

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

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

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

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 undertaken to tailor the Cost CRF tool to each participating country.



Case Report Form - Cost



National Stroke Research Institute

PATIENT STUDY NUMBER

PATIENT INITIALS

3) CHANGE IN LIVING ARRANGEMENTS

As a consequence of your stroke, have you needed to change your place of residence?

If NO, proceed to question 4.

* Please note: if subject has been a hospital inpatient this is NOT a change of residence

3 months Yes No Unknown

3-12 months Yes No Unknown

DATE OF MOVE

LOCATION

1) / /

- Own home or unit
- Home of relative/friend
- SRS
- Hostel
- Nursing home
- Other

2) / /

- Own home or unit
- Home of relative/friend
- SRS
- Hostel
- Nursing home
- Other

3) / /

- Own home or unit
- Home of relative/friend
- SRS
- Hostel
- Nursing home
- Other

4) / /

- Own home or unit
- Home of relative/friend
- SRS
- Hostel
- Nursing home
- Other

4) AMBULANCE TRANSFERS: EMERGENCY AND NON-EMERGENCY

As a consequence of your stroke, have you required ambulance transport after your acute admission to hospital?*

If NO, please proceed to question 5

3 months Yes No Unknown

3-12 months Yes No Unknown

Count number of ambulance trips (recruitment to 3 months)

Count number of ambulance trips (from 3 to 12 months)

* Include post-acute transfers (eg - acute to rehab)



52036



Case Report Form - Cost



National Stroke Research Institute

PATIENT STUDY NUMBER

PATIENT INITIALS

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 No Unknown

3-12 months Yes No Unknown

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)

Time 1 - Rehabilitation service name	Rehab service code	Start date	Cease date	Total number of SESSIONS	If patient not discharged at 12 month assessment, cross box.
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
Time 2 - Rehabilitation service name	Rehab service code	Start date	Cease date	Total number of SESSIONS	If patient not discharged at 12 month assessment, cross box.
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
Time 3 - Rehabilitation service name	Rehab service code	Start date	Cease date	Total number of SESSIONS	If patient not discharged at 12 month assessment, cross box.
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
Time 4 - Rehabilitation service name	Rehab service code	Start date	Cease date	Total number of SESSIONS	If patient not discharged at 12 month assessment, cross box.
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>



52036



Case Report Form - Cost



PATIENT STUDY NUMBER

PATIENT INITIALS

10) HOME MODIFICATIONS

Has your home been modified as a consequence of your stroke?
e.g. installation of rails, bathroom modifications, installation of ramp(s), kitchen modifications etc

3 months Yes No Unknown

3-12 months Yes No Unknown

If NO, proceed to question 11

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

SUPPLIERS

1 = Hospital/rehabilitation centre
2 = Patient/family

3 = Veteran's Affairs
4 = Local Council

5 = Housing commission
6 = Charity

7 = Other (specify)

Type of modification
(check box for each type supplied)

Rail(s) for steps/stairs

Who supplied the modification?

1 2 3 4 5 6 7

If supplier is "other", please specify

Cost to you/family* - \$

Ramp(s)

1 2 3 4 5 6 7

Cost to you/family* - \$

Platform step(s)

1 2 3 4 5 6 7

Cost to you/family* - \$

Shower, bath and toilet rail(s)

1 2 3 4 5 6 7

Cost to you/family* - \$

Shower(s) modification

1 2 3 4 5 6 7

Cost to you/family* - \$

Toilet(s) modification

1 2 3 4 5 6 7

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 7

Cost to you/family* - \$

Other modification (specify below)

Other home modification - 1

1 2 3 4 5 6 7

Cost to you/family* - \$

Other home modification - 2

1 2 3 4 5 6 7

Cost to you/family* - \$

If total costs includes any aids, describe in brief below (see also list of aids on page 33):

* 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 \$



52036



Case Report Form - Cost



National Stroke Research Institute

PATIENT STUDY NUMBER

PATIENT INITIALS

3) CHANGE IN LIVING ARRANGEMENTS

As a consequence of your stroke, have you needed to change your place of residence?

If NO, proceed to question 4.

* Please note: if subject has been a hospital inpatient this is NOT a change of residence

3 months Yes No Unknown

3-12 months Yes No Unknown

DATE OF MOVE

LOCATION

1) / /

- Own home or unit
- Home of relative/friend
- SRS
- Hostel
- Nursing home
- Other

2) / /

- Own home or unit
- Home of relative/friend
- SRS
- Hostel
- Nursing home
- Other

3) / /

- Own home or unit
- Home of relative/friend
- SRS
- Hostel
- Nursing home
- Other

4) / /

- Own home or unit
- Home of relative/friend
- SRS
- Hostel
- Nursing home
- Other

4) AMBULANCE TRANSFERS: EMERGENCY AND NON-EMERGENCY

As a consequence of your stroke, have you required ambulance transport after your acute admission to hospital?*

If NO, please proceed to question 5

3 months Yes No Unknown

3-12 months Yes No Unknown

Count number of ambulance trips (recruitment to 3 months)

