	0(0%)	0(0%)	0(0%)	23(7.4%)	10(3.3%)	0(0%)	3(4.7%)	9(14.5%)	2(3.3%)
8 Rehabilitation provided at home/nursing 9 facility	67(3.2%)	11(2.1%)	10(1.9%)	0(0%)	0(0%)	23(7.4%)	1(3.7%)	0(0%)	3(4.7%)	7(11.3%)	1(1.6%)
Individual allied health visit [§]	0(0%)	-	-	-	-	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Private physiotherapy	76(3.6%)	12(2.3%)	11(2.1%)	0(0%)	1(1.1%)	27(8.7%)	13(4.4%)	1(1.6%)	3(4.7%)	7(11.3%)	1(1.6%)
Respite care	77(3.7%)	12(2.3%)	11(2.1%)	1(1.1%)	1(1.1%)	27(8.7%)	13(4.4%)	1(1.6%)	3(4.7%)	7(11.3%)	1(1.6%)
Subtotal (medical cost)	94(10.7%)	14(2.7%)	13(2.4%)	1(1%)	1(1.1%)	36(11.6%)	14(4.7%)	1(1.6%)	3(4.7%)	9(14.5%)	2(3.3%)
5 Accommodation moves	60(2.9%)	15(2.9%)	11(2.1%)	1(1.1%)	1(1.1%)	15(4.8%)	10(3.3%)	0(0%)	2(3.1%)	5(8.1%)	0(0%)
6 Community services	230(10.9%)	63(12.1%)	87(16.4%)	4(4.3%)	5(5.3%)	32(10.3%)	27(9.0%)	1(1.6%)	3(4.7%)	7(11.3%)	1(1.6%)
Home modifications	13(0.6%)	3(2.6%)	6(1.1%)	0(0%)	1(1.1%)	0(0%)	2(0.7%)	0(0%)	1(1.6%)	0(0%)	0(0%)
Special aids and equipment	48(2.3%)	7(1.3%)	8(1.5%)	1(1.1%)	1(1.1%)	16(5.1%)	14(4.7%)	1(1.6%)	0(0%)	0(0%)	0(0%)
Informal care	72(3.4%)	11(2.1%)	12(2.3%)	0(0%)	1(1.1%)	26(8.4%)	10(3.3%)	1(1.6%)	3(4.7%)	7(11.3%)	1(1.6%)
Living-in maids [‡]	-	-	-	-	-	-	-	1(1.6%)	3(4.7%)	7(11.3%)	2(3.3%)
Subtotal (non-medical cost)	304(14.5%)	77(14.8)%	97(18.2%)	6(6.4%)	7(7.4%)	54(17.4%)	46(15.4%)	2(3.1%)	5(7.8%)	8(12.9%)	2(3.3%)
Productivity cost	225(10.7%)	50(9.6%)	46(8.7%)	14(14.9%)	10(10.5%)	27(8.7%)	23(7.7%)	17(25.6%)	13(20.3%)	14(22.6%)	11(18.0%)
Total cost (exc. productivity cost)	319(15.2%)	80(15.3%)	97(18.2%)	6(6.4%)	7(7.4%)	61(19.6%)	48(16.1%)	2(3.1%)	5(7.8%)	10(16.1%)	3(4.9%)
6 Total cost	512(24.3%)	124(23.8%)	136(25.6%)	20(21.3%)	16(16.8%)	80(25.7%)	68(22.7%)	17(26.6%)	16(25.0%)	22(35.5%)	13(21.3%)

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[§]only applicable to UK, Singapore and Malaysia patients; [†]only applicable to Singapore and Malaysia patients

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Resource use items with missing data	Predictor of missingness
Stroke-related rehospitalisation	Age (p=0.001)
Rehabilitation hospital admission	Age (p=0.009), NIHSCORE (p=0.037)
Outpatient rehabilitation program	Age (p=-0.003)
Rehabilitation service provided at home/nursing facility	Age (p=0.014),
Community services used prior to stroke	NIHSCORE (p=0.001)
Community services used at 3 months	Age (p=0.003)
Community services used at 12 months	NIHSCORE (p=0.008)
Aids or special equipment uses at 3 months	Age (p=0.012)
Aids or special equipment uses at 12 months	Age (p=0.035), NIHSCORE (p=0.013)
Private physiotherapy uses at 3 months	Age (p<0.0001)
Private physiotherapy uses at 12 months	Age (p=0.006), NIHSCORE (p=0.034)
Respite care use at 3 months	Age (p<0.0001)
Respite care use at 12 months	Age (p=0.017), NIHSCORE (P=0.018)
Informal care use at 3 months	Age (p=0.003)
Informal care use at 12 months	Age (p<0.0001)

If any of the other variables were able to predict the missingness of a given variable representing resource use, the MAR assumption was deemed to be held true. More specifically, multiple imputations were used to replace the missing values (missing mRS, AQoL-4D data or cost categories) with plausible estimates, and generated 30 datasets. Results were provided as pooled estimates of these sets. Identical analyses were carried out to estimate the incremental costs and benefits between groups on the basis of imputed data following the methods outlined in the statistical analysis section above. As the probability of all the resource use items being missing could be predicted by one or more of the other variables, it is likely that the Missing-at-Random (MAR) assumption could be held true. (https://www.ssc.wisc.edu/sscc/pubs/stata_mi_decide.htm).

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Supplementary document 5. Outcomes

Table I. Results of mRS score at 3 and 12 months follow-up

Modified Rankin	UC group		VEM group)
Scale Score	n=1050		n=1054	
	3M	12M	3M	12M
0	96	132	90	137
1	204	231	200	219
2	225	175	190	166
3	218	199	238	186
4	127	95	140	113
5	103	83	92	59
6	72	118	88	139
Total	1045	1033	1038	1019
Missing data	5	17	16	35

Number of patients falling into each category

Since there was no significant intervention effect together with no accepted willingness-to- pay (WTP) per unit increase in probability of achieving a better mRS outcome, further estimation of the ICER was considered not meaningful (i.e. no cost-effectiveness plane or cost-effectiveness acceptability curve could be generated).

Tuble II	Table II. Time and cost associated with derivering v Ewi and OC (mean, 757001)					
	VEM		UC		Between group difference	
	Total time	Cost (AUD)	Total time	Cost (AUD)	Total time	Cost (AUD)
	(min)		(min)		(min)	
Physiotherapist	243	\$117	95	\$48	147	\$69
	(232, 254)	(\$111, \$123)	(90, 101)	(\$45, \$51)	$(135, 159)^*$	(\$63, \$75)*
Nurse [†]	494	\$225	439	\$202	55	\$23
	(456, 532)	(\$207, \$244)	(404, 474)	(\$185, \$219)	$(4, 106)^*$	(-\$2, \$48)
Total cost	-	\$342	-	\$250	-	\$92
		(\$320, \$364)		(\$231, \$269)		(\$63, \$121)*

Table II. Time and cost associated with delivering VEM and UC (mean, 95%CI)

VEM: very early mobilisation; UC: usual care; CI: confidence interval

*p<0.0001 (adjusted for age, baseline NIHSS and mRS); [†] nurse's time devoted to delivery of VEM/UC was not recorded in the process of data collection, so the physiotherapist time was used as a proxy

Because VEM and UC were supplied by the same group of physiotherapists and nurses, the key difference was that a patient randomised to VEM received early rehabilitation within 24 hours of stroke onset and more out-of-bed mobilisation sessions of early mobilisation.

The total health practitioner (physiotherapist and nurses) time devoted to the delivery of the VEM and UC differed significantly, with the VEM group receiving substantially longer mean service time from both the physiotherapist (VEM: 243 mins, 95%CI: 232 to 254 vs UC: 95 mins, 95%CI: 90 to 101, p<0.0001) and nurse (VEM: 494 mins, 95%CI: 456 to 532 vs UC: 439 mins, 95%CI: 404 to 474, p<0.0001). The resultant difference in costs between groups was significant (\$92, 95%CI: \$63 to \$121, p<0.0001).

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Supplementary document 6. Sensitivity analyses

Generally, the difference in QALY gains between VEM and UC groups were fairly consistent across different methods.

Table I. Between-group differences based on the Generalised Linear Model_base case analysis vs. multiple imputation analysis

	ITT (not imputed)			ITT (imputed)		
	mRS score	QALYs	Cost (AUD)	mRS	QALYs	Cost (AUD)
Health Sector Perspec	ctive	<u></u>				
Total medical costs	0.030	-0.013	\$1082	0.042	-0.019	\$940
	(-0.022, 0.082)	(-0.041, 0.016)	(-\$2399, \$4563)	(-0.008, 0.092)	(-0.046, 0.007)	(-\$2584, \$4465)
Societal Perspective	I		90	l	1	I
Total cost (excl.	0.030	-0.013	-\$6	0.042	-0.019	\$1704
productivity cost)	(-0.022, 0.082)	(-0.041, 0.016)	(-\$5703, \$5690)	(-0.008, 0.092)	(-0.046, 0.007)	(-\$5423, \$8832)
Total cost (incl. productivity cost)	0.030	-0.013	\$102	0.042	-0.019	\$1413
	(-0.022, 0.082)	(-0.041, 0.016)	(-\$6945, \$7149)	(-0.008, 0.092)	(-0.046, 0.007)	(-\$5940, \$8766)
TT: intention to treatment; the p-value was >0.05 for		-		6	00	1.

	Adding country dumn	Adding country dummies			
	mRS	QALYs	Cost		
Total medical costs	0.031(-0.021, 0.083)	-0.013(-0.042, 0.015)	\$704 (-\$1968, \$3376)		
Total cost (excl. productivity cost)	0.031(-0.021, 0.083)	-0.013(-0.042, 0.015)	-\$335 (-\$4953, \$4283)		
Total cost (incl. productivity cost)	0.031(-0.021, 0.083)	-0.013(-0.042, 0.015)	-\$238 (-\$6012, \$5537)		

Table II. Between-group differences based on the Generalised Linear Model

mRS: modified Rankin Scale; QALYs: Quality-adjusted Life Years

*the p-value was >0.05 for the between-group difference in mRS score, QALYs and cost

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Table III. Cost-utility analysis based on multiple imputation analysis

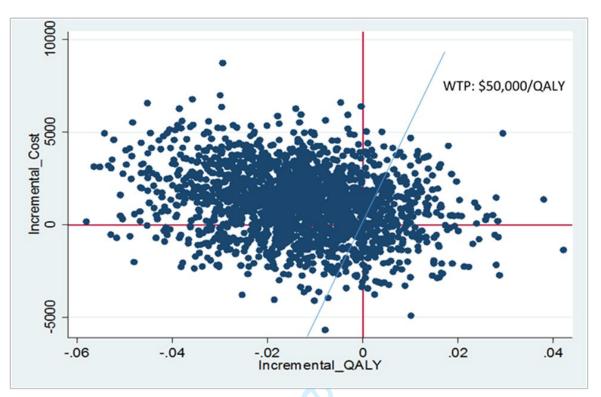
	Efficacy (QALYs)	Cost (AUD)	Probability of being cost-effective
Health Sector Perspect	ve		
Total medical costs	-0.019	\$940	25%
	(-0.044, 0.005)	(-\$4622, \$4682)	
Societal Perspective			
Total cost (excl.	-0.019	\$1704	20%
productivity cost)	(-0.044, 0.005)	(-\$3817, \$7226)	
Total cost (incl.	-0.019	\$1413	23%
productivity cost)	(-0.044, 0.005)	(-\$4044, \$6871)	

QALYs: Quality-adjusted Life Years; AUD: Australian dollar.

*the p-value was >0.05 for the between-group difference in QALYs and cost

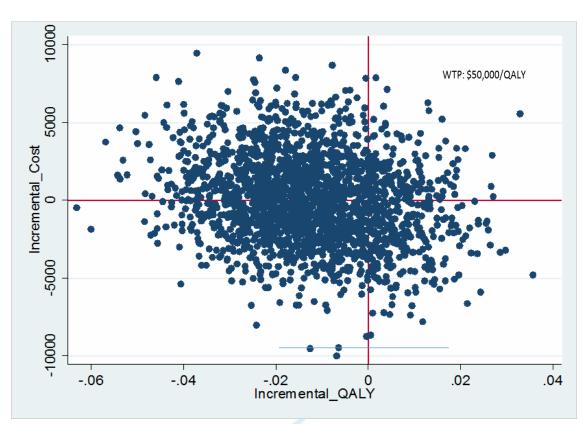
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Supplementary document 7: Figures



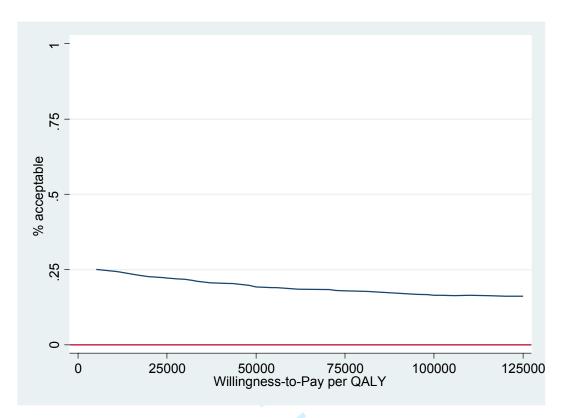
*Probability of VEM being cost-effective is 19%; WTP: willingness-to-pay; QALY: quality adjusted life year

Figure I Cost-effectiveness plane_health sector perspective



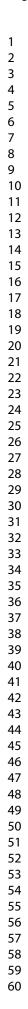
*Probability of VEM being cost-effective is 42%; WTP: willingness-to-pay; QALY: quality-adjusted life year

Figure II Cost-effectiveness plane_ societal perspective (excl. productivity cost)



Note: The probability of VEM being cost-effective decreases with the increasing WTP/QALY threshold because the VEM is associated with less costs

Figure III Cost-effectiveness acceptability curve for medical cost



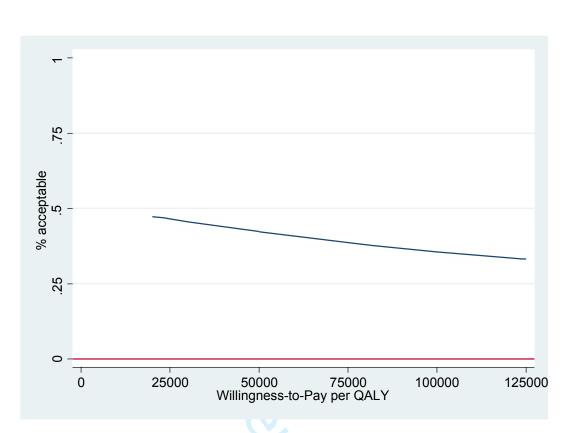


Figure IV Cost-effectiveness acceptability curve for total cost excluding productivity cost

Note: The probability of VEM being cost-effective decreases with the increasing WTP/QALY threshold because the VEM is associated with less costs

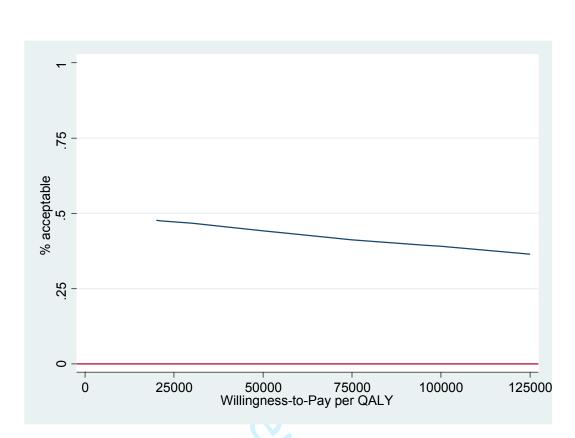


Figure V Cost-effectiveness acceptability curve for total cost including productivity cost

Note: The probability of VEM being cost-effective decreases with the increasing WTP/QALY threshold because the VEM is associated with less costs

