

# Medical Decision Making

## Honest outcome mapping: using statistical simulation to map health consequences onto a common scale

Journal:	<i>Medical Decision Making</i>
Manuscript ID:	Draft
Manuscript Type:	Original Manuscript
Date Submitted by the Author:	n/a
Complete List of Authors:	Minton, Jonathan; University of Glasgow, College of Social Sciences Stevenson, Matthew; University of Sheffield, School of Health and Related Research Crott, Ralph; Catholic University of Louvain, IRSS
APPLICATION AREAS:	Stroke < NEUROLOGY, PERFORMANCE MEASUREMENT, PREVENTIVE SERVICES
DETAILED METHODOLOGY:	ECONOMICS (HEALTH), Cost Utility Analysis < ECONOMICS (HEALTH), EVIDENCE SYNTHESIS, MATHEMATICAL MODELS AND DECISION ANALYSIS, Discrete Event Simulation < MATHEMATICAL MODELS AND DECISION ANALYSIS, Simulation Methods (Monte Carlo Methods,simulation, etc) < MATHEMATICAL MODELS AND DECISION ANALYSIS, PREFERENCES AND QUALITY OF LIFE, EQ-5D < PREFERENCES AND QUALITY OF LIFE, QOL in Special Populations < PREFERENCES AND QUALITY OF LIFE, Utility Inconsistencies < PREFERENCES AND QUALITY OF LIFE, Utility Measurement < PREFERENCES AND QUALITY OF LIFE, STATISTICAL METHODS

SCHOLARONE™  
Manuscripts

**Title Page**

***Title***

Honest outcome mapping: using statistical simulation to map health consequences onto a common scale

***Names, addresses, and positions of all authors***

**Corresponding Author:**

Jonathan Minton PhD  
Research Associate  
Advanced Quantitative Methods Network (AQMeN)  
The University of Glasgow  
Adam Smith Building  
Glasgow  
G12 8RT

**Second Author:**

Professor Matthew Stevenson PhD  
Professor of Health Economics  
Health Economic and Decision Science  
School of Health and Related Research  
The University of Sheffield  
Regent Court  
30 Regent Street  
Sheffield  
S1 4DA

**Third Author:**

Dr Ralph Crott PhD  
Associate Research Fellow  
IRSS  
Catholic University of Louvain  
Brussels  
Belgium

***Details of funding***

*Financial support for this study was provided in part by a grant from the National Institute for Health Research Health Technology Assessment Programme (Project code 08/45/01). The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report.*

**Word Count:**

3852 words

For Peer Review

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Abstract**

**Background:** Disease severity is often measured using different and incompatible systems of classification. This is problematic in economic evaluations if costs and consequences (health related quality of life (HRQoL) are reported using different systems of classification. Methods for mapping between categories are required to allow these different sources of evidence to be used. Using stroke as a case study, this paper describes a method for mapping HRQoL from more (seven) to fewer (three or four) categories in a way which does not underrepresent the additional uncertainty involved in this indirect use of evidence.

**Methods:** An informal Bayesian simulation approach was used to estimate, with credible intervals (CrIs), the estimated mean HRQoLs of patients in each of three discrete states (dead, dependent stroke, independent stroke), given summary data reported for each of seven discrete states. The approach incorporates the known uncertainty about both the expected HRQoL in each of the seven states and known uncertainty about the proportion of patients in each of the seven categories. The three-state estimates produced were compared with older estimates to assess face validity.

**Results:** Three-state and four-state mappings were performed. The new three-state estimates produced were similar to much older estimates, but differed in ways which suggest improved patient outcomes due to a better quality of stroke care.

**Limitations:** A number of assumptions needed to be made in order to produce estimates of the HRQoL in each of the reduced states.

**Conclusions:** Data reported at different levels of aggregation can be used alongside each other using a method which appropriately incorporates multiple sources of parameter uncertainty into the estimates produced.

# 1. Manuscript

## 1.1. Introduction

This paper describes a simulation-based approach for mapping utility scores reported for a larger number of states onto a smaller number of states, where the frequency of patients in each outcome state is also reported. The method uses a data reduction technique that involves simulated data reconstitution as an intermediate stage. The method differs from regression-type mapping or cross-walking approaches in that it involves producing simple representations of the individual level data as an intermediate stage to mapping from a larger number to a smaller number of utility states. (1)

We provide two case studies. In the first case study, we show how the approach is used for estimating utility multipliers associated with being in an independent or dependent state following a stroke, given utility estimates and proportions reported by Modified Rankin Scale (mRS), which has seven mutually exclusive stroke severity states. (2) In the second case study, we show how the approach can be extended to produce estimates for the mean utility values associated with states on the Glasgow Outcome Scale (GOS) for traumatic brain injuries. Both examples make use of the data reported in an MDM paper reporting mRS outcomes, but involve collapsing the seven states into three states in the first example, and four states in the second example. In the first example, a single source of data is used to estimate both the mean utilities within each of the mRS states and the proportion of patients in each state, whilst in the second example this source of data is used to estimate the mean utilities, but the proportions in each state are estimated using a different data source.

The method described was developed when constructing a model of the consequences of prescribing oral anticoagulants (OACs) in the management of atrial fibrillation (AF). (3,4) OACs reduce stroke risk but can lead to intracranial haemorrhages (ICHs) which can cause brain injury. Like strokes, ICHs can be fatal, and cause qualitatively similar kinds of disablement and quality of life impairment. The management of AF therefore involves balancing the costs and consequences of prescribing compared with not prescribing an OAC. (3,4) Being able to derive estimates for the consequences of both stroke and ICH therefore improves the consistency of the estimates used and validity of the model results.

## 1.2. Method

### 1.2.1. Information required

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1 In order to use the approach described here, two sorts of information and one assumption is  
2 needed. The first type of information needed is the mean utilities associated with each of the larger  
3 number of health states (mRS states in this paper). The second type of information needed is the  
4 distribution