Count number of ambulance trips (from 3 to 12 months)

* Include post-acute transfers (eg - acute to rehab)



52036



Case Report Form - Cost



National Stroke Research Institute

PATIENT STUDY NUMBER

PATIENT INITIALS

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 No Unknown

3-12 months Yes No Unknown

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)

Time 1 - Rehabilitation service name	Rehab service code	Start date	Cease date	Total number of SESSIONS	If patient not discharged at 12 month assessment, cross box.
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
Time 2 - Rehabilitation service name	Rehab service code	Start date	Cease date	Total number of SESSIONS	If patient not discharged at 12 month assessment, cross box.
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
Time 3 - Rehabilitation service name	Rehab service code	Start date	Cease date	Total number of SESSIONS	If patient not discharged at 12 month assessment, cross box.
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
Time 4 - Rehabilitation service name	Rehab service code	Start date	Cease date	Total number of SESSIONS	If patient not discharged at 12 month assessment, cross box.
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>



52036



Case Report Form - Cost



PATIENT STUDY NUMBER

PATIENT INITIALS

9) COMMUNITY SERVICES

9a) Did you receive any community services in the year PRIOR to your stroke?

Yes No Unknown

Community services are individual care services provided at home and do NOT include rehabilitation therapy.

If NO, proceed to question 9b.

If YES, which service/s did you receive in the year PRIOR to your stroke?

How many times in the past year did you receive the service?

Community service codes

- 1 = Nursing Service
- 2 = Delivered Meals
- 3 = Personal Care (Bath/Shower)
- 4 = Housework help
- 5 = Gardening/home maintenance
- 6 = Home respite
- 7 = Other service, specify

Which service did you receive? (One service code per line)

1 2 3 4 5 6 7

1 2 3 4 5 6 7

1 2 3 4 5 6 7

1 2 3 4 5 6 7

If "other" (code 7), please specify

9b) Have you received community services SINCE the stroke?

Community services are individual care services provided at home and do NOT include rehabilitation therapy.

If NO, proceed to question 10.

If YES, which service/s did you receive AFTER your stroke?

For each service, complete a separate line. If a service is ongoing at 3 month interview, enter data for 3 months, and then add service data for 3-12 months on a separate line.

3 months Yes No Unknown

3-12 months Yes No Unknown

Community service codes

- 1 = Nursing Service
- 2 = Delivered Meals
- 3 = Personal Care (Bath/Shower)
- 4 = Housework help
- 5 = Gardening/home maintenance
- 6 = Home respite
- 7 = Other service, specify

Which service did you receive? (One service code per line)

1 2 3 4 5 6 7

1 2 3 4 5 6 7

1 2 3 4 5 6 7

1 2 3 4 5 6 7

1 2 3 4 5 6 7

1 2 3 4 5 6 7

If "other" (code 7), please specify

How many times did you receive the service?

How many hours per service?

Note: hours per service NOT applicable to delivered meals



52036



Case Report Form - Cost



National Stroke Research Institute

PATIENT STUDY NUMBER

PATIENT INITIALS

12) PRIVATE PHYSIOTHERAPY

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

3 months Yes No Unknown

If no, proceed to question 13

3-12 months Yes No Unknown

If yes, number of sessions - 3 months

3-12 months

13) RESPITE CARE

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

3 months Yes No Unknown

If NO, proceed to question 14

3-12 months Yes No Unknown

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

3-12 months

14) EMPLOYMENT STATUS/ PAID WORK

Were you working up to the time of your stroke?

Yes No Unknown

If YES, what was the nature of this work?

Full time Part time

How many hours did you work each week?

Since the stroke, have you returned to this work?

3 months Yes No Unknown

3-12 months Yes No Unknown

Have you returned to normal hours or decreased hours?

3 months Normal Decreased

3-12 months Normal Decreased

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

Record average amount per week over the 3 month period

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

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



52036



Case Report Form - Cost



PATIENT STUDY NUMBER

--	--	--	--

PATIENT INITIALS

--	--	--

15) INFORMAL CARE - 3 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.

15a) OVER THE LAST WEEK, have you received any assistance with your daily activities from a carer as a result of the stroke? Yes No

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

15b) 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 question 15c)

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

Hours

--	--	--

15c) 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 15d)

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

Hours

--	--	--

15d) 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

--	--	--



52036



Case Report Form - Cost



PATIENT STUDY NUMBER

--	--	--	--	--

PATIENT INITIALS

--	--	--

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

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 question 16c)

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

Hours

--	--	--

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)

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

Hours

--	--	--

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.

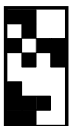
If NO, you have finished the questions.

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



52036

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.