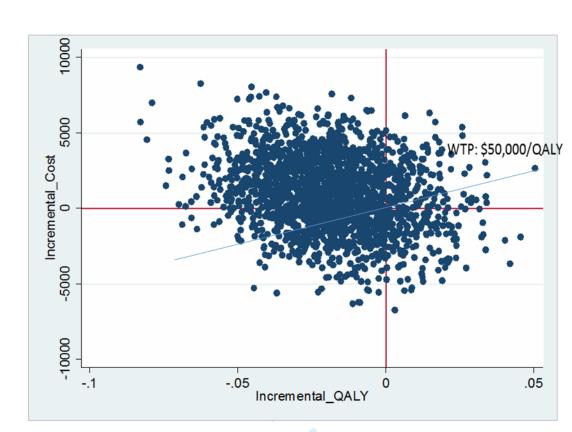


Figure VI Cost-effectiveness plane_health sector perspective (multiple imputation analysis)

WTP: willingness-to-pay; QALY: quality-adjusted life year

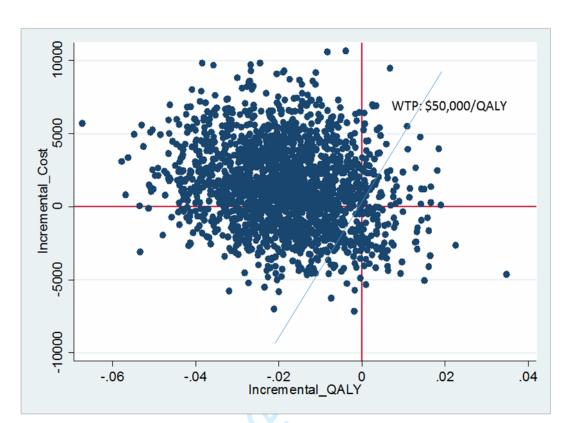
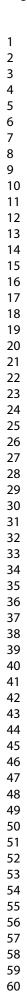
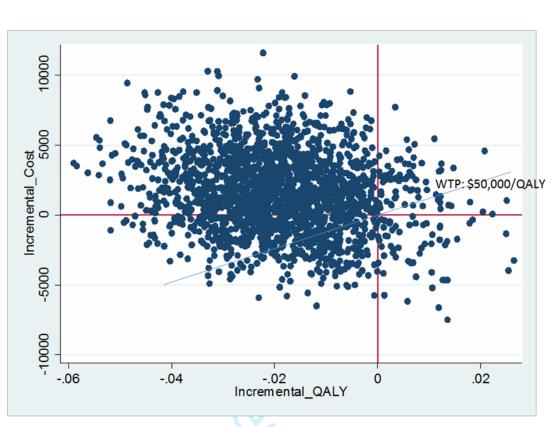


Figure VII Cost-effectiveness plane_ societal perspective including productivity cost (multiple imputation analysis)

WTP: willingness-to-pay; QALY: quality-adjusted life year







WTP: willingness-to-pay; QALY: quality-adjusted life year

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1. Claesson L, Gosman-Hedstrom G, Johannesson M, Fagerberg B, Blomstrand C. Resource utilization and costs of stroke unit care integrated in a care continuum: A 1-year controlled, prospective, randomized study in elderly patients: the Goteborg 70+ Stroke Study. Stroke 2000;31(11):2569-77.

2. 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(2):390-6.

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Section/item Item No Record		ommendation		
Title and abstract				
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	4-5	
Introduction				
Background and objectives	3	Provide an explicit statement of the broader context for the study.	7	
		Present the study question and its relevance for health policy or practice decisions.	8	
Methods				
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	12	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	9	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	9	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	8	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	11	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	11	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	8-9	
Measurement of effectiveness	11a	Single study-based estimates: Describe fully the design features of the single effectiveness stud and why the single study was a sufficient source of clinical effectiveness data.	^{ly} 12	
	11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.		
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	9	
Estimating resources and costs	13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	9-1	
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.		
Currency, price date, and 14 Report the dates of the estimated resource quantities and estimated unit costs to the year of reported costs if nec		Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	10	
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providinga figure to show model structure is strongly recommended.		
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.		
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	11-	
Results				
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	N/	
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	14	
Characterising uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	14	
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.		
haracterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained byvariationsbetweensubgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.		

generalisability, and current For peer reviewing single shell by deneralisability of the conclusions reached. Discuss

Conflicts of interest 24 Describe any potential for conflict of interest of study contributors in accordance with j	Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conc and reporting of the analysis. Describe other non-monetary sources of support.
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Primary Subject Heading :	Neurology
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Stroke < NEUROLOGY, rehabilitation, AVERT, economic evaluation, cost- effectiveness analysis, cost-utility analysis



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Title Page

Title

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

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Word count

Abstract

Objectives While Very Early Mobilisation (VEM) intervention for stroke patients was shown not to be effective at 3 months, 12 -month clinical and economic 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 (0-2 vs 3-6) 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 (ITT) basis and 95% confidence intervals (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 AUD\$102, 95%CI:

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 -\$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.

Trial registration Australian New Zealand ClinicalTrials Registry, number ACTRN12606000185561.

Strength and limitations

- 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.

Introduction

Stroke is one of the biggest killers and a leading cause of disability worldwide.¹² 65% 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.⁴⁵ 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 2,104 patients enrolled from Australia, New Zealand, United Kingdom, Singapore and Malaysia.¹⁰ The evidence from this trial indicated that at three 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 0-2 compared to that in the usual care (UC) group.¹⁰ In the research field of stroke, primary endpoint is usually assessed at month 3 after stroke¹¹⁻¹⁴, 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 (i.e. 12 months) comprehensive measurement of costs relating to stroke care (i.e. 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 (i.e., 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.

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This examination also benefits healthcare funders (i.e. 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 (UC), 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 (CHEERS) 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 (UC) 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-4D (AQoL-4D)¹⁷ were used as the effectiveness measures in the economic evaluation. The AQoL-4D instrument is a multi-

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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 0-2) and "poor" (mRS 3-6) based on patients outcomes at 12-month follow up.¹⁰ The difference in the probability of patients achieving a favourable mRS outcome (mRS 0-2) 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 (i.e. most of patients were not able to respond to these questions at baseline), the mRS score at baseline¹⁰ was used as a surrogate measure of patient utility during the acute phase. The detailed methods of this work are reported elsewhere¹⁹ 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

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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 (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 health care 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 program (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 United Kingdom, Singapore and Malaysia only.

Non-healthcare resource use

The quantity of resources used was recorded for the following non-heath care 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),

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changes to employment (employment status and weekly hours of working both prior to and post-stroke).

Resource use reported at 3 (i.e. resources used between 0 and 3 months) and 12 (i.e. 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 (Supplementary document 3). Unit costs from a country with a similar economic status and healthcare system were used where local countryspecific unit costs were unavailable.

All costs are expressed in Australian dollars (AUD) for the 2015 reference year value and can be converted to United States dollar (USD) using the Purchasing Power Parity rate 1 USD=1.463 AUD²⁰ (December 2015). The currency of other countries was converted to AUD using the corresponding exchange rate. The country-specific Consumer Price Index (CPI) 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 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 interquartile ranges (IQRs) due the skewness of the raw data. Means and standard deviations (SDs) were also reported. Base case analysis of the economic evaluation was performed based on the Intention-to-Treat (ITT) population²¹ 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 mRS¹⁵ 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 (i.e. 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% confidence intervals (CIs) around mean difference in costs and effects for cost-effectiveness analysis. To

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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 (i.e. excluding non-healthcare costs and productivity cost). The differences between groups in terms of costs and benefits (i.e. 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 14.0 statistical package (StataCorp. 2015. Release 14. StataCorp LP.) e e

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 missing²⁶ (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, 2,104 patients (VEM 1,054; UC 1,050) were recruited across 58 sites from Australia (N=1,054, 24 sites), New Zealand (N=189, 1 site), United Kingdom (N=610, 29 sites), Singapore (N=128, 1 site) and Malaysia (N=123, 1 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 randomisation¹⁰. Baseline characteristics were similar between the two treatment groups¹⁰.

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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 Supplementary document 5: Table I.

Resource use and costs

Page 15 of 82

BMJ Open

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 patients experienced rehabilitation hospital admission and more than a quarter of 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 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, whilst 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 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: \$7,238 to \$63,835) than in the VEM group (\$19,271, IQR: \$6,294 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 \$4,561) than in the VEM group (\$358, IQR: \$0 to \$3,334). 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: \$7,257 to \$63,824) compared to the VEM group (\$25,675, IQR: \$6,766 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 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, \$4563) for the total medical cost (Supplementary document 6: Table I) and \$3 (95%CI: -\$5, \$12) for the productivity cost per person at 12 months; the between-group difference in the total non-health care cost was -\$1300 (95%CI: -\$3361, \$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 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 Supplementary document 7: Figures I to V.

Sensitivity analyses

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Inclusion of a country dummy variable in the analysis produced similar results to the base case (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. (Supplementary document 6: Table III and 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% confidence intervals mostly Discussion overlapping (Table 4).

The 12 months within-trial cost-effectiveness analysis showed that VEM was unlikely to be cost-effective than 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 one year study period were comparable from a health sector perspective. The findings from this economic evaluation is also underpinning an adapted version of trial underway to investigate the effectiveness of optimal rehabilitation in patients with mild to moderate stroke (i.e. 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 to 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 health care 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% confidence intervals 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

BMJ Open

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 tended to receive rehabilitation services in an outpatient (i.e. up to 52% of patients received the outpatients rehabilitation program services) rather than inpatient (i.e. only up to 2% patients were admitted to rehabilitation hospital) setting; and patients were less likely to utilise ambulant transfer and apply home modifications, as compared to 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 program. 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 health-related quality of life (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 Whilst 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 to approximate the difference in QALY gains over one 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.

Whilst 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

Page 21 of 82

BMJ Open

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 (i.e. base case of pooling all countries) and disaggregated (i.e. 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. Firstly, 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 (i.e. comparable results in costs and benefits between treatment groups). Secondly, unit costs originating from individual countries were assigned to value resource use. The differences in health care 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 to 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 one-year, however given its poorer outcomes at 3 months, VEM cannot be recommended to clinicians, patients or policymakers.

Acknowledgements

Page 23 of 82

BMJ Open

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Authors' Contribution

Conception/design, revising and final approval: LG, LS, LC, OW, MM, JC, FE, JB, HD, MMoodie. Methodology: LG, MM, LS, LC, MMoodie, OW. Data analysis: LG, LS, MM, LC. Drafting: LG, MMoodie.

Competing Interests Statement

All authors confirm that there is nothing to declare.

Data Availability Statement

No additional data available

to peer teries only

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Tables

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

	AU (N=1054)		NZ (N=189)		UK (N=610))	SG (N=128)	1	MA (N=123)		All Countri	es
	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 rehospita	lisation											
% 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 rehabilitat	ion hospital [‡]			8								
% 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 rehabilitatio	n program				4 01							
% 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											
0/ 0 / 1	N/A	N/A	N/A	N/A	19	15	-	2	20	25	-	-
% of pts using	1			N/A	8(2-12)	8(4-15)		2(2-2)	8(3-10)	16(8-31)	-	-

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% 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(
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(
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-
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(2
Community services used of	over 12 months	after stroke		104								
% of pts using	30	35	32	28	31	28	-	3	6	-	27	28
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(1
Home modifications under	taken over 12 n	nonths										
% 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-
Aids and appliances used o	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-
Working prior to stroke	1		1			1	1					
% 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(2
Proportion working at 12 r	nonths	1	1	1	1	<u>I</u>	1	1		1	1	1
% 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(1

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% of patients	-	-	-	-	-	-	19	16	5	10	-	-
No. of maids	-	-	-	-	-	-	1(1-1)	1(1-1)	1(1-1)	1(1-1)	-	-
Patients from Singap	oore and Malaysia w	ho had a maid at	12 months follow	ing stroke	_	-	23	22	5	7		-
1					_		1(1-1)	1(1-1)	1(1-1)	1(1-1)		
No of moids					-	-		1 1(1-1)	1 1(1-1)	1 1(1-1)	-	-
	-	-										
	care at 12 months		,									
No. of maids Receipt of informal of % of patients	care at 12 months	39	37	33	41	40	30	36	42	44	37	39

ITT: Intention-to-treat; AU: Australia; NZ: New Zealand; UK: United Kingdom; SG: Singapore; MA: Malaysia; LOS: length of stay; pts: patients; No.: number; hrs: hours; mod: modification; -: no such resource use; all numbers were expressed as median and interquartile range (IQR); ¹includes any admissions to rehabilitation hospital following the indexed stroke;

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

2 Table 2 C		i esources used	u over 12 mont				~~~~					
В	AU (N=1054)		NZ (N=189)		UK (N=610)		SG (N=128)		MA (N=123)		All Countries	
4	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC	VEM	UC
5					He	ealth care cost (Al	UD)					
Acute hospi												
Median,	\$6294	\$6294	\$6104	\$6104	\$2763	\$3109	\$1493	\$1493	\$1363	\$1363	\$6294	\$6294
IQR	(6294, 9553)	(6294, 9553)	(4370, 6104)	(4370, 6104)	(1382, 6563)	(1727, 6563)	(1493, 1809)	(1493, 1493)	(1363, 1572)	(1363, 1572)	(2279, 9535)	(2418, 9553)
⁸ Mean, SD	\$9883 (9484)	\$10010(10508)	\$6635 (3244)	\$6549 (3555)	\$5714(7876)	\$5885 (7101)	\$1721 (547)	\$1676 (432)	\$1482 (212)	\$1472 (200)	\$7369 (8469)	\$7521 (8916)
9 Stroke-relate	ed rehospitalisatio	n										
1 0 Median,	\$0	\$0	\$0	\$0	\$227	\$227	\$111	\$111	\$68	\$68	\$111	\$111
1 1 QR	(0, 3850)	(0, 3850)	(0, 325)	(0, 2243)	(227, 1401)	(227, 227)	(111, 111)	(111, 111)	(68, 68)	(68, 68)	(0, 1401)	(0, 610)
	\$6030 (17114)	\$6473 (21590)	\$651 (1371)	\$1507 (2828)	\$4524 (13968)	\$3494(11349)	\$2756 (7565)	\$1679 (3465)	\$714 (1608)	\$603 (1479)	\$4610 (14518)	\$4551 (16707)
Admission to rehab hospital												
Median,	\$13134	\$13134	\$11262	\$11262	\$0	\$0	\$0	\$1298	\$0	\$0	\$0	\$1136
ĮĮQR	(0, 36371)	(0, 38391)	(0, 30983)	(0, 26486)	(0, 29788)	(0, 29788)	(0, 2921)	(0, 3570)	(0, 0)	(0, 0)	(0, 29788)	(0, 29788)
Mean, SD	\$25667 (38892)	\$26648(38315)	\$16871(18536)	\$15573(16848)	\$12539(19682)	\$11758 (18390)	\$1815 (2759)	\$2798 (5082)	\$0(0)	\$43 (234)	\$18197 (31241)	\$18458 (30811)
Outpatient rehab program												
18 _{Median}	\$0 (0, 2451)	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$33	\$0	\$0	\$0
1 9 QR		(0, 1913)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 36)	(0, 265)	(0, 249)	(0, 478)	(0, 239)
2 M ean, 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 provi	Rehab provided at home/nursing facility											
→Median,	\$0	\$0	\$1168	\$212	\$922	\$0	\$0	\$0	\$0	\$0	\$0	\$0
j jqr	(0, 717)	(0, 956)	(0, 4299)	(0, 3821)	(0, 11064)	(0, 11064)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 1913)	(0, 1913)
Mean, SD	\$1382 (4069)	\$1551 (4252)	\$3171 (4960)	\$3111 (5754)	\$12085 (28516)	\$11051 (26723)	\$93 (570)	\$5 (42)	\$97 (719)	\$7 (53)	\$4447 (16294)	\$4180 (15203)
	llied health visit								•			
²⁵ Median,	N/A	N/A	N/A	N/A	\$0	\$0	\$0	\$0	\$0	\$0	N/A	N/A
2 6 QR					(0,0)	(0,0)	(0,0)	(0,179)	(0,0)	(0,0)		
	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
28Ambulance	transfers	•							•			
>% Iedian,	\$508	\$508	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
BOR	(0, 1015)	(0, 1015)	(0, 646)	(0, 646)	(0, 1150)	(0, 575)	(0, 265)	(0, 265)	(0, 0)	(0, 0)	(0, 611)	(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 phys	siotherapy		•							•		
Median,	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
^B ³ QR	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)
	\$70 (375)	\$124 (797)	\$245 (1308)	\$4 (36)	\$128 (780)	\$174 (2102)	\$238 (1096)	\$333 (1938)	\$4 (19)	\$1 (9)	\$109 (693)	\$132 (1336)
B Respite care								u	•			
B6Median,	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
B [†] QR	(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	\$48 (355)	\$20 (182)	\$7 (46)	\$2 (15)	\$9 (95)	\$58 (686)	\$0 (0)	\$0 (0)	\$0 (0)	\$1 (8)	\$27 (259)	\$27 (386)
39 39	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
40	1	1				31		1				·]
41						21						

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Page 32 of	82
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1												
5 Sub-total												
Median	\$29278	\$29441	\$20621	\$23722	\$18896	\$20843	\$4525	\$4687	\$1713	\$1746	\$19271	\$20411
(IQR)	(8218, 63622)	(9811, 62489)	(6068, 46909)	(7316, 40162)	(4030, 48999)	(3682, 47908)	(1604, 8668)	(2724, 10926)	(1431, 2532)	(1431, 2348)	(6294, 52637)	(7238, 63835)
d Mean	\$45620 (51458)	\$47453(53715)	\$28898 (25011)	\$27986(22676)	\$34863 (42509)	\$32842 (39517)	\$7681 (8828)	\$8358 (8787)	\$2385(1587)	\$2269(1574)	\$36351 (45620)	\$36604 (46309)
5 (SD)	. ,	, , , , , , , , , , , , , , , , , , ,				, í						
б		`			N	on-health care cos	st	·				
7 Accommoda	ation moves											
8 Median,	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
9 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)
1 Mean, SD	\$2089 (8518)	\$2482 (9323)	\$5975 (19614)	\$9135 (26918)	\$2901 (12958)	\$2532 (11125)	\$72 (578)	\$108 (507)	\$425 (1893)	\$104 (501)	\$2460 (11036)	\$2821 (12212)
Community												
Median,	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
¹ f QR	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 430)	(0, 174)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)
Mean, SD	\$570 (2681)	\$1091 (8556)	\$238 (950)	\$1022 (4113)	\$22275(294988)	\$10738 (57306)	\$0 (0)	\$244 (1902)	\$21 (110)	\$0 (0)	\$6870 (160318)	\$3786 (31893)
	Home modifications											
15Median,	\$0 (0, 0)	\$0 (0)	\$0 (0)	\$0	\$0	\$0 (0)	\$0	\$0	\$0	\$0	\$0	\$0 (0, 0)
160R	(0, 0)	(0,0)	(0,0)	(0,0)	(0, 0)	(0,0)	(0, 0)	(0, 0)	(0,0)	(0,0)	(0, 0)	(0, 0)
1 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)
10-	8 pecial aids and equipment											
1 Median,	\$0 (0, 222)	\$0 (0, 218)	\$70	\$103	\$27	\$0	\$0 (0, 240)	\$0	\$15	\$36	\$0	\$0 (0, 41.4)
1QR	(0, 332)	(0, 318)	(0, 549)	(0, 357)	(0, 786)	(0, 846)	(0, 240)	(0, 210)	(0, 218)	(0, 186)	(0, 414)	(0, 414)
Mean, SD	\$1986 (7668)	\$2787 (10396)	\$2198 (7993)	\$1798 (7229)	\$1354(3649)	\$1720 (5083)	\$1117 (5843)	\$1079 (5483)	\$153 (252)	\$193 (658)	\$1660 (6426)	\$2141 (8328)
² Informal car		¢40	φ14	\$ 0	\$2 0	\$20	AAAAAAAAAAAAA				\$24	\$24
2 2 Median, 2 3 QR	\$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)
24Mean, SD	(0, 303) \$414 (747)	(0, 433) \$405 (758)	\$236 (536)	\$152 (311)	\$324 (516)	\$324 (645)	(0, 114) \$144 (285)	\$159 (300)	\$43 (57)	\$27 (34)	\$335 (633)	\$322 (660)
24vicali, 3D 25 Jiving-in m		\$403 (738)	\$250 (550)	\$152 (511)	\$524 (510)	\$324 (043)	\$144 (283)	\$139 (300)	\$45 (57)	\$27 (34)	\$333 (033)	\$322 (000)
	N/A	N/A	N/A	N/A	N/A	N/A	\$0	\$0	\$0	\$0	N/A	N/A
2 ∂ ∕ledian, 1 JQR	IN/A	IN/A	IN/A	N/A	IN/A	IN/A	\$0 (0,0)	(0,0)	(0,0)	(0,0)	IN/A	IN/A
27 Mean SD	N/A	N/A	N/A	N/A	N/A	N/A	\$3154 (8146)	\$4268(11338)	\$179 (930)	\$83 (504)	N/A	N/A
Mean, SD	10/11	10/11	14/14	11/21	10/21	14/24	\$5151 (0110)	\$1200(11550)	\$175 (550)	\$05 (50 l)	10/21	10/11
29 Median	\$459	\$673	\$381	\$638	\$758	\$471	\$25	\$194	\$74	\$57	\$358	\$438
B0 (IGR)	(0, 3334)	(0, 5209)	(0, 3674)	(103, 14551)	(0, 5097)	(0, 4725)	(0, 1293)	(0, 6999)	(0, 285)	(0, 318)	(0, 3334)	(0, 4561)
B1 Mean	\$6104 (15582)	\$6985 (17554)	\$7752 (17751)	\$11981(27676)	\$27892(306917)	\$15345(61750)	\$4802 (10366)	\$6177 (13942)	\$861 (2272)	\$484 (1113)	\$12043 (164026)	\$9360 (36504)
32 (SD)												
33						Productivity cost						
B ₄ ∕ledian,	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
J QR	(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	\$33203	\$35143	\$29934	\$32216	\$25374	\$30537	\$6960	\$8810	\$2016	\$1816	\$25675	\$27042
^{B8} (IGR)	(9687, 71902)	(12696, 74070)	(8528, 65781)	(15710, 68292)	(4712, 64285)	(4629, 67012)	(1674, 26187)	(3426, 19493)	(1561, 3994)	(1537, 3301)		(7257, 63824)
BMean (SD)	\$52456(57264)	\$56408(62536)	\$40381(37242)	\$43901(43170)	\$65530(332044)	\$49627(78644)	\$15036(16921)	\$16340(19650)	\$3609(3985)	\$2938(2350)	\$50448(184931)	\$47627(64249)
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1 Where only a low proportion (i.e. 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
	ation hospital on discharge from hospital as the rehabilitation service immediately following the acute stroke hospitalisation is not
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Table 3. Baseline cost-utility analysis_ITT

	QALYs	Per capita mean cost (AUD)							
Health care perspective									
Total medical costs	-0.013	\$1082							
	(-0.041, 0.016)	(-\$2520 <i>,</i> \$4685)							
Societal perspective	Societal perspective								
Total medical and non-medical	-0.013	-\$6							
costs (excl. productivity cost)	(-0.041, 0.016)	(-\$5476 <i>,</i> \$5463)							
Total medical and non-medical	-0.013	\$102							
costs (incl. productivity cost)	(-0.041, 0.016)	(-\$6907, \$7111)							
	(0.0 11, 0.010)	(,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,							

ITT: Intention-to-treat; QALYs: Quality-adjusted Life Years; AUD: Australian dollar; excl: excluding; incl: including

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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	\$948	-\$2836	\$2937	-\$81	\$137
costs	(-\$4352, \$6248)	(-\$8403, \$2730)	(-\$3635, \$9509)	(-\$2789, \$2627)	(-\$324, \$599)
Total non-	-\$1318	-\$3959	-\$1387	-\$3164	\$200
medical costs	(-\$3038, \$403)	(-\$7769, -\$150)	(-\$7331, \$4557)	(-\$6834, \$505)	(-\$232, \$631)
Total cost	-\$1735	-\$8981	\$1870	-\$2636	\$479
(incl.	(-\$8482, 5013)	(-\$18380, \$418)	(-\$13955, \$17694)	(-\$9233, \$3961)	(-\$487, \$1446)
productivity)					
Total cost	-\$1185	-\$7610	\$2552	-\$1534	\$416
(excl.	(-\$7184, \$4815)	(-\$15302, \$82)	(-\$11377, \$16481)	(-\$6464, \$3395)	(-\$364, \$1196)
productivity)					
QALY gains	-0.036	0.086	-0.010	0.008	0.003
~ 0	(-0.076, 0.003)	(-0.003, 0.176)	(-0.064, 0.044)	(-0.106, 0.123)	(-0.126, 0.132)

AU: Australia; NZ: New Zealand; UK: United Kingdom; SG: Singapore; MA: Malaysia; QALY: Quality-adjusted Life Year.

*the p-value was >0.05 for the between-group difference in QALYs and cost

JSG (-0.003, 0... J Kingdom; SG; (up difference in QAL

Supplementary document 1: Mapping baseline mRS score to utility of AQoL-4D

Methods

Generalized additive model (GAM) with spline smother was used to map AQoL from premorbid mRS, stroke severity, and/ or age group. The performance of the models was evaluated using mean absolute, mean squared errors (MAE and MSE) and R2. 10-fold cross- validation was implemented for model validation. The mapped baseline utility of AQoL-4D was used in the following models.

The analyses are structured as follows:

Model 1:

a) A complete case model with the utility value at 12 months as an output, group as an input, and pre- morbid mRS as a covariate;

b) A complete case model with the utility value at 12 months as an output, group as an input, and pre- morbid mRS + stroke severity as covariates;

c) A complete case model with the utility value at 12 months as an output, group as an input, and pre-morbid mRS + stroke severity + age group as covariates;

d) Sensitivity analyses for the unadjusted model using pattern-mixture models that confirm that there is no statistically significant difference between the groups for the plausible range of changes of a parameter that describes the departure from the assumed "missing-at-random" pattern.

Model 2:

a) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output and group as an input;

b) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output and group as an input + stroke severity as a covariate;

c) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output and group as an input + stroke severity and age group as covariates;

d) Sensitivity analyses for the unadjusted model using pattern-mixture models that confirm that there is no statistically significant difference between the groups for the plausible range of changes of a parameter that describes the departure from the assumed "missing-at-random" pattern.

Model 3:

a) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output, group as an input, and baseline mapped utility value as a covariate;

b) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output, group as an input, and baseline mapped utility value + stroke severity as covariates;

c) A complete case model with the difference between utility value at 12 months and baseline mapped utility value as an output, group as an input, and baseline mapped utility value + stroke severity + age group as covariates;

d) Sensitivity analyses for the unadjusted model using pattern-mixture models that confirm that there is no statistically significant difference between the groups for the plausible range of changes of a parameter that describes the departure from the assumed "missing-at-random" pattern.

Model 4:

a) A complete case model with the utility value at 12 months as an output, group as an input, and baseline mapped utility value as a covariate;

b) A complete case model with the utility value at 12 months as an output, group as an input, and baseline mapped utility value + stroke severity as covariates;

c) A complete case model with the utility value at 12 months as an output, group as an input, and baseline mapped utility value + stroke severity + age group as covariates;

d) Sensitivity analyses for the unadjusted model using pattern-mixture models that confirm that there is no statistically significant difference between the groups for the plausible range of changes of a parameter that describes the departure from the assumed "missing-at-random" pattern.

Results

Table I. Difference in utility values between treatment groups by different models

	a	b	c	d	
				1	2
Model 1	-0.011	-0.015	-0.016	-0.026	0.006
	(-0.042, 0.020)	(-0.042, 0.011)	(-0.042,0.010)	(-0.062,	(-0.030,
				0.009)	0.041)
Model 2	-0.001	-0.007	-0.008	-0.007	0.005
	(-0.046, 0.044)	(-0.047, 0.034)	(-0.048, 0.031)	(-0.062,	(-0.050,
				0.048)	0.060)
Model 3 [*]	-0.008	-0.014	-0.015	-0.014	0.002
	(-0.043, 0.026)	(-0.043, 0.016)	(-0.043, 0.014)	(-0.052,	(-0.050,
				0.033)	0.045)
Model 4	-0.008	-0.014	-0.015	-0.026	0.006
	(-0.043, 0.026)	(-0.043, 0.016)	(-0.043, 0.014)	(-0.062,	(-0.030,
				0.010)	0.042)

*models 2 and 3 used the mapped baseline AQol utility to estimate the QALY gains over 12 month for each patient.

utility value to calculate the difference in QALYs between treatment groups (results from models 2 and 3) yielded similar results to the primary analysis (-0.013, 95%CI [-0.043, 0.018]), and the 95% confidence

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Supplementary document 2: Cost Case Report Form (CRF)

The Cost CRF was originally developed via pathway analysis during Phase II of AVERT to identify resource items associated with the trial11. Since the Phase II of AVERT trial was a national project and resource utilisation tools were tailored to the Australian setting, the form was further modified to accommodate international differences in the acute service delivery, rehabilitation and post-acute care. An extensive review of country-specific literature and consultation with international AVERT project team members based in each country were ie Cosi ... undertaken to tailor the Cost CRF tool to each participating country.

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Case Report Form - Cost

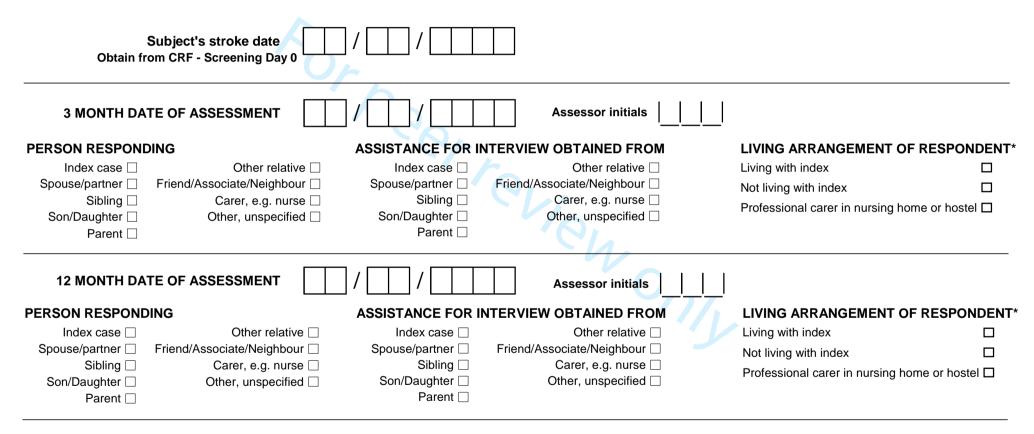


National Stroke PATIENT STUDY NUMBER Research Institute

PATIENT INITIALS

NOTE: this one form is to be completed AND faxed following BOTH the 3 and 12 month interviews. When CRF Cost complete at 3 months AND at 12 months, fax all pages 25-36 to the Data Fax.