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

Resource items	Unit cost (AUD)				
	AU	NZ	UK	SG	MA
<i>Healthcare</i>					
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 facility (per/session)	\$239	\$212	\$922	\$36	\$51
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
<i>Non-healthcare</i>					
Community services	<i>Not listed here due to the number of items</i>				
Home modifications	<i>Cost was provided by individual patients</i>				
Special aids and equipment	<i>Not listed here due to the substantial number of items</i>				
Accommodation changes	<i>Not listed here due to the number of items</i>				
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 ¹		

<i>Unit cost for intervention[#]</i>					
Hospital physiotherapist (per hour)	\$33	\$32	\$30	\$21	\$5
Hospital nurse (per hour)	\$30	\$25	\$29	\$21	\$5

AU: Australia; NZ: New Zealand; UK: United Kingdom; SG: Singapore; MA: Malaysia;

Sources of CPI:

Australian Bureau of Statistics. Consumer price index inflation calculator. Accessed from: <http://www.Abs.Gov.Au/websitedbs/d3310114.Nsf/home/consumer+price+index+inflation+calculator>. 2017

Office for National Statistics. Inflation and price indices. Accessed from:

<https://www.Ons.Gov.Uk/economy/inflationandpriceindices>. 2017

Department of Statistics Singapore. Consumer price index. Accessed from: <https://data.Gov.Sg/dataset/consumer-price-index-annual>. 2017

Statistics New Zealand. Consumer price index, accessed from:

http://www.Stats.Govt.Nz/browse_for_stats/economic_indicators/cpi_inflation/info-releases.aspx. 2017

Department of Statistics Malaysia OP. Consumer price index malaysia. Accessed from:

https://www.Dosm.Gov.My/v1/index.php?R=column/cthemebycat&cat=106&bul_id=zi9pmutpvzixb042mlptt1buellazz09&menu_id=bthzthqxn1zqmvf6a2i4rkzondfkqt09. 2017

* severity was determined by baseline NIHSS score; † severity was classified by baseline mRS score; ‡ it is the per day cost; § cost was assigned according to the baseline mRS score (mild 0-2; moderate 3-5; severe 6); ¶ the National Survey of Household Income was provided on gender basis, so the weekly earnings for UK patients were assigned corresponding to this; # hourly wage of hospital physiotherapist and nurse were assigned; N/A: not applicable. Main sources of unit cost: AU: Independent Hospital Pricing Authority (IHPA), Australia, National Efficient Price Data (2015-16); National Hospital Cost Data collection (<https://www.ihsa.gov.au/publications/australian-public-hospitals-cost-report-2013-2014-round-18>); Department of Health, Revised residential care subsidies (<https://agedcare.health.gov.au/aged-care-funding/aged-care-subsidies-and-supplements>); Australian Bureau of Statistics (<http://www.abs.gov.au/AUSSTATS/abs@.nsf/allprimarymainfeatures/E9FF9F13B417A488CA257F630014DF30?opendocument>); NZ: Ministry of Health (<http://www.health.govt.nz/nz-health-statistics/data-references/weighted-inlier-equivalent-separations>); World Health Organisation (<http://www.who.int/choice/country/nzl/cost/en/>); Cost Resource Manual Version 2.2 (<https://www.pharmac.govt.nz/assets/pfpa-v2-2-cost-resource-manual.pdf>); study by Te Ao et al 2011 (Te Ao BJ et al. Are stroke units cost effective? Evidence from a New Zealand stroke incidence and population-based study. *Int. J. Stroke.* 2012;7:623-630); Statistics New Zealand (http://www.stats.govt.nz/browse_for_stats/income-and-work/employment_and_unemployment/LabourMarketStatistics_HOTJun15qtr.aspx); District Health Board, Multi Employer Agreement, New Zealand Nurses Organisation (<http://www.bopdnh.govt.nz/media/58613/psa-ronz-allied-meca-2015-2017.pdf>); UK: National Health Service (NHS) reference costs 2014 to 2015, United Kingdom (<https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015>); NICE Technology Appraisal (Davis,S., Holmes,M., Simpson,E., Sutton,A. Alteplase for the treatment of acute ischaemic stroke [review of technology appraisal 122]: A Single Technology Appraisal. *SCHARR, The University of Sheffield* 2012, <https://www.nice.org.uk/guidance/ta264/documents/stroke-acute-ischaemic-alteplase-review-of-ta122-evidence-review-group-report2>); Personal Social Services Research Unit (PSSRU) (<http://www.pssru.ac.uk/>); Information Services Division, Scotland (<http://www.isdscotland.org/>); Annual Survey of Hours and Earnings 2015, Office for National Statistics (<https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/bulletins/annualsurveyofhoursandearnings/2015provisionalresults>); Payscale UK (http://www.payscale.com/research/UK/Job=Care_Worker/Hourly_Rate); NHS pay and benefits (<https://www.healthcareers.nhs.uk/about/careers-nhs/nhs-pay-and-benefits/agenda-change-pay-rates>); SG: Ministry of Health, Hospital Bill Sizes, Singapore (https://www.moh.gov.sg/content/moh_web/home/costs_and_financing/HospitalBillSize/stroke.html); Outpatient Charges, Singapore General Hospital (<https://www.sgh.com.sg/patient-services/charges-payment/pages/outpatient-charges.aspx>); Charges, Ren Ci Hospital (<http://www.renci.org.sg/patients-guide/charges-2/>); Hospital rates and charges, Bright Vision Hospital (<http://www.bvh.org.sg/hospital-rate-charge.html>); Ministry of Manpower (<http://stats.mom.gov.sg/Pages/Occupational-Wages-Tables2014.aspx>); MA: study by Mohd Nordin et al 2012 (Mohd Nordin et al.: Estimating cost of in-patient medical care for stroke using Casemix data. *BMC Health Services Research* 2012 12(Suppl 1):P10.); Ministry of Health Malaysia (<http://www.moh.gov.my/english.php/pages/view/160>); Study by Akhavan Hejazi et al 2015 (Akhavan Hejazi SM, et al. Cost of post-stroke outpatient care in malaysia. *Singapore Med. J.* 2015;56:116-119); Department of Statistics Malaysia (<https://www.dosm.gov.my/v1/index.php?r=column/pdfPrev&id=czRyNkJlBDFyYXJFbU5YTVJlV1BHZZ09>).

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).

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	
	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%)
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%)
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%)
Rehabilitation provided at home/nursing 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%)
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%)
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%)

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

Table II. Missing pattern analysis based on logit regression

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. Outcomes

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

Modified Rankin Scale Score	UC group n=1050		VEM group 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).

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

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

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, $p < 0.0001$).

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 Perspective						
Total medical costs	0.030 (-0.022, 0.082)	-0.013 (-0.041, 0.016)	\$1082 (-\$2399, \$4563)	0.042 (-0.008, 0.092)	-0.019 (-0.046, 0.007)	\$940 (-\$2584, \$4465)
Societal Perspective						
Total cost (excl. productivity cost)	0.030 (-0.022, 0.082)	-0.013 (-0.041, 0.016)	-\$6 (-\$5703, \$5690)	0.042 (-0.008, 0.092)	-0.019 (-0.046, 0.007)	\$1704 (-\$5423, \$8832)
Total cost (incl. productivity cost)	0.030 (-0.022, 0.082)	-0.013 (-0.041, 0.016)	\$102 (-\$6945, \$7149)	0.042 (-0.008, 0.092)	-0.019 (-0.046, 0.007)	\$1413 (-\$5940, \$8766)

ITT: intention to treatment; mRS: modified Rankin Scale; AUD: Australian dollars

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

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

	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)

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

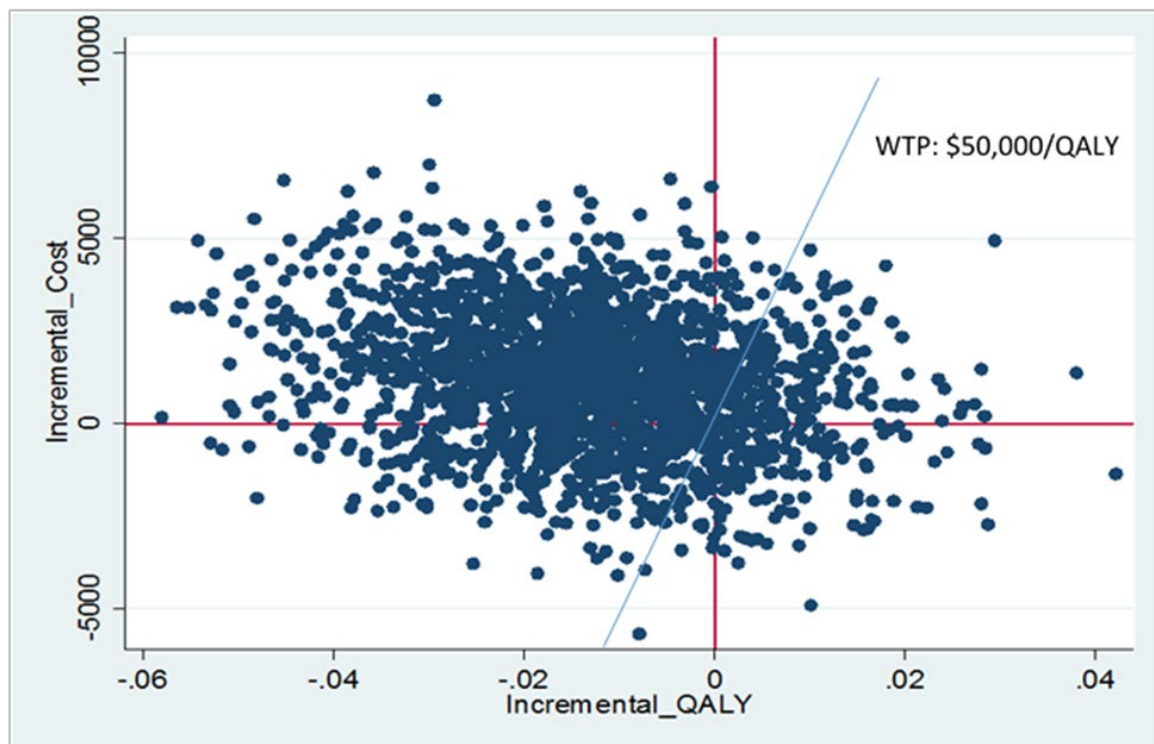
Table III. Cost-utility analysis based on multiple imputation analysis