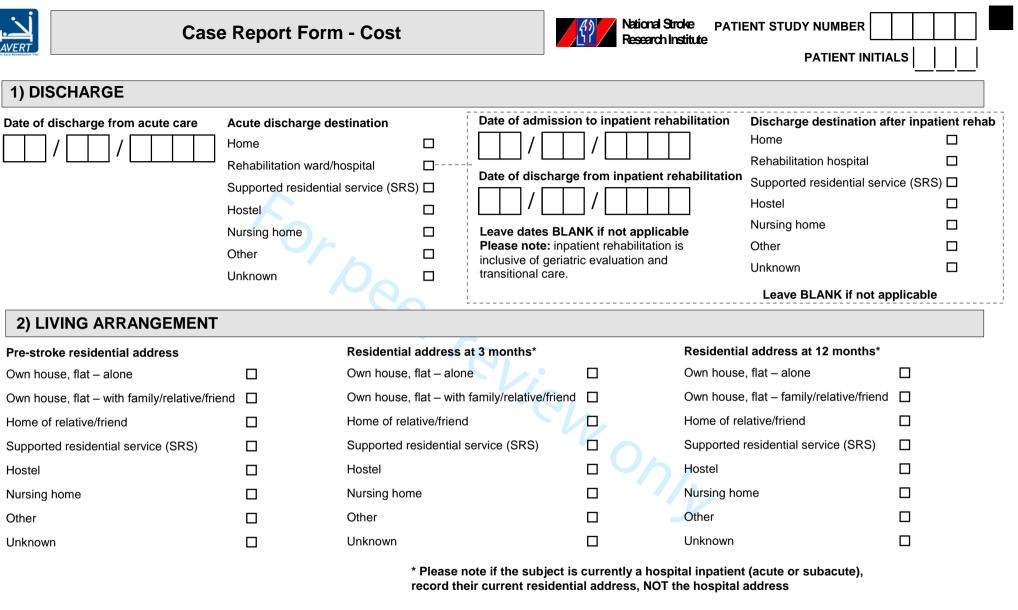
Instructions to the person responding: These questions are about health care provided as a consequence of the stroke which occurred on (give date of stroke) or as a result of any further stroke. I will be asking about health care such as visits to hospital, rehabilitation, therapy at home, equipment and work. To help us work out the cost of stroke to the community, and to you and your family, I will be asking about how often services were provided and their cost.



* Please note: this is the 'normal' living arrangement of the respondent with respect to the subject, even if the subject is currently in hospital

Page 41 of 82

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3) CHANGE IN LIVING ARRANGE	MENTS					
As a consequence of your stroke, have you ne	eeded to change your p	lace of residence?	3 months	Yes 🗌	No 🔲 🛛	Jnknown 🗖
If NO, proceed to question 4. * Please note: if subject has been a hospital	inpatient this is NOT a o	change of residence	3-12 months	Yes 🗌	No 🔲 🛛	Jnknown 🗖
DATE OF MOVE	LOCATION					
1) / / /	Home of relative/friend SRS Hostel Nursing home					
2) / /	Own home or unit Home of relative/friend SRS Hostel Nursing home					
3) / /	Hostel Nursing home					
4) / /	Home of relative/friend SRS Hostel					
4) AMBULANCE TRANSFERS: EN		ION-EMERGENCY				
As a consequence of your stroke, have you re If NO, please proceed to question 5	equired ambulance tran	sport after your acute admission to hospital?	* 3 months	s Yes 🗌	No 🗖	Unknown 🗖
			3-12 mor	ths Yes 🗌	No 🗖	Unknown 🗌
Count number of ambulance trips (recruit Count number of ambulance trips (fro		* Include post-acute transfers (eg - acute	e to rehab)			

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5) HOSPITALISATION OR EMERGENCY DEP	PARTMENT AT	TENDANCES			
5a) Have you been readmitted to hospital or attended the e or for any stroke related problems?	mergency departm		3 months Yes		
(ONLY include information for admissions and attendance stroke-related problems and CRF completion manual for fu		d problems (see below for summary list of	3-12 months Yes	No 🗖	Unknown 🗖
If NO, proceed to question 6					
5b) If YES, Start with the earliest admission or attendance. If p dates BLANK (complete dates at 12 month assessment)	atient NOT discharg	ged at 3 month assessment, leave discharge			If patient not discharged a
Admission or Attendance 1 - Hospital name	Hospital code	Date admitted	Date discharged		12 month assessment cross box.
Admission or Attendance 2 - Hospital name	Hospital code	Date admitted	Date discharged		
Admission or Attendance 3 - Hospital name	Hospital code	Date admitted	Date discharged		
Admission or Attendance 4 - Hospital name	Hospital code	Date admitted	Date discharged		
Admission or Attendance 5 - Hospital name	Hospital code	Date admitted	Date discharged		
Stroke related problems include: 1. Recurrent stroke, 2. TIA or 9. Fractures, 10. DVT, 11. Pulmonary Embolism, 12. Complication enema or other procedure to investigate GI haemorrhage, 16. Comprocedural management of of an atrial septal defect or patent for or cognitive impairment, 23. Constipation - investigation or treatment	ons of stroke treatmen erebral angiography, 1 ramen ovale, 20. Surg	t or stroke prevention, 13. Haemorrhage, 14. Nutritional 7. Carotid endarectomy, 18. Carotid (or other cerebral ve ical or electrophysiological procedure to treat AF, 21. Ina	problem, 15. Gastroscopy/col- essel) angioplasty and/or sten ability to manage at home, 22.	onoscopy/bar ting 19. Surge	ium ery or





National Stroke PATIENT STUDY NUMBER

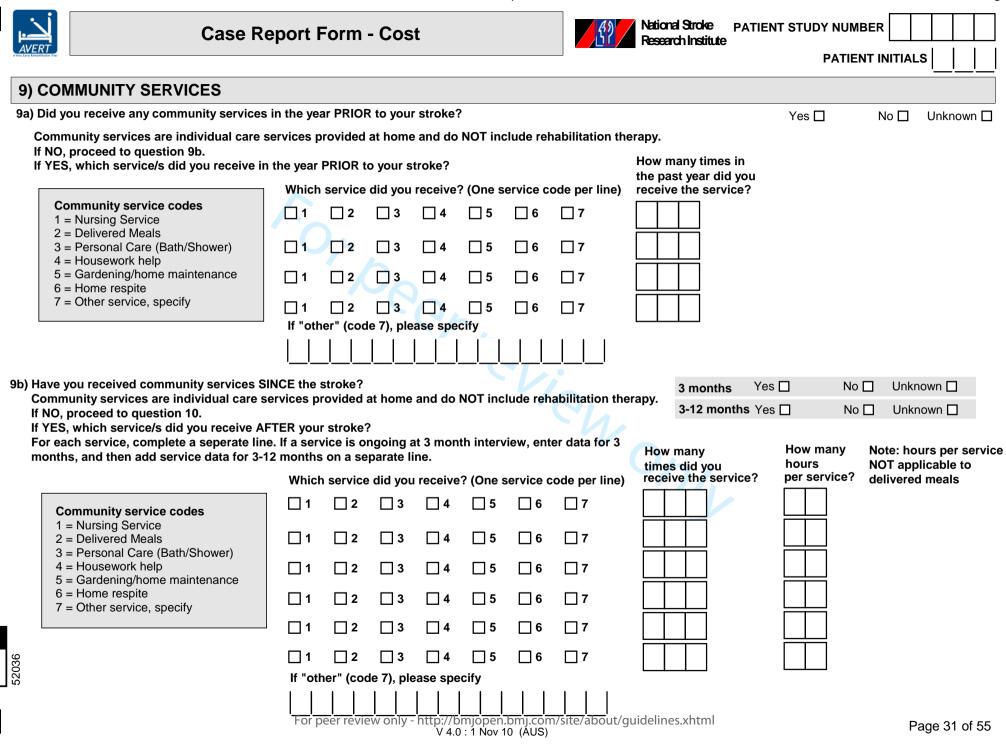
	Case Report F	orm - Cost	<u></u> 51	Research Institute	PA		;
6) INPATIENT F	REHABILITATION ADMISSI	ON					<u>''</u>
-	give date of stroke), were you adm		Hospital or other hospital	3 months	Yes 🗖	No 🔲 Un	known 🗖
where you received a evaluation' and 'transit	ehabilitation treatment? Please incl	ude admissions with the	care type 'rehabilitation', 'ge	riatric 3-12 months	Yes 🗖	No 🔲 🛛 Un	known 🗖
If NO, proceed to que If YES, complete inpa		scharge dates BLANK (c	omplete dates at 12 month a				lf patien discharg <u>12 mont</u>
Admission 1- I	Rehabilitation hospital name	Rehab hospit code	al Date admitted		Date dischar	qed	assessn
	0				/ / [cross bo
Admission 2-	Rehabilitation hospital name	Rehab hospit code	al Date admitted		Date dischar	ged	
					/ / [
Admission 3-	Rehabilitation hospital name	Rehab hospit	Date admitted		Date dischar	ged	
					/ 🗍 / [
7) OUTPATIEN	IT REHABILITATION PROG	BRAM					
	re you attending an outpatient reha		consequence of your stro	ke? 3 months	Yes 🗌	No 🗖	Unknown
An outpatient rehabi	apy, occupational therapy, speech itation program is any rehabilitation p or community facility.	therapy, etc rogram where the patien	attends a facility. The progr	ram can be 3-12 mor	ths Yes 🗌	No 🗖	Unknown
If NO, proceed to qu	lestion 8.						If pa
	patient rehabilitation details, starting f irged at 3 month assessment, leave d			(complete dates at 12 mo	nth assessment	Total	disc
·		Rehab facility				of DAYS	<u>12 m</u> asse
Admission 1 - O	itpatient rehabilitation name	code	Date admitted	Date dis	scharged		d _{cros}
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Admission 2 - O	utpatient rehabilitation name	Rehab facility code	Date admitted	Date dis	scharged		
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Admission 3 - Ou	tpatient rehabilitation name	Rehab facility code	Date admitted	Date dis	scharged		
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Page 45 of 82

44 45

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	Case Repo	ort Form - Cost	National Stroke PATIENT STUDY NUME Research Institute	
8) REHABIL	ITATION SERVICES PRO	VIDED AT HOME OR IN A NURSING HO	ME	
		o you at home or a nursing home siotherapy, occupational therapy, speech	3 months Yes No	
) sessions. If patient NOT dis	rehabilitation details, starting from	the first visit since your stroke. Count number of eave discharge dates and number of sessions BLANK	3-12 months Yes □ No □	Unknown
Time 1 - Rehabilitat	ion service name	Rehab service code Start date Image: Start date Image: Start date		al <u>12 month</u> mber of <u>3550005</u> SSIONS cross box.
7 3 5 5 6 7 7 7 7 7 7 7 7 7 7 7 7 7	ion service name	Rehab service code Start date Image: Image of the service code Image of the service code	Cease date	
2 3 Time 3 - Rehabilitat 4	ion service name	Rehab service code Start date Image: Start date Image: Start date	Cease date	
5 7 Time 4 - Rehabilitat 3 9	ion service name	Rehab service code Start date Image: Start date Image: Start date	Cease date	
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10) HOME MODIFICATIONS

Has your home been modified as a consequence of your stroke?

Case Report Form - Cost

e.g. installation of rails, bathroom modifications, installation of ramp(s), kitchen modifications etc



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Yes 🗆

3 months

PATI	FNT	INITI	AI S

No 🗆

Unknown 🗌

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If NO, proceed to question 11 If YES, please indicate the type of modification	s, who supplied the modifications and estin	mate any personal cost to you	3-12 months	Yes 🗌 No 🗌	Unknown 🗌
Type of modification	SUPPLIERS 1 = Hospital/rehabilitation centre 2 = Patient/family	3 = Veteran's Affairs 4 = Local Council	5 = Housing commis 6 = Charity	sion 7 = Ot	her (specify)
(check box for each type supplied)	Who supplied the modificat	ion? If supplier is "o	ther", please specify		
☐ Rail(s) for steps/stairs				Cost to you/family* - \$	
□ Ramp(s)		6 [] 7 [] [] []		Cost to you/family* - \$	
☐ Platform step(s)		6 0 7 0 0		Cost to you/family* - \$	
\Box Shower, bath and toilet rail(s)		□6 □7		Cost to you/family* - \$	
Shower(s) modification		□ 6 □ 7 <u> </u>		Cost to you/family* - \$	
☐ Toilet(s) modification	□1 □2 □3 □4 □5	6 0 7 1 1 1		Cost to you/family* - \$	
Remove/modify door(s) from shower/toilet/bath	□1 □2 □3 □4 □5	□ 6 □ 7 		Cost to you/family* - \$	
☐ Kitchen modifications	□1 □2 □3 □4 □5	6 0 7 0 0		Cost to you/family* - \$	
Other modification (specify below) Other home modification - 1					
		5 🗆 6 🗆 7 _ _ _		Cost to you/family* - \$	
Other home modification - 2		6 [] 7 [] [] []		Cost to you/family* - \$	
If total costs includes any aids, describe	e in brief below (see also list of aids on p			all cost is provided, ple difications above, and p	

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itemised costs listed above:

total cost here, INCLUSIVE of any known

Overall Cost \$

Page 32 of 55







Pip Baladitation The					PATIENT INITIALS
11) SPECIAL EQUIPMENT AND	AIDS				
ave you been given, hired or purchased ar	ny special equipment, aids or special	food as a consequence of stroke?	3 months	Yes 🗌	No 🗌 Unknown 🗌
Prompt: These may have been provided by ar f NO, proceed to question 12	n Occupational Therapist or Physiothera	apist. What about a?	3-12 months	Yes 🗌	No 🗌 Unknown 🗌
Walking aids	Mobility aids	Eating aids			Kitchen aids
□ Single point stick	Manual wheelchair	Built-up cutlery			Tap handles
☐ Three or four point stick	Electric wheelchair/scooter	Plate guard			Chopping board
☐ Walking frame - pick up	Car steering wheel knob	☐ Non-slip mat			Modified knife
Walking frame - wheelie		Special food e.g. NG/PEG			Uitamiser/blender
Walking frame - gutter (forearm suppt)		If yes, number of days used:			□ Non-slip mat
		3-12 months			General aids
Lounge and bedroom equipment Chair platform/blocks raise	Bathroom equipment	Continence aids			Long handled aid
Cushion to relieve pressure	☐ Toilet surround	□ Bedpan			Blood pressure machine
Special chair (NOT wheelchair)					Treadmill
Table - bedside/wheelie	Bathroom and grooming aids Shower shoir/steel	☐ Incontinence sheet (bed protect	ctor)		Stationary bike
Bed platform/block raise	Shower chair/stool	☐ Incontinence sheet (kylie/bluey			☐ Intercom (portable)
	Over bath seat	If yes, number of days used - 3 mo	·		Modified tap handles If yes, number supplied
	Hand held shower	☐ Incontinence pads 3-12 mc	┝╾┿╼┽╼┥		
☐ Hospital bed (eg - height/tilt adjust)	☐ Non-slip mat				Personal alarm
☐ Mobile hoist/lifter		If yes, number of days used - 3 mo			If yes, number of days supp
Any other aids/equipment, specify		Catheter 3-12 mo			3 months
		If yes, number of days used - 3 mo	onths		3-12 months
		3-12 ma	onths		

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Page 49 of 82

BMJ Open



Case Report Form - Cost



PATIENT INITIALS

stroke) or as a result	When CRF Cost con person responding: These quest of any further stroke. I will be as	mplete at 3 months AND a stions are about health ca king about health care su		e Data Fax. stroke which occurred on (give date of therapy at home, equipment and work. To
Obtain fi	Subject's stroke date			
3 MONTH DA			Assessor initials	
PERSON RESPON	DING	ASSISTANCE FOR I	NTERVIEW OBTAINED FROM	LIVING ARRANGEMENT OF RESPONDEN
Index case	Other relative	Index case 🗌	Other relative	Living with index
Spouse/partner 🗌	Friend/Associate/Neighbour	Spouse/partner 🗌 🗸	Friend/Associate/Neighbour	Not living with index
Sibling 🗌	Carer, e.g. nurse 🗌	Sibling 🗌	Carer, e.g. nurse 🗌	Professional carer in nursing home or hostel
Son/Daughter 🗌 Parent 🗌	Other, unspecified 🗌	Son/Daughter 🗌 Parent 🗌	Other, unspecified	
12 MONTH DA			Assessor initials	<u> </u>
PERSON RESPON	DING	ASSISTANCE FOR I		LIVING ARRANGEMENT OF RESPONDEN
Index case	Other relative	Index case	Other relative	Living with index
Spouse/partner	Friend/Associate/Neighbour	Spouse/partner	Friend/Associate/Neighbour	Not living with index
Sibling	Carer, e.g. nurse 🗌	Sibling 🗌	Carer, e.g. nurse 🗌	Professional carer in nursing home or hostel
Son/Daughter 🗌 Parent 🗌	Other, unspecified 🗌	Son/Daughter 🗌 Parent 🗌	Other, unspecified \Box	
				* Please note: this is the 'normal' living arrangement of the respondent with respect to the subject, even if the subject is currently in hospital



Case Report Form - Cost



National Stroke PATIENT STUDY NUMBER Research Institute

PATIEN

ITIALS	

1) DISCHARGE							
Date of discharge from acute care	Acute discharge de	stination	Date of admissior	to inpatient rehal	oilitation	Discharge destination af	ter inpatient reha
	Home]/[]]		Home	
	Rehabilitation ward/h	ospital 🛛 🗖				Rehabilitation hospital	
	Supported residential	l service (SRS) 🗖	Date of discharge	from inpatient ref	abilitation	Supported residential servi	ice (SRS) 🗖
	Hostel					Hostel	
	Nursing home		Leave dates BLA	NK if not applicabl	е	Nursing home	
	Other		Please note: inpat inclusive of geriatri			Other	
	Unknown		transitional care.	c evaluation and		Unknown	
						Leave BLANK if not ap	plicable
2) LIVING ARRANGEMENT							
Pre-stroke residential address		Residential address a	t 3 months*		Residentia	I address at 12 months*	
Own house, flat – alone		Own house, flat – alone	9		Own house	, flat – alone	
Own house, flat – with family/relative/frien	nd 🗖	Own house, flat – with	family/relative/friend		Own house	, flat – family/relative/friend	
Home of relative/friend		Home of relative/friend			Home of re	ative/friend	
Supported residential service (SRS)		Supported residential s	ervice (SRS)		Supported	esidential service (SRS)	
Hostel		Hostel			Hostel		
Nursing home		Nursing home			Nursing hor	ne	
Other		Other			Other		
Unknown		Unknown			Unknown		
			ote if the subject is ir current residentia			(acute or subacute), address	



Page 51 of 82

 BMJ Open



Case Report Form - Cost



National Stroke PATIENT STUDY NUMBER Research Institute

PATIENT INITIALS

3) CHANGE IN LIVING ARRANGE	MENTS					
As a consequence of your stroke, have you n If NO, proceed to question 4.	eeded to change your plac	e of residence?	3 months	Yes 🗌	No 🗖	Unknown 🗌
* Please note: if subject has been a hospital	inpatient this is NOT a cha	nge of residence	3-12 months	Yes 🗖	No 🗖	Unknown 🗖
DATE OF MOVE	LOCATION					
1) / / /	Own home or unitImage: Constraint of the second					
2) / /	Own home or unit Image: Constraint of the second secon					
3)	Own home or unit Image: Constraint of the constraint of					
4) / /	Own home or unit Image: Constraint of the second					
4) AMBULANCE TRANSFERS: EI	MERGENCY AND NO	N-EMERGENCY				
As a consequence of your stroke, have you If NO, please proceed to question 5	required ambulance transp	ort after your acute admission to hospital?	* 3 month	s Yes □	No 🗆] Unknown 🗌
			3-12 mo	nths Yes 🗌	No 🗆] Unknown 🗌
Count number of ambulance trips (recruin		* Include post-acute transfers (eg - acut	e to rehab)			





National Stroke PATIENT STUDY NUMBER Research Institute

 	 ~	

	TENDANCES		
e emergency departm	ent as a consequence of another stroke	3 months Yes No	
		3-12 months Yes I No I	Unknown [
f patient NOT discharg	ged at 3 month assessment, leave discharge		If patient no discharged
Hospital code	Date admitted	Date discharged	<u>12 month</u> assessmen cross box.
Hospital code	Date admitted	Date discharged	
Hospital code	Date admitted	Date discharged	
Hospital code	Date admitted /	Date discharged /	
Hospital code	Date admitted	Date discharged	
ſ	ces for stroke-related f patient NOT discharg Hospital code Hospital code Hospital code	code Date admitted Hospital Date admitted Code Date admitted Hospital Date admitted Code Date admitted Hospital Image: Code Hospital Image: Code	ces for stroke-related problems (see below for summary list of rfurther clarification) 3-12 months Yes No f patient NOT discharged at 3 month assessment, leave discharge Date discharged Image: Imag

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Page 53 of 82

6)	INPATIENT REHABILITATION ADMISSI									
	r your stroke on (give date of stroke), were you adm		a Rehabilitatio	n Hospita	l or other h	ospital	2	months	Yes 🗖	
	re you received rehabilitation treatment? Please incl			-		=		-12 months		
	uation' and 'transitional care'						5			
If YE	ES, complete inpatient rehabilitation admission details, s	0								
lf pa	tient NOT discharged at 3 month assessment, leave dis	scharge	dates BLANK (c Rehab hospi	-	ates at 12 r	nonth assess	ment)			
	Admission 1- Rehabilitation hospital name		code		Date ad	mitted			Date discl	harg
						/			/ 🗌 /	/ [
			Rehab hospi	tal						
	Admission 2- Rehabilitation hospital name		code		Date ad	, The second sec			Date disc	harg
				L_L_I		/				
	Admission 3- Rehabilitation hospital name		Rehab hospi code	tal	Date ad	mitted			Date disc	harg
										1
					/				/ /	
									<u>′ </u>	′ L
	OUTPATIENT REHABILITATION PROG					/			/ ,	′
Die	d you attend or are you attending an outpatient reha	abilitatio		a consequ	lence of yo	/		3 months	7 7 s Yes [′ <u> </u>
Die e.g An	d you attend or are you attending an outpatient reha J. with physiotherapy, occupational therapy, speech outpatient rehabilitation program is any rehabilitation p	abilitatio htherapy	, etc	-	-		n be		s Yes [
Die e.g An loc	d you attend or are you attending an outpatient reha J. with physiotherapy, occupational therapy, speech	abilitatio htherapy	, etc	-	-		n be		-	
Die e.g An loc If N If Y	d you attend or are you attending an outpatient reha g. with physiotherapy, occupational therapy, speech outpatient rehabilitation program is any rehabilitation p rated at a hospital or community facility. NO, proceed to question 8. YES, complete outpatient rehabilitation details, starting f	abilitatio therapy program v from you	y, etc where the patien ir first outpatient	it attends a	a facility. Th	e program ca		3-12 mor	nths Yes]
Die e.g An loc If N If Y	d you attend or are you attending an outpatient reha g. with physiotherapy, occupational therapy, speech outpatient rehabilitation program is any rehabilitation p rated at a hospital or community facility. IO, proceed to question 8.	abilitatio therapy program v from you discharge	y, etc where the patien ir first outpatient e dates and num	t attends a rehabilitat ber of day	a facility. Th tion visit. vs attended	e program ca BLANK (com		3-12 mor	n ths Yes []
Die e.g An loc If N If Y If p	d you attend or are you attending an outpatient reha g. with physiotherapy, occupational therapy, speech outpatient rehabilitation program is any rehabilitation p rated at a hospital or community facility. NO, proceed to question 8. YES, complete outpatient rehabilitation details, starting f	abilitatio therapy program v from you discharge	y, etc where the patien in first outpatient e dates and num hab facility	t attends a rehabilitat ber of day	a facility. Th	e program ca BLANK (com		3-12 mor	nths Yes]
Die e.g An loc If N If Y If p	d you attend or are you attending an outpatient reha g. with physiotherapy, occupational therapy, speech outpatient rehabilitation program is any rehabilitation p ated at a hospital or community facility. IO, proceed to question 8. YES, complete outpatient rehabilitation details, starting f batient NOT discharged at 3 month assessment, leave d	abilitatio therapy program v from you discharge Reḥ	y, etc where the patien in first outpatient e dates and num hab facility	t attends a rehabilitat ber of day	a facility. Th tion visit. vs attended	e program ca BLANK (com		3-12 mor	n ths Yes []
Die e.g An loc If N If Y	d you attend or are you attending an outpatient reha g. with physiotherapy, occupational therapy, speech outpatient rehabilitation program is any rehabilitation p rated at a hospital or community facility. JO, proceed to question 8. (ES, complete outpatient rehabilitation details, starting f ratient NOT discharged at 3 month assessment, leave d Admission 1 - Outpatient rehabilitation name	abilitatio therapy program v from you discharge Reh cod	y, etc where the patient in first outpatient dates and num ab facility e ab facility	rehabilitat ber of day Date	a facility. Tr tion visit. vs attended admitted	e program ca BLANK (com		3-12 mor es at 12 mor Date dis	nths Yes [nth assessm scharged]
Die e.g An loc If N If Y	d you attend or are you attending an outpatient reha g. with physiotherapy, occupational therapy, speech outpatient rehabilitation program is any rehabilitation p ated at a hospital or community facility. IO, proceed to question 8. YES, complete outpatient rehabilitation details, starting f batient NOT discharged at 3 month assessment, leave d	abilitatio therapy program v from you discharge Reh cod	y, etc where the patient in first outpatient dates and num ab facility e ab facility	rehabilitat ber of day Date	a facility. Th tion visit. vs attended	e program ca BLANK (com		3-12 mor es at 12 mor Date dis	n ths Yes []
Die e.g An loc If N If Y	d you attend or are you attending an outpatient reha g. with physiotherapy, occupational therapy, speech outpatient rehabilitation program is any rehabilitation p rated at a hospital or community facility. JO, proceed to question 8. (ES, complete outpatient rehabilitation details, starting f ratient NOT discharged at 3 month assessment, leave d Admission 1 - Outpatient rehabilitation name	abilitatio therapy program v from you discharge Reh cod	y, etc where the patient in first outpatient dates and num ab facility e ab facility	rehabilitat ber of day Date	a facility. Tr tion visit. vs attended admitted	e program ca BLANK (com		3-12 mor es at 12 mor Date dis	nths Yes [nth assessm scharged]
Did e.g An loc If N If Y	d you attend or are you attending an outpatient reha g. with physiotherapy, occupational therapy, speech outpatient rehabilitation program is any rehabilitation p rated at a hospital or community facility. NO, proceed to question 8. (ES, complete outpatient rehabilitation details, starting f ratient NOT discharged at 3 month assessment, leave d Admission 1 - Outpatient rehabilitation name Admission 2 - Outpatient rehabilitation name	abilitatio therapy program v from you discharge Reh cod Reh cod Reh cod	y, etc where the patien in first outpatient e dates and num ab facility e ab facility e ab facility	it attends a rehabilitat ber of day Date J / Date	a facility. The standard statement of the statement of th	BLANK (com		3-12 mor es at 12 mor Date dis) / Date dis	nths Yes [nth assessm scharged] / scharged] /]
Did e.g An loc If N If Y If p	d you attend or are you attending an outpatient reha g. with physiotherapy, occupational therapy, speech outpatient rehabilitation program is any rehabilitation p rated at a hospital or community facility. JO, proceed to question 8. (ES, complete outpatient rehabilitation details, starting f ratient NOT discharged at 3 month assessment, leave d Admission 1 - Outpatient rehabilitation name	abilitatio therapy program v from you discharge Reh cod Reh cod	y, etc where the patien in first outpatient e dates and num ab facility e ab facility e ab facility	it attends a rehabilitat ber of day Date J / Date	a facility. Tr tion visit. vs attended admitted	BLANK (com		3-12 mor es at 12 mor Date dis) / Date dis	nths Yes [nth assessm scharged]

Page 29 of 55

PATIENT INITIALS

No 🗖

No 🗖

No 🗖

No 🗌

Total

number

of DAYS attended

Unknown 🗖

Unknown 🗖

If patient not discharged at 12 month assessment,

cross box.

Unknown 🗖

Unknown 🗖

If patient not discharged at

assessment,

cross box.

<u>12 month</u>



 Case Report Form - Cost



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8) REHABILITATION SERVICES PROVIDED AT HOME OR IN A NURSING HOME Have you had a rehabilitation program provided to you at home or a nursing home as a consequence of your stroke? e.g. with physiotherapy, occupational therapy, speech 3 months Yes If NO, proceed to question 9. If YES, complete rehabilitation details, starting from the first visit since your stroke. Count number of sessions. 3-12 months Yes If patient NOT discharged at 3 month assessment, leave discharge dates and number of sessions BLANK (complete dates at 12 month assessment) Rehab service code Start date Cease date	No 🗌 Unknown No 🗌 Unknown Total	
as a consequence of your stroke? e.g. with physiotherapy, occupational therapy, speech If NO, proceed to question 9. If YES, complete rehabilitation details, starting from the first visit since your stroke. Count number of sessions. If patient NOT discharged at 3 month assessment, leave discharge dates and number of sessions BLANK (complete dates at 12 month assessment) Rehab service	No 🗌 Unknown Total	If patient i
If NO, proceed to question 9. If YES, complete rehabilitation details, starting from the first visit since your stroke. Count number of sessions. If patient NOT discharged at 3 month assessment, leave discharge dates and number of sessions BLANK (complete dates at 12 month assessment) Rehab service	Total	lf patient i
If patient NOT discharged at 3 month assessment, leave discharge dates and number of sessions BLANK (complete dates at 12 month assessment) Rehab service		
	number of SESSIONS	<u>12 month</u> assessme cross box
me 2 - Rehabilitation service name Rehab service Start date Cease date		
ne 3 - Rehabilitation service name Rehab service code Start date Cease date		
ne 4 - Rehabilitation service name Rehab service code Start date Cease date		