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

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

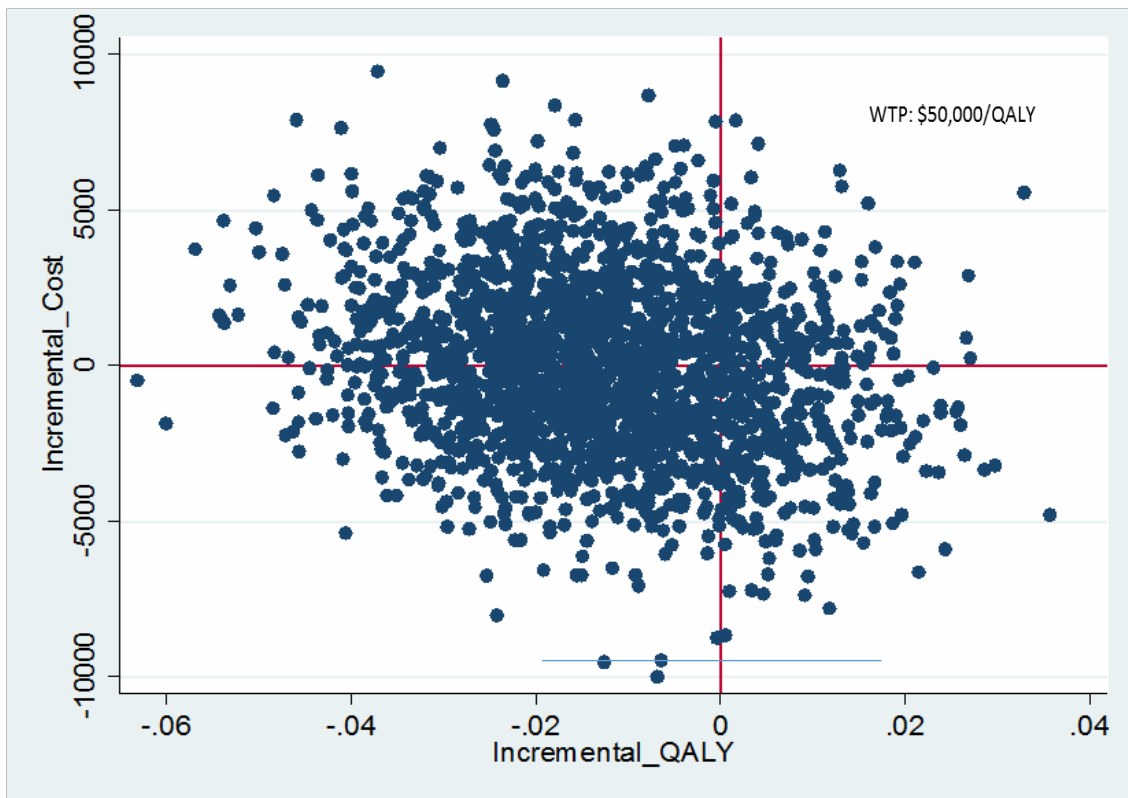
*the p-value was >0.05 for the between-group difference in QALYs and cost

Supplementary document 7: Figures



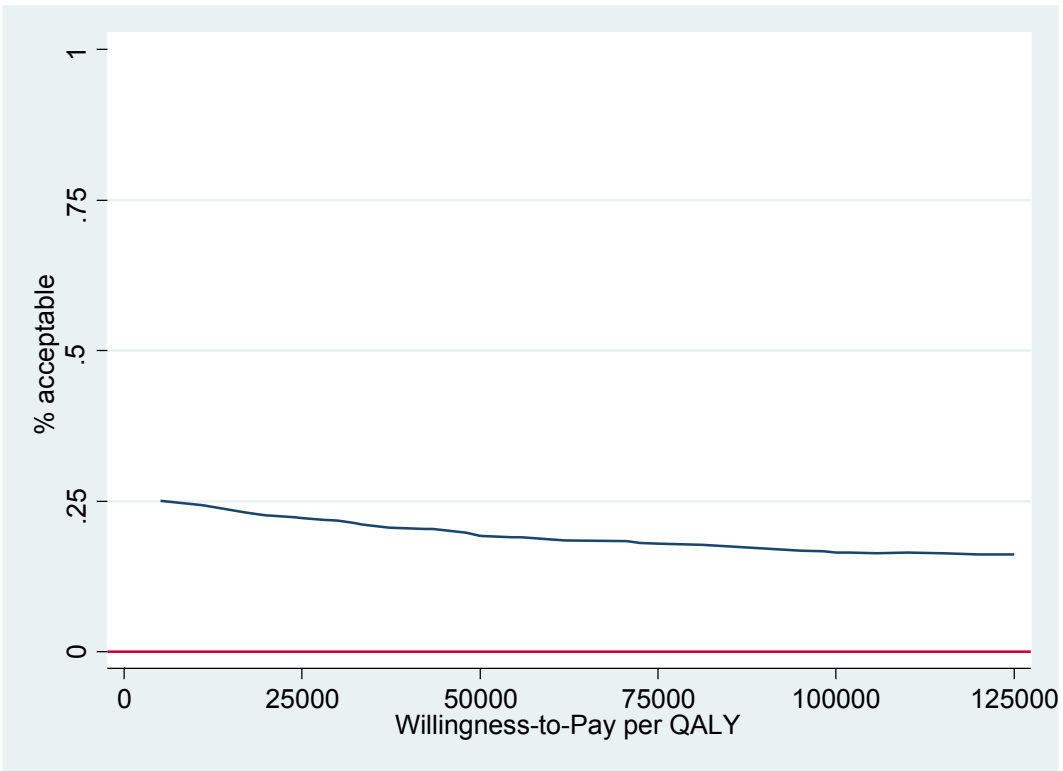
*Probability of VEM being cost-effective is 19%; WTP: willingness-to-pay; QALY: quality adjusted life year

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

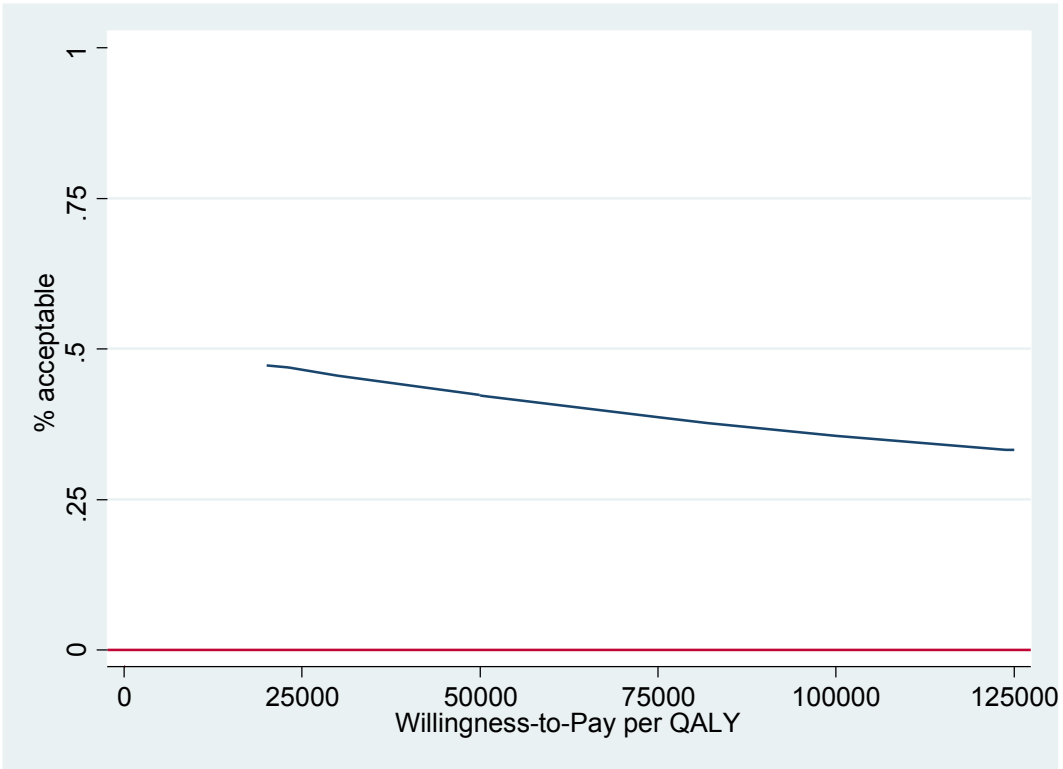


Figure IV Cost-effectiveness acceptability curve for total cost excluding productivity cost