Page 55 of 82

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		eport Forn	ו - Cos	t		52	National Stroke PATIE Research Institute	ENT STUDY NUN PATIE	
9) COMMUNITY SER	VICES								'.
9a) Did you receive any com	nmunity services	in the year PRI	OR to your	stroke?				Yes 🗌	No 🔲 Unkn
Community services are	individual care s	services provide	ed at home	and do NOT	include re	habilitation th	nerapy.		
If NO, proceed to question							How many times in		
If YES, which service/s d	lia you receive in	-	-				the past year did you		
0		Which servio	e did you	receive? (On	e service o	code per line)	receive the service?		
Community service c 1 = Nursing Service	codes		3		5 🗌 6	7 []			
2 = Delivered Meals					- □.	— -			
3 = Personal Care (Ba 4 = Housework help	itn/Snower)		□ 3		5 []6	7 []			
5 = Gardening/home m	naintenance		3	□4 □	5 🗌 6	□ 7			
6 = Home respite 7 = Other service, spec	cify				5 🗌 6				
		lf "other" (c	_						
			_						
9b) Have you received comm	nunity services S	INCE the stroke	?				3 months Ye	es 🔲 🛛 No	o 🔲 🛛 Unknown 🗖
Community services are		ervices provide	d at home	and do NOT	include rel	habilitation the			o 🔲 Unknown 🗖
If NO, proceed to questio		FTFR your strok	e?						
IT YES, Which service/s d	io vou receive Al								
If YES, which service/s di For each service, comple	ete a seperate line	e. If a service is	ongoing a		erview, en	ter data for 3		How many	Note: hours no
	ete a seperate line	e. If a service is	ongoing a		erview, en	ter data for 3	How many times did you	How many hours	
For each service, comple	ete a seperate line	e. If a service is 12 months on a	ongoing a separate li	ne.		ter data for 3 code per line)	times did you		NOT applicable
For each service, comple months, and then add se	ete a seperate line ervice data for 3-1	e. If a service is 12 months on a	ongoing a separate li ce did you	ne.	ne service		times did you	hours	NOT applicable
For each service, comple	ete a seperate line ervice data for 3-1	e. If a service is 12 months on a Which servi	ongoing a separate li ce did you : 3	ne. receive? (Or	ne service 5 🗌 6	code per line)	times did you	hours	NOT applicable
For each service, comple months, and then add se Community service of 1 = Nursing Service 2 = Delivered Meals	ete a seperate line ervice data for 3-1 codes	e. If a service is 12 months on a Which servi	ongoing a separate li ce did you : 3	ne. receive? (Or	ne service 5 🗌 6	code per line)	times did you	hours	NOT applicable
For each service, comple months, and then add se Community service of 1 = Nursing Service 2 = Delivered Meals 3 = Personal Care (Ba	ete a seperate line ervice data for 3-1 codes	e. If a service is 12 months on a Which servi	ongoing a separate li ce did you 2	ne. receive? (Or 4 4	ne service 5	code per line) 7 7 7	times did you	hours	NOT applicable
For each service, comple months, and then add se Community service of 1 = Nursing Service 2 = Delivered Meals 3 = Personal Care (Ba 4 = Housework help 5 = Gardening/home r	ete a seperate line ervice data for 3-1 codes ath/Shower)	e. If a service is 12 months on a Which servi 1 2 1 2 1 2 1 2	ongoing a separate li ce did you 2 3 2 3 2 3 2 3	ne. receive? (Or 4 4 4 4 4 4 4 4 4 4	ne service 5	code per line) 7 7 7 7 7	times did you	hours	NOT applicable
For each service, complements, and then add service, and then add service at a serv	ete a seperate line ervice data for 3-1 codes ath/Shower) maintenance	e. If a service is 12 months on a Which servi	ongoing a separate li ce did you 2 3 2 3 2 3 2 3	ne. receive? (Or 4 4	ne service 5	code per line) 7 7 7	times did you	hours	NOT applicable
For each service, comple months, and then add se Community service of 1 = Nursing Service 2 = Delivered Meals 3 = Personal Care (Ba 4 = Housework help 5 = Gardening/home r	ete a seperate line ervice data for 3-1 codes ath/Shower) maintenance	e. If a service is 12 months on a Which servi 1 1 2 1 2 1 2 1 2	ongoing a separate li ce did you 2 3 2 3 2 3 2 3 2 3	ne. receive? (Or 4 4 4 4 4 4 4 4 4 4	ne service 5	code per line) 7 7 7 7 7 7 7	times did you	hours	NOT applicable
For each service, complements, and then add service, and then add service at a serv	ete a seperate line ervice data for 3-1 codes ath/Shower) maintenance	e. If a service is 12 months on a Which servi 1 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1	ongoing a separate li ce did you 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3	ne. receive? (Or 4 4 4 4 4 4 4 4 4	ne service 5	code per line) 7 7 7 7 7 7 7 7 7	times did you	hours	Note: hours per NOT applicable delivered meals
For each service, complements, and then add service, and then add service at a serv	ete a seperate line ervice data for 3-1 codes ath/Shower) maintenance	e. If a service is 12 months on a Which servi 1 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1	ongoing a separate li ce did you ? 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3	ne. receive? (Or 4 4 4 4 4 4 4 4 4 4 4 4 4	ne service 5	code per line) 7 7 7 7 7 7 7 7 7	times did you	hours	NOT applicable
For each service, complements, and then add service, and then add service at a serv	ete a seperate line ervice data for 3-1 codes ath/Shower) maintenance	e. If a service is 12 months on a Which servi 1 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1	ongoing a separate li ce did you ? 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3	ne. receive? (Or 4 4 4 4 4 4 4 4 4	ne service 5	code per line) 7 7 7 7 7 7 7 7 7	times did you	hours	NOT applicable
For each service, complements, and then add service, and then add service at a serv	ete a seperate line ervice data for 3-1 codes ath/Shower) maintenance	e. If a service is 12 months on a Which servi 1 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1	ongoing a separate li ce did you 2 3 3 2 3 3 2 3 3 2 3 3 2 3 3 3 3 3 3	ne. receive? (Or 4 4 4 4 4 4 4 4 4 4 4 4 4	ne service (5	code per line) 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	times did you receive the service?	hours	NOT applicable
For each service, complements, and then add service, and then add service at a serv	ete a seperate line ervice data for 3-1 codes ath/Shower) maintenance	e. If a service is 12 months on a Which servi 1 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1	ongoing a separate li ce did you 2 3 3 2 3 3 2 3 3 2 3 3 2 3 3 3 2 3 3 3 3 3 3 3 3 3 4 5 5 5 5 5 5 5 5 5 5	ne. receive? (Or 4 4 4 4 4 4 4 4 4 4 4 4 4	ne service 1 5	code per line) 7 7 7 7 7 7 7 7 7 7 7 7 7 7	times did you	hours	NOT applicable
For each service, complements, and then add service, and then add service at a serv	ete a seperate line ervice data for 3-1 codes ath/Shower) maintenance	e. If a service is 12 months on a Which servi 1 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1	ongoing a separate li ce did you 2 3 3 2 3 3 2 3 3 2 3 3 2 3 3 3 2 3 3 3 3 3 3 3 3 3 4 5 5 5 5 5 5 5 5 5 5	ne. receive? (Or 4 4 4 4 4 4 4 4 4 4 4 4 4	ne service (5	code per line) 7 7 7 7 7 7 7 7 7 7 7 7 7 7	times did you receive the service?	hours	NOT applicabl delivered mea



Has e.g.

1 2

3

4 5



PATIENT STUDY NUMBER

PATIENT	INITIALS

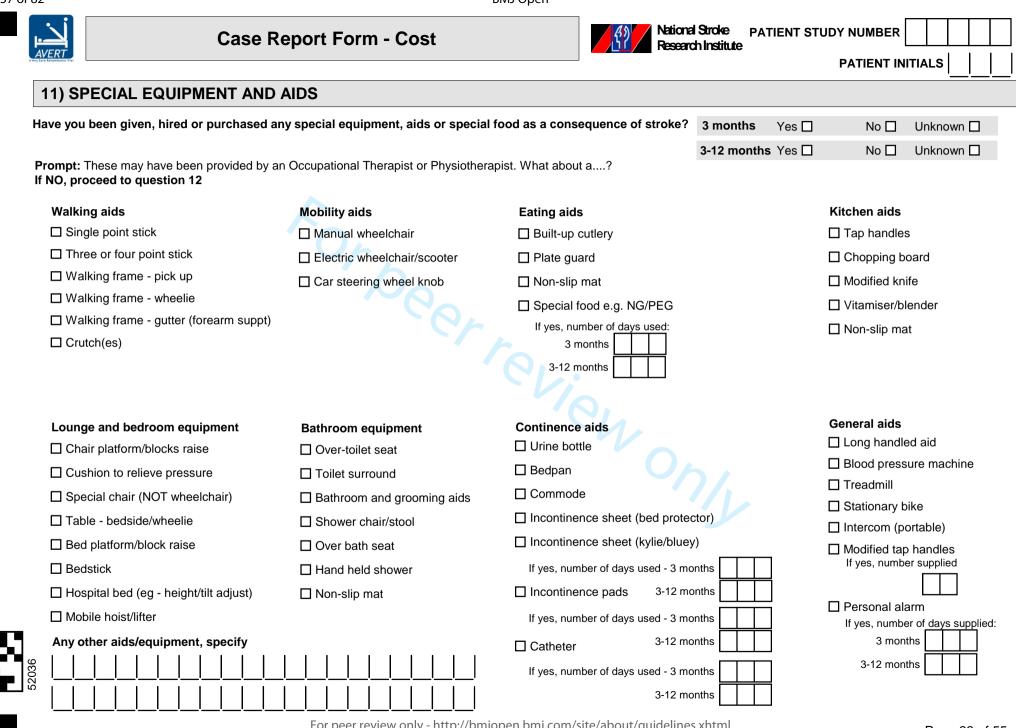
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46

Has your home been modified as a conseque e.g. installation of rails, bathroom modification		adifications ato	3 months	Yes 🗌 🛛 No 🗌	Unknown 🗌
If NO, proceed to question 11	ons, instantion of ramp(s), kitchen m	odifications etc	3-12 months	Yes 🗌 🛛 No 🗌	Unknown 🗌
If YES, please indicate the type of modifications,	, who supplied the modifications and esti	mate any personal cost to you.			
Type of modification	SUPPLIERS 1 = Hospital/rehabilitation centre 2 = Patient/family	3 = Veteran's Affairs 4 = Local Council	5 = Housing commis 6 = Charity	sion 7 = O	ther (specify)
(check box for each type supplied)	Who supplied the modificat	tion? If supplier is "o	other", please specify		
Rail(s) for steps/stairs		5 🗆 6 🗆 7 📃 📃		Cost to you/family* - \$	
☐ Ramp(s)		5 🗆 6 🗆 7 📗 📗		Cost to you/family* - \$	
□ Platform step(s)		5 [] 6 [] 7 [] [] []		Cost to you/family* - \$	
\Box Shower, bath and toilet rail(s)		5 🗆 6 🗆 7 📘 📘		Cost to you/family* - \$	
Shower(s) modification		5 🗆 6 🗆 7 📙 📙		Cost to you/family* - \$	
☐ Toilet(s) modification		5 🗆 6 🗆 7 📘 📘		Cost to you/family* - \$	
Remove/modify door(s) from shower/toilet/bath		5 🗆 6 🗆 7 📗 📗		Cost to you/family* - \$	
Kitchen modifications		5 🗆 6 🗆 7 📗 📗		Cost to you/family* - \$	
Other modification (specify below) Other home modification - 1					
		5 🗆 6 🗆 7 📘 📕		Cost to you/family* - \$	
Other home modification - 2		5 🗆 6 🗆 7 📗		Cost to you/family* - \$	
If total costs includes any aids, describe i	n brief below (see also list of aids on	page 33):	type of mo total cost	rall cost is provided, ple odifications above, and p here, INCLUSIVE of any osts listed above:	provide the
				Overall Cost \$	

Page 57 of 82

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3-12 months

No \square

If YES, what was the nature of this work?

How many hours did you work each week?

3 months

3 months

3-12 months

3-12 months

Unknown 🗌

Yes 🗖

Yes 🗖

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12) PRIVATE PHYSIOTHERAPY

3-12 months

14) EMPLOYMENT STATUS/ PAID WORK

Were you working up to the time of your stroke?

Since the stroke, have you returned to this work?

Have you returned to normal hours or decreased hours?

If yes, how many days of respite have you received since your stroke? 3 months

How many hours per week of work have you performed since the last assessment?

Record average amount per week over the period 3 to 12 months

Record average amount per week over the 3 month period

If no, proceed to question 13

13) RESPITE CARE

If NO, proceed to question 14

If yes, number of sessions - 3 months

Have you paid for private physiotherapy sessions after your stroke? (NOT while a hospital inpatient)

As a consequence of your stroke, have you been admitted to a respite bed in a nursing home or hospital?

Yes 🗆



Full time

No 🗖

No 🗖

Normal

Normal

National Stroke PATIENT STUDY NUMBER Research Institute

Yes 🗖

Yes 🗌

3 months

3 months

Part time

Unknown 🗖

Unknown 🗌

Decreased

Decreased

If more than 0 but less than 1hr, record as 1

3-12 months Yes □

3-12 months Yes

PATIENT INITIALS

No 🗆

No \square

No 🗌

No \square

Unknown

Unknown

Unknown

Unknown

Page 34 of 55

Page 58 of 82

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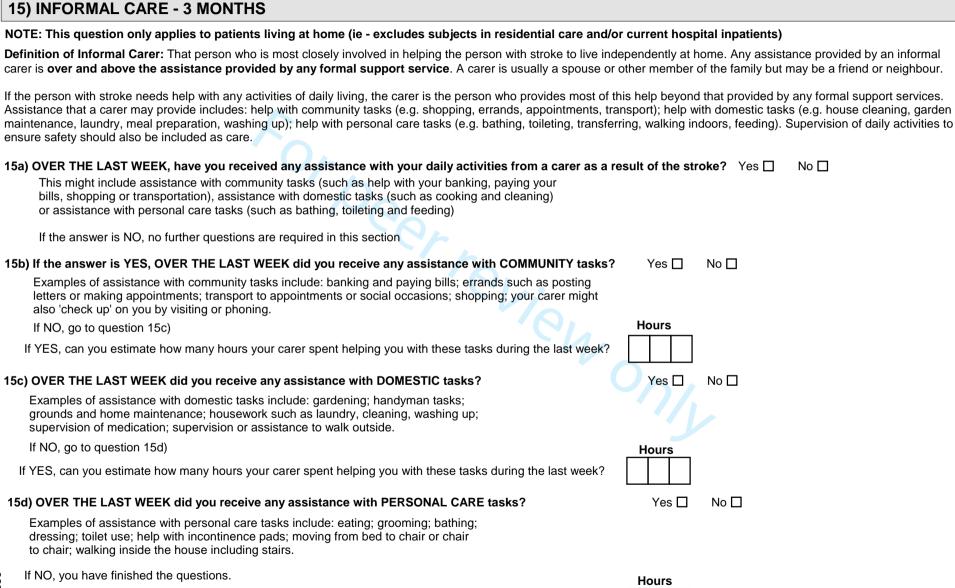
BMJ Open



Case Report Form - Cost



National Stroke PATIENT STUDY NUMBER Research Institute



If YES, can you estimate how many hours your carer spent helping you with these tasks during the last week?

Hours						





National Stroke PATIENT STUDY NUMBER Research Institute

PATIENT INITIALS

45 46

16) INFORMAL CARE - 12 MONTHS NOTE: This question only applies to patients living at home (ie - excludes subjects in residential care and/or current hospital inpatients) Definition of Informal Carer: That person who is most closely involved in helping the person with stroke to live independently at home. Any assistance provided by an informal carer is over and above the assistance provided by any formal support service. A carer is usually a spouse or other member of the family but may be a friend or neighbour. If the person with stroke needs help with any activities of daily living, the carer is the person who provides most of this help beyond that provided by any formal support services. Assistance that a carer may provide includes: help with community tasks (e.g. shopping, errands, appointments, transport); help with domestic tasks (e.g. house cleaning, garden maintenance, laundry, meal preparation, washing up); help with personal care tasks (e.g. bathing, toileting, transferring, walking indoors, feeding). Supervision of daily activities to ensure safety should also be included as care. 16a) OVER THE LAST WEEK, have you received any assistance with your daily activities from a carer as a result of the stroke? Yes No \square This might include assistance with community tasks (such as help with your banking, paying your bills, shopping or transportation), assistance with domestic tasks (such as cooking and cleaning) or assistance with personal care tasks (such as bathing, toileting and feeding) If the answer is NO, no further questions are required in this section 16b) If the answer is YES, OVER THE LAST WEEK did you receive any assistance with COMMUNITY tasks? Yes 🗆 No 🗖 Examples of assistance with community tasks include: banking and paying bills; errands such as posting letters or making appointments: transport to appointments or social occasions; shopping; your carer might also 'check up' on you by visiting or phoning. If NO, go to guestion 16c) Hours If YES, can you estimate how many hours your carer spent helping you with these tasks during the last week? 16c) OVER THE LAST WEEK did you receive any assistance with DOMESTIC tasks? Yes 🛛 No 🗆 Examples of assistance with domestic tasks include: gardening; handyman tasks; grounds and home maintenance; housework such as laundry, cleaning, washing up; supervision of medication: supervision or assistance to walk outside. If NO, go to question 16d) Hours If YES, can you estimate how many hours your carer spent helping you with these tasks during the last week? 16d) OVER THE LAST WEEK did you receive any assistance with PERSONAL CARE tasks? Yes 🗆 No 🗆 Examples of assistance with personal care tasks include: eating; grooming; bathing; dressing; toilet use; help with incontinence pads; moving from bed to chair or chair to chair; walking inside the house including stairs. If NO, you have finished the questions.

If YES, can you estimate how many hours your carer spent helping you with these tasks during the last week?

Hours							

End Case Report Form - Cost For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml V 4.0 : 1 Nov 10 (AUS)

Supplementary document 3: Unit costs and valuation of costs

Unit costs for hospitalisation, rehabilitation, non-health sector costs and productivity costs

Acute stroke hospitalisation costing: Unit costs for acute stroke hospitalisation for all countries at baseline were categorised by stroke severity, using the National Institute of Health Stroke Scale (NIHSS) to group patients into three severity levels: mild (0-7), moderate (8-16) and severe (>16). (1)(2) It was assumed that severity as classified by the NIHSS was consistent with the stroke severity that corresponded to three levels of unit cost for acute hospitalisation. Length of Stay (LoS) together with stroke severity were used to estimate the cost of acute hospitalisation for Australia and New Zealand patients (i.e. the cost of acute hospitalisation was weighted by the LoS). LoS was taken as the difference between the date of hospital discharge and date of hospital admission (plus one day or not) in accordance with country-specific practice. For the other countries, only stroke severity was considered in the assignment of a unit cost to acute stroke hospitalisation due to insufficient health sector data.

Re-hospitalisation and rehabilitation costing: Due to the diversity of causes for patients being readmitted to hospital after the index stroke, the average daily cost of hospitalisation for all disease conditions from individual countries in combination with LoS was used to gauge the cost of readmission for stroke-related causes, while the average cost for an emergency department visit was assigned whenever a patient was hospitalised for one day only. Similarly, the unit cost of rehabilitation hospital admission was taken from the national average cost for all disease conditions. The median cost was used where there was more than one unit cost identified for the same resource item.

Non-health sector costs: Unit costs of non-health sector resource items (e.g. community service, accommodation changes, special aids and equipment) were sourced on a country- specific basis from official websites or published literature where applicable. No unit cost was retrieved for home modification items since the cost of home modifications was generally reported in the Cost CRF.

Productivity cost: Lost productivity was valued based on a human capital approach using average earnings across all occupations up to normal retirement age. The average wage of a

professional carer was adopted to estimate the cost of informal care.

The currency of other countries was converted to AUD using the corresponding exchange rate. The country-specific Consumer Price Index (CPI) from the health sector was employed to adjust costs not valued in the year of 2015.

All the unit costs from participating countries are summarised in Table I.

Resource items		ι	Unit cost (AUD)						
	AU	NZ	UK	SG	MA				
Healthcare									
Acute hospitalisation [*]									
Severe (per episode)	\$19157	\$10867	\$15327	\$4371	\$2066				
Moderate (per episode)	\$9553	\$6104	\$8115	\$2126	\$1572				
Mild (per episode)	\$6279	\$4370	\$4272	\$1493	\$1363				
Stroke-related rehospitalisation (per day)	\$1925	\$320	\$701	\$789	\$230				
Emergency department attendance (per attendance)	\$610	\$325	\$227	\$111	\$68				
Rehabilitation hospital admission [†]									
Severe (per episode)	\$1010 [‡]	\$8032	\$19136 [§]	\$157 [‡]	\$1293				
Moderate (per episode)		\$5727	\$29788 [§]						
Mild (per episode)		\$5727	\$13920 [§]						
Same day (per episode)		\$758	N/A						
Outpatient rehab visit (per/session)	\$239	\$164	\$213	\$36	\$17				
Rehab services at home/nursing	\$239	\$212	\$922	\$36	\$51				
facility (per/session)									
Private physiotherapy (per session)	\$64	\$153	\$162	\$116	\$8				
Respite care (per hour)	\$45	\$14	\$26	\$15	\$2				
Individual allied health visit									
Physiotherapy	N/A	N/A	\$243	\$239	\$8				
Occupational therapy	N/A	N/A	\$243	\$36	\$7				
Speech and language therapy	N/A	N/A	\$69	\$36	\$4				
Ambulance transfer	\$508	\$646	\$575	\$265	\$52				
Non-healthcare									
Community services	Not listed here due to the number of items								
Home modifications	Cost was provided by individual patients								
Special aids and equipment	Not listed here due to the substantial number of items								
Accommodation changes	Not listed h	ere due to t	he number of	f items					
Professional carer (per hour)	\$24	\$14	\$14	\$10	\$2				
Living-in maid (per month)	N/A	N/A	N/A	\$571	\$103				
Average weekly earnings									
Male	\$1137	\$621	\$1152	\$973	\$137				
Female	1 1		\$957 [°]						

 Table I. Unit cost (in Australian dollars) across five countries, 2015 reference year

Unit cost for intervention [#]					
Hospital physiotherapist (per	\$33	\$32	\$30	\$21	\$5
hour) Hospital nurse (per hour)	\$30	\$25	\$29	\$21	\$5
AU: Australia; NZ: New Zealand; UK: U					Ψ5
Sources of CPI:					
Australian Bureau of Statistics. Consumer from:Http://www.Abs.Gov.Au/websitedb				x+inflation+cald	culator, 2017
Office for National Statistics. Inflation an	d price indices	. Accessed fro			<u></u> , ,
Https://www.Ons.Gov.Uk/economy/inflat Department of Statistics Singapore. Const			from: Https://dat	a Gov Sø/datase	t/consumer_nr
index-annual. 2017		CA. THEESSER	110111. <u>111(ps.//dat</u>	a. Gov. 5g/ datase	deonsumer-pr
Statistics New Zealand. Consumer price i			inflation/infa_n	-l	17
<u>Http://www.Stats.Govt.Nz/browse_for_st</u> Department of Statistics Malaysia OP. Co					1/
Https://www.Dosm.Gov.My/v1/index.Php	p?R=column/ci	themebycat&c	cat=106&bul_id	=zi9pmutpvzixb	042mlptt1bue
menu_id=bthzthqxn1zqmvf6a2i4rkzondfl	<u>kqt09</u> . 2017				
* severity was determined by baseline NIF	ISS saara. Taa	uarity was ala	agified by becali	no mPS sooro: ti	t is the nor
day cost; [§] cost was assigned according to					
Survey of Household Income was provide					
corresponding to this; [#] hourly wage of ho					
Main sources of unit cost: AU: Independe Data (2015-16); National Hospital Cost D					
hospitals-cost-report-2013-2014-round-18	3); Department	of Health, Re	evised residential	l care subsidies	an-puone-
(https://agedcare.health.gov.au/aged-care-					ureau of
Statistics (http://www.abs.gov.au/AUSSTATS/abs(a nof/allprima	rumainfaatura	c/F0FF0F12B/1	7 & 1880 & 25754	52001/DE20
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NZ: Ministry of Health (<u>http://www.healt</u>					
separations); World Health Organisation (Version 2.2 (https://www.pharmac.govt.n					
(Te Ao BJ et al. Are stroke units cost effe					
based study. Int. J. Stroke. 2012;7:623-63					
(<u>http://www.stats.govt.nz/browse_for_sta</u> work/employment_and_unemployment/L			PJun15atr.aspx)	: District Health	Board. Multi
Employer Agreement, New Zealand Nurs					
meca-2015-2017.pdf); UK: National Health Service (NHS) refer	ence costs 201	4 to 2015 Un	ited Kingdom		
(https://www.gov.uk/government/publica				CE Technology	Appraisal
(Davis,S., Holmes,M., Simpson,E., Sutton					
technology appraisal 122]: A Single Tech https://www.nice.org.uk/guidance/ta264/c					
review-group-report2); Personal Social Socia	ervices Researc	ch Unit (PSSR	U)(<u>http://www.</u>	<u>pssru.ac.uk/</u>); Int	formation
Services Division, Scotland (<u>http://www.i</u> National Statistics	sdscotland.org	/); Annual Su	rvey of Hours ar	nd Earnings 2015	5, Office for
(https://www.ons.gov.uk/employmentand	labourmarket/r	peopleinwork/	earningsandwor	kinghours/bullet	ins/annualsur
veyofhoursandearnings/2015provisionalre	<u>esults</u>); Payscal	le ÛK		-	
(http://www.payscale.com/research/UK/J (https://www.healthcareers.nhs.uk/about/d					
SG: Ministry of Health, Hospital Bill Siz	es, Singapore		•		
(https://www.moh.gov.sg/content/moh_w					
Charges, Singapore General Hospital (<u>htt</u> <u>charges.aspx</u>); Charges, Ren Ci Hospital (
charges, Bright Vision Hospital (http://www	ww.bvh.org.sg/	hospital-rate-	charge.html); M		
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(<u>http://stats.mom.gov.sg/Pages/Occupatio</u>	lohd Mandin		a post of in ment	ennnemear care	for strales
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MA: study by Mohd Nordin et al 2012 (M using Casemix data. BMC Health Service (http://www.moh.gov.my/english.php/pag	es Research 201 ges/view/160);	al.: Estimatin 12 12(Suppl 1 Study by Akh):P10.); Ministry avan Hejazi et a	of Health Mala l 2015(Akhavan	ysia Hejazi SM,
MA: study by Mohd Nordin et al 2012 (M using Casemix data. BMC Health Service (<u>http://www.moh.gov.my/english.php/pag</u> et al. Cost of post-stroke outpatient care in	es Research 201 ges/view/160);	al.: Estimatin 12 12(Suppl 1 Study by Akh):P10.); Ministry avan Hejazi et a	of Health Mala l 2015(Akhavan	ysia Hejazi SM,
MA: study by Mohd Nordin et al 2012 (M using Casemix data. BMC Health Service (http://www.moh.gov.my/english.php/pag	s Research 201 ges/view/160); n malaysia. Sin	al.: Estimatin 12 12(Suppl 1 Study by Akh gapore Med.):P10.); Ministry avan Hejazi et a J. 2015;56:116-1	v of Health Mala l 2015(Akhavan l 19); Departmen	ysia Hejazi SM, t of Statistics

Valuation of costs

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 (i.e. excluding non- healthcare costs and productivity cost).

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Page 65 of 82

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Supplementary document 4. Missing cost data analyses

Table I. Number of missing data for each cost item

Cost variable	Missing										
3	Total	AU		NZ		UK		SG		MA	
Ф 1	N=2104	VEM N=522	UC N=532	VEM N=94	UC N=95	VEM N=311	UC N=299	VEM N=64	UC N=64	VEM N=62	UC N=61
2 Acute hospitalisation	1(0.05%)	1(0.2%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
3 Stroke-related rehospitalisation	51(2.4%)	8(1.5%)	7(1.3%)	0(0%)	0(0%)	17(5.5%)	8(2.7%)	0(0%)	3(4.7%)	7(11.3%)	1(1.6%)
Ambulance transfer	53(2.5%)	8(1.5%)	10(1.9%)	0(0%)	0(0%)	16(5.1%)	7(2.3%)	1(1.6%)	3(4.7%)	7(11.3%)	1(1.6%)
Rehabilitation hospital admission	55(2.6%)	9(1.7%)	9(1.7%)	0(0%)	0(0%)	18(5.8%)	8(2.7%)	0(0%)	3(4.7%)	7(11.3%)	1(1.6%)
7 Outpatient rehabilitation program	47(2.2%)	0(0%)	0(0%)	0(0%)	0(0%)	23(7.4%)	10(3.3%)	0(0%)	3(4.7%)	9(14.5%)	2(3.3%)
8 Rehabilitation provided at home/nursing9 facility	67(3.2%)	11(2.1%)	10(1.9%)	0(0%)	0(0%)	23(7.4%)	1(3.7%)	0(0%)	3(4.7%)	7(11.3%)	1(1.6%)
• Individual allied health visit [§]	0(0%)	-	-	- /_	-	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Private physiotherapy	76(3.6%)	12(2.3%)	11(2.1%)	0(0%)	1(1.1%)	27(8.7%)	13(4.4%)	1(1.6%)	3(4.7%)	7(11.3%)	1(1.6%)
Respite care	77(3.7%)	12(2.3%)	11(2.1%)	1(1.1%)	1(1.1%)	27(8.7%)	13(4.4%)	1(1.6%)	3(4.7%)	7(11.3%)	1(1.6%)
Subtotal (medical cost)	94(10.7%)	14(2.7%)	13(2.4%)	1(1%)	1(1.1%)	36(11.6%)	14(4.7%)	1(1.6%)	3(4.7%)	9(14.5%)	2(3.3%)
5 Accommodation moves	60(2.9%)	15(2.9%)	11(2.1%)	1(1.1%)	1(1.1%)	15(4.8%)	10(3.3%)	0(0%)	2(3.1%)	5(8.1%)	0(0%)
6 Community services	230(10.9%)	63(12.1%)	87(16.4%)	4(4.3%)	5(5.3%)	32(10.3%)	27(9.0%)	1(1.6%)	3(4.7%)	7(11.3%)	1(1.6%)
Home modifications	13(0.6%)	3(2.6%)	6(1.1%)	0(0%)	1(1.1%)	0(0%)	2(0.7%)	0(0%)	1(1.6%)	0(0%)	0(0%)
Special aids and equipment	48(2.3%)	7(1.3%)	8(1.5%)	1(1.1%)	1(1.1%)	16(5.1%)	14(4.7%)	1(1.6%)	0(0%)	0(0%)	0(0%)
Informal care	72(3.4%)	11(2.1%)	12(2.3%)	0(0%)	1(1.1%)	26(8.4%)	10(3.3%)	1(1.6%)	3(4.7%)	7(11.3%)	1(1.6%)
1 Living-in maids [‡]	-	-	-	-	-	-	-	1(1.6%)	3(4.7%)	7(11.3%)	2(3.3%)
² Subtotal (non-medical cost)	304(14.5%)	77(14.8)%	97(18.2%)	6(6.4%)	7(7.4%)	54(17.4%)	46(15.4%)	2(3.1%)	5(7.8%)	8(12.9%)	2(3.3%)
Productivity cost	225(10.7%)	50(9.6%)	46(8.7%)	14(14.9%)	10(10.5%)	27(8.7%)	23(7.7%)	17(25.6%)	13(20.3%)	14(22.6%)	11(18.0%)
Total cost (exc. productivity cost)	319(15.2%)	80(15.3%)	97(18.2%)	6(6.4%)	7(7.4%)	61(19.6%)	48(16.1%)	2(3.1%)	5(7.8%)	10(16.1%)	3(4.9%)
6 Total cost	512(24.3%)	124(23.8%)	136(25.6%)	20(21.3%)	16(16.8%)	80(25.7%)	68(22.7%)	17(26.6%)	16(25.0%)	22(35.5%)	13(21.3%)

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[§]only applicable to UK, Singapore and Malaysia patients; [†]only applicable to Singapore and Malaysia patients

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Resource use items with missing data	Predictor of missingness
Stroke-related rehospitalisation	Age (p=0.001)
Rehabilitation hospital admission	Age (p=0.009), NIHSCORE (p=0.037)
Outpatient rehabilitation program	Age (p=-0.003)
Rehabilitation service provided at home/nursing facility	Age (p=0.014),
Community services used prior to stroke	NIHSCORE (p=0.001)
Community services used at 3 months	Age (p=0.003)
Community services used at 12 months	NIHSCORE (p=0.008)
Aids or special equipment uses at 3 months	Age (p=0.012)
Aids or special equipment uses at 12 months	Age (p=0.035), NIHSCORE (p=0.013)
Private physiotherapy uses at 3 months	Age (p<0.0001)
Private physiotherapy uses at 12 months	Age (p=0.006), NIHSCORE (p=0.034)
Respite care use at 3 months	Age (p<0.0001)
Respite care use at 12 months	Age (p=0.017), NIHSCORE (P=0.018)
Informal care use at 3 months	Age (p=0.003)
Informal care use at 12 months	Age (p<0.0001)

If any of the other variables were able to predict the missingness of a given variable representing resource use, the MAR assumption was deemed to be held true. More specifically, multiple imputations were used to replace the missing values (missing mRS, AQoL-4D data or cost categories) with plausible estimates, and generated 30 datasets. Results were provided as pooled estimates of these sets. Identical analyses were carried out to estimate the incremental costs and benefits between groups on the basis of imputed data following the methods outlined in the statistical analysis section above. As the probability of all the resource use items being missing could be predicted by one or more of the other variables, it is likely that the Missing-at-Random (MAR) assumption could be held true. (https://www.ssc.wisc.edu/sscc/pubs/stata_mi_decide.htm).

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Supplementary document 5. Outcomes

Table I. Results of mRS score at 3 and 12 months follow-up

Modified Rankin	UC group		VEM group)
Scale Score	n=1050		n=1054	
	3M	12M	3M	12M
0	96	132	90	137
1	204	231	200	219
2	225	175	190	166
3	218	199	238	186
4	127	95	140	113
5	103	83	92	59
6	72	118	88	139
Total	1045	1033	1038	1019
Missing data	5	17	16	35

Number of patients falling into each category

Since there was no significant intervention effect together with no accepted willingness-to- pay (WTP) per unit increase in probability of achieving a better mRS outcome, further estimation of the ICER was considered not meaningful (i.e. no cost-effectiveness plane or cost-effectiveness acceptability curve could be generated).

Tuble II	r	st associated with	achi cring +		, , ,	
	VEM		UC		Between group	difference
	Total time	Cost (AUD)	Total time	Cost (AUD)	Total time	Cost (AUD)
	(min)		(min)		(min)	
Physiotherapist	243	\$117	95	\$48	147	\$69
	(232, 254)	(\$111, \$123)	(90, 101)	(\$45, \$51)	$(135, 159)^*$	(\$63, \$75) [*]
Nurse [†]	494	\$225	439	\$202	55	\$23
	(456, 532)	(\$207, \$244)	(404, 474)	(\$185, \$219)	$(4, 106)^*$	(-\$2, \$48)
Total cost	-	\$342	-	\$250	-	\$92
		(\$320, \$364)		(\$231, \$269)		(\$63, \$121)*

Table II. Time and cost associated with delivering VEM and UC (mean, 95%CI)

VEM: very early mobilisation; UC: usual care; CI: confidence interval

*p<0.0001 (adjusted for age, baseline NIHSS and mRS); [†] nurse's time devoted to delivery of VEM/UC was not recorded in the process of data collection, so the physiotherapist time was used as a proxy

Because VEM and UC were supplied by the same group of physiotherapists and nurses, the key difference was that a patient randomised to VEM received early rehabilitation within 24 hours of stroke onset and more out-of-bed mobilisation sessions of early mobilisation.

The total health practitioner (physiotherapist and nurses) time devoted to the delivery of the VEM and UC differed significantly, with the VEM group receiving substantially longer mean service time from both the physiotherapist (VEM: 243 mins, 95%CI: 232 to 254 vs UC: 95 mins, 95%CI: 90 to 101, p<0.0001) and nurse (VEM: 494 mins, 95%CI: 456 to 532 vs UC: 439 mins, 95%CI: 404 to 474, p<0.0001). The resultant difference in costs between groups was significant (\$92, 95%CI: \$63 to \$121, p<0.0001).

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Supplementary document 6. Sensitivity analyses

Generally, the difference in QALY gains between VEM and UC groups were fairly consistent across different methods.

Table I. Between-group differences based on the Generalised Linear Model_base case analysis vs. multiple imputation analysis

	ITT (not imputed	l)		ITT (imputed)		
	mRS score	QALYs	Cost (AUD)	mRS	QALYs	Cost (AUD)
Health Sector Perspec	ctive	<u></u>				
Total medical costs	0.030	-0.013	\$1082	0.042	-0.019	\$940
	(-0.022, 0.082)	(-0.041, 0.016)	(-\$2399, \$4563)	(-0.008, 0.092)	(-0.046, 0.007)	(-\$2584, \$4465)
Societal Perspective	I		90	l	1	I
Total cost (excl.	0.030	-0.013	-\$6	0.042	-0.019	\$1704
productivity cost)	(-0.022, 0.082)	(-0.041, 0.016)	(-\$5703, \$5690)	(-0.008, 0.092)	(-0.046, 0.007)	(-\$5423, \$8832)
Total cost (incl.	0.030	-0.013	\$102	0.042	-0.019	\$1413
productivity cost)	(-0.022, 0.082)	(-0.041, 0.016)	(-\$6945, \$7149)	(-0.008, 0.092)	(-0.046, 0.007)	(-\$5940, \$8766)
TT: intention to treatment; the p-value was >0.05 for		-		6	00	1.

	Adding country dumn	iies	
	mRS	QALYs	Cost
Total medical costs	0.031(-0.021, 0.083)	-0.013(-0.042, 0.015)	\$704 (-\$1968, \$3376)
Total cost (excl. productivity cost)	0.031(-0.021, 0.083)	-0.013(-0.042, 0.015)	-\$335 (-\$4953, \$4283)
Total cost (incl. productivity cost)	0.031(-0.021, 0.083)	-0.013(-0.042, 0.015)	-\$238 (-\$6012, \$5537)

Table II. Between-group differences based on the Generalised Linear Model

mRS: modified Rankin Scale; QALYs: Quality-adjusted Life Years

*the p-value was >0.05 for the between-group difference in mRS score, QALYs and cost

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Table III. Cost-utility analysis based on multiple imputation analysis

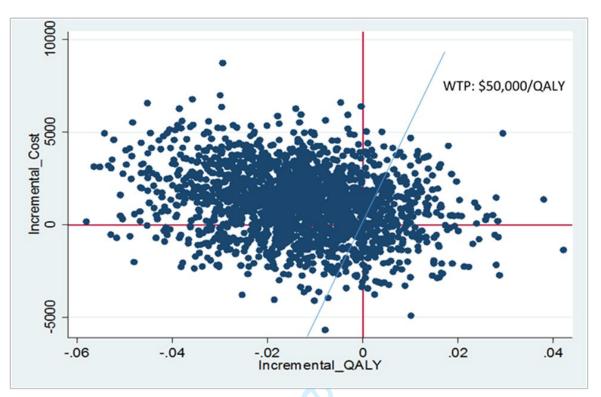
	Efficacy (QALYs)	Cost (AUD)	Probability of being cost-effective
Health Sector Perspect	ve		
Total medical costs	-0.019	\$940	25%
	(-0.044, 0.005)	(-\$4622, \$4682)	
Societal Perspective			
Total cost (excl.	-0.019	\$1704	20%
productivity cost)	(-0.044, 0.005)	(-\$3817, \$7226)	
Total cost (incl.	-0.019	\$1413	23%
productivity cost)	(-0.044, 0.005)	(-\$4044, \$6871)	

QALYs: Quality-adjusted Life Years; AUD: Australian dollar.

*the p-value was >0.05 for the between-group difference in QALYs and cost

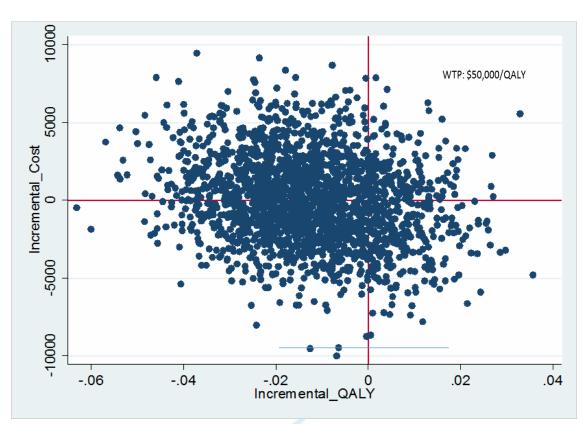
.a. dollar. .crence in QALS

Supplementary document 7: Figures



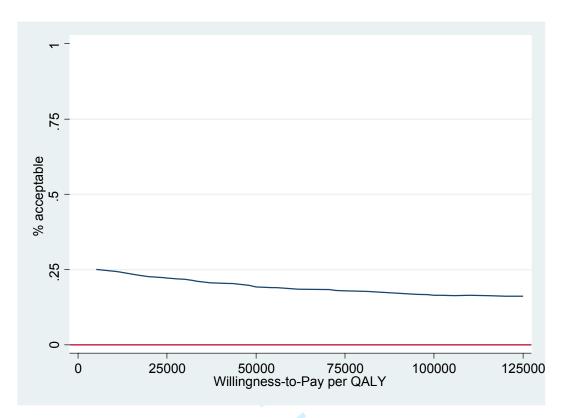
*Probability of VEM being cost-effective is 19%; WTP: willingness-to-pay; QALY: quality adjusted life year

Figure I Cost-effectiveness plane_health sector perspective



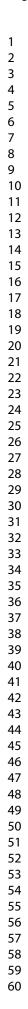
*Probability of VEM being cost-effective is 42%; WTP: willingness-to-pay; QALY: quality-adjusted life year

Figure II Cost-effectiveness plane_ societal perspective (excl. productivity cost)



Note: The probability of VEM being cost-effective decreases with the increasing WTP/QALY threshold because the VEM is associated with less costs

Figure III Cost-effectiveness acceptability curve for medical cost



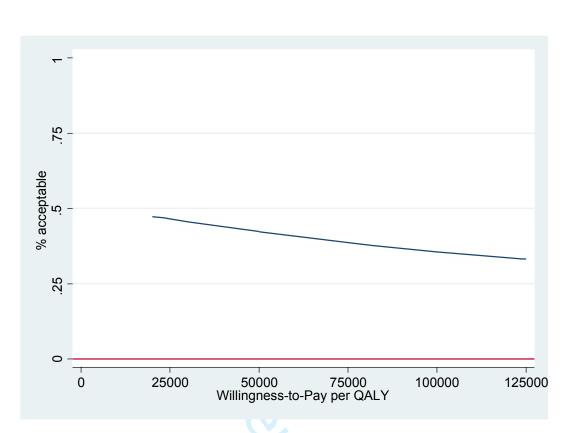


Figure IV Cost-effectiveness acceptability curve for total cost excluding productivity cost

Note: The probability of VEM being cost-effective decreases with the increasing WTP/QALY threshold because the VEM is associated with less costs

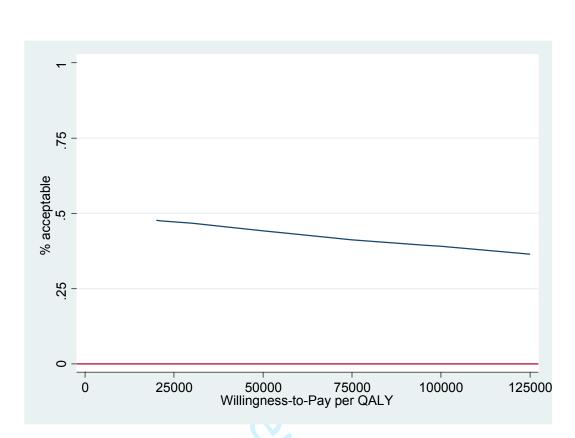


Figure V Cost-effectiveness acceptability curve for total cost including productivity cost

Note: The probability of VEM being cost-effective decreases with the increasing WTP/QALY threshold because the VEM is associated with less costs

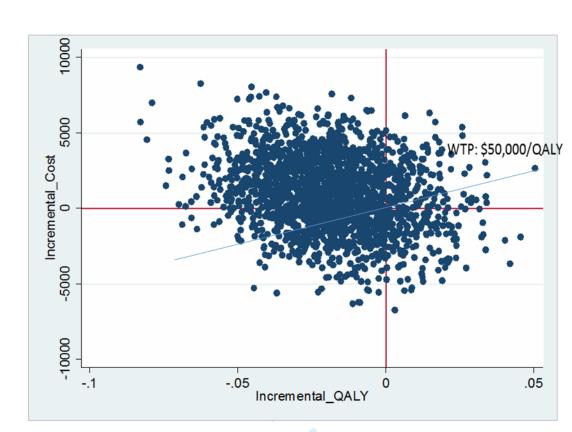


Figure VI Cost-effectiveness plane_health sector perspective (multiple imputation analysis)

WTP: willingness-to-pay; QALY: quality-adjusted life year

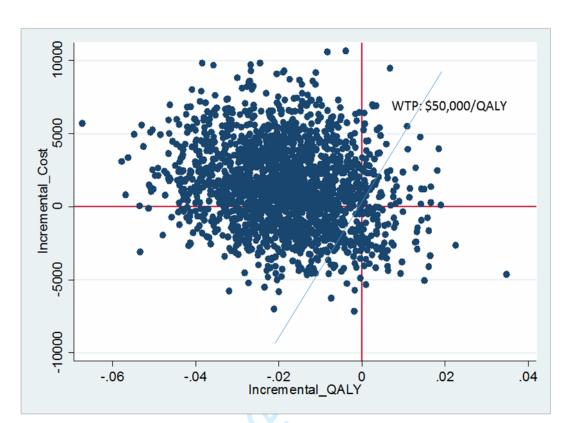
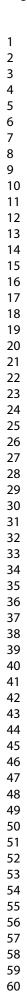
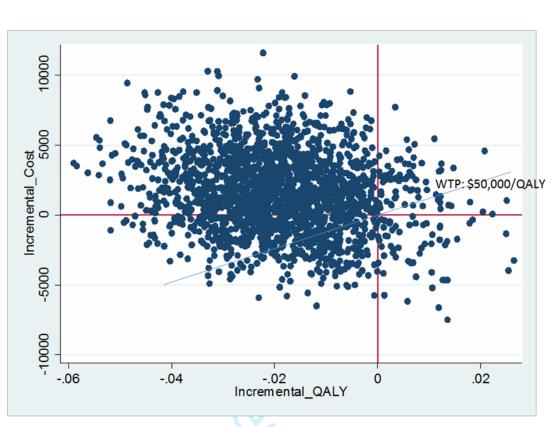


Figure VII Cost-effectiveness plane_ societal perspective including productivity cost (multiple imputation analysis)

WTP: willingness-to-pay; QALY: quality-adjusted life year







WTP: willingness-to-pay; QALY: quality-adjusted life year

References

1. Claesson L, Gosman-Hedstrom G, Johannesson M, Fagerberg B, Blomstrand C. Resource utilization and costs of stroke unit care integrated in a care continuum: A 1-year controlled, prospective, randomized study in elderly patients: the Goteborg 70+ Stroke Study. Stroke 2000;31(11):2569-77.

2. 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(2):390-6.

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Section/item	Item No	Recommendation	page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	4-5
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	7
		Present the study question and its relevance for health policy or practice decisions.	8
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	12
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	9
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	9
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	8
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	11
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	11
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	8-9
Measurement of effectiveness	11a	Single study-based estimates: Describe fully the design features of the single effectiveness stude and why the single study was a sufficient source of clinical effectiveness data.	^{ly} 12
	11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	9
Estimating resources and costs	13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	9-1
	13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	10
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	11-
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	N/
Incremental costs and outcomes	emental costs and outcomes 19 For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.		14-
Characterising uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	14
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
haracterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained byvariations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
tudy findings, limitations,	22	Summarise key study findings and describe how they support the conclusions reached. Discuss	16-
operationability and ourrent.		limitations doubtho/dbnaralisability labeth's findings isod/bdusthatfindings fit with our doubt thousand and	

generalisability, and current For peer reviewing single shell by deneralisability of the conclusions reached. Discuss

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Other		
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conc and reporting of the analysis. Describe other non-monetary sources of support.
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal pol In the absence of a journal policy, we recommend authors comply with International Committ of Medical Journal Editors recommendations.
For consistency, the CHEE	RS statement che	ecklist format is based on the format of the CONSORT statementchecklist