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

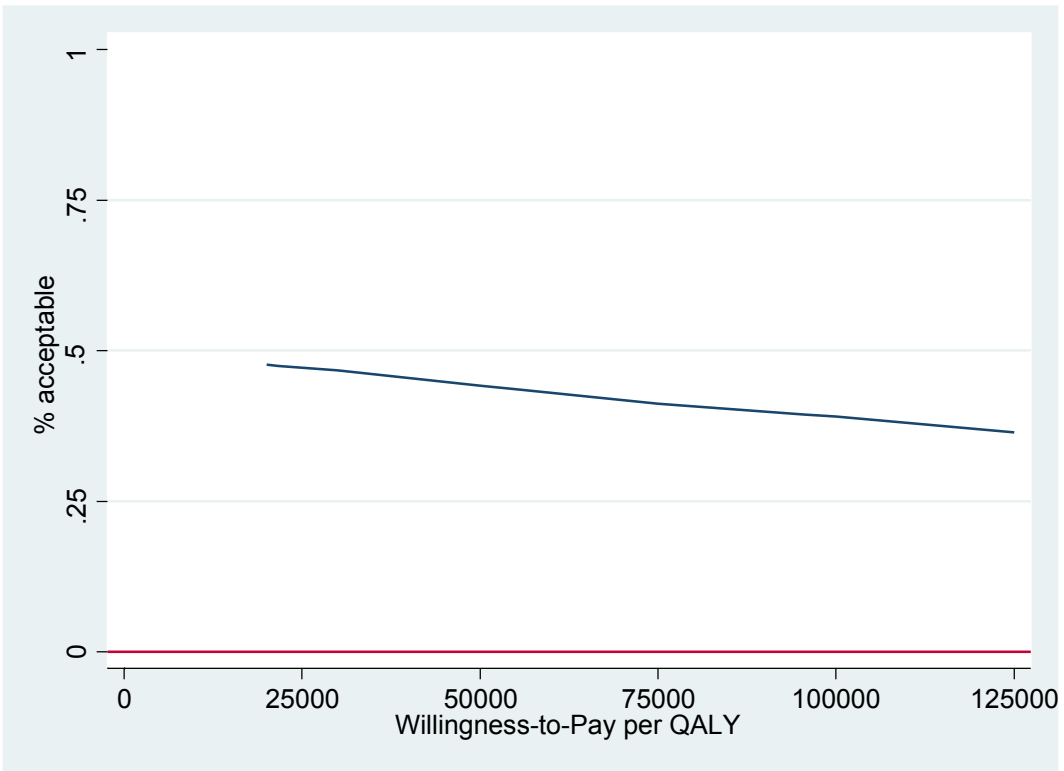


Figure V Cost-effectiveness acceptability curve for total cost including productivity cost

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

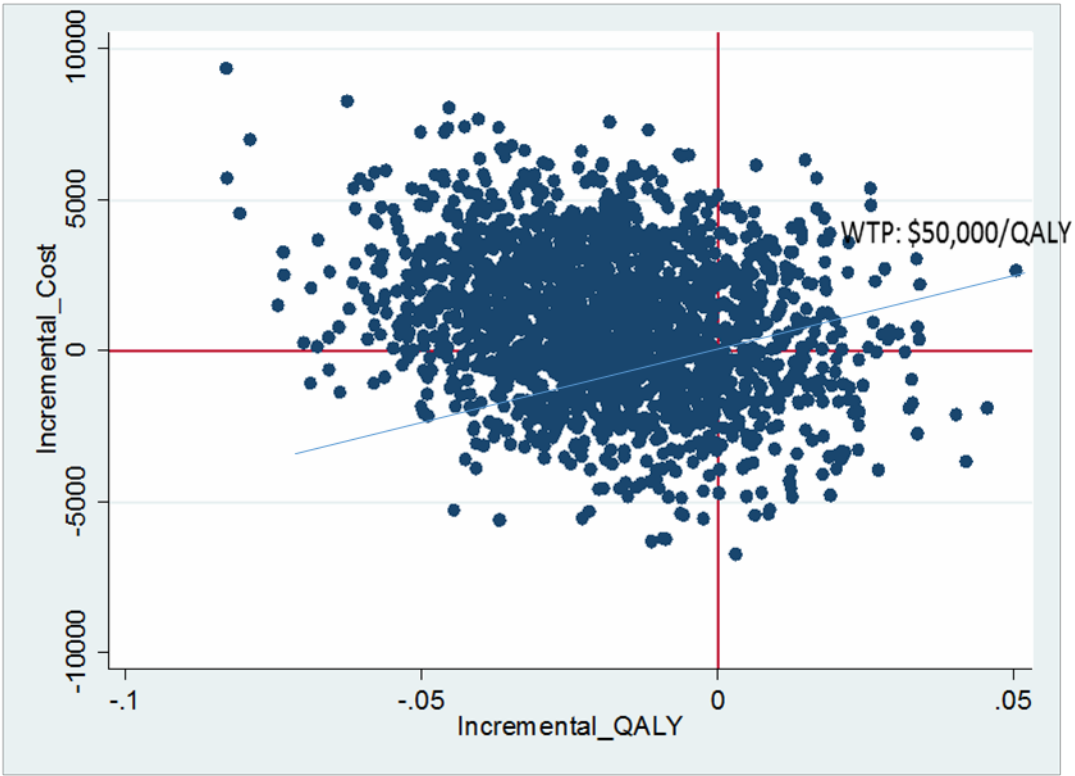


Figure VI Cost-effectiveness plane_ health sector perspective (multiple imputation analysis)

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

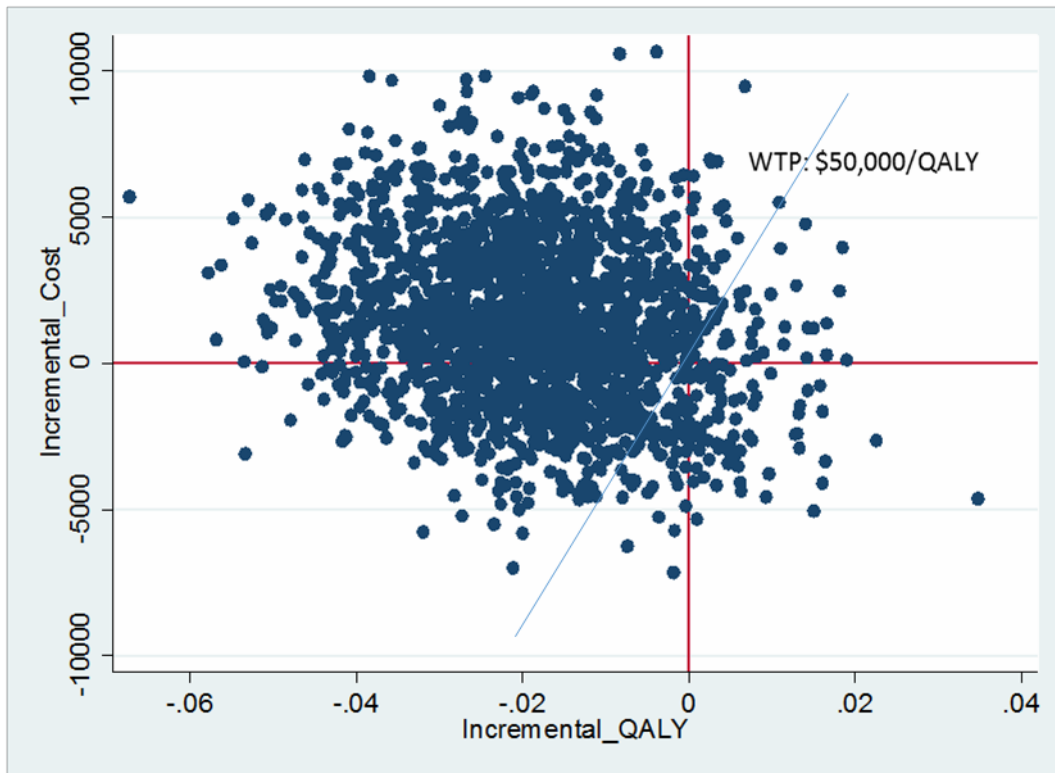


Figure VII Cost-effectiveness plane_ societal perspective including productivity cost (multiple imputation analysis)

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

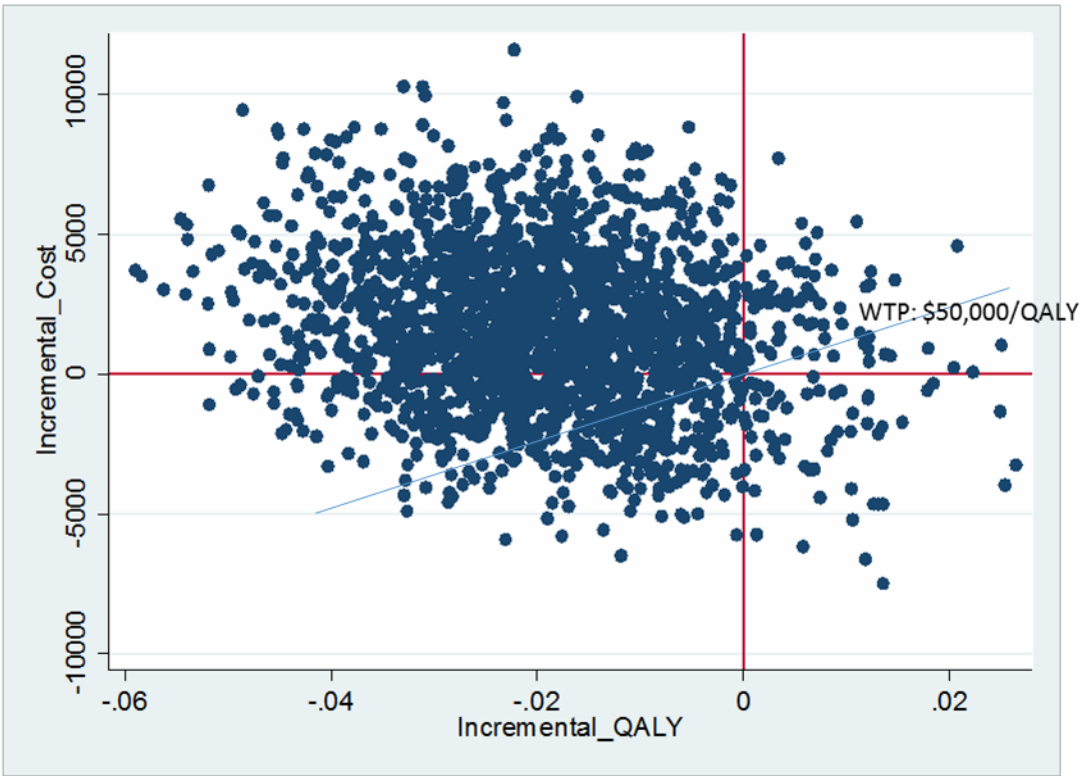


Figure VIII Cost-effectiveness plane_ societal perspective excluding productivity cost (multiple imputation analysis)

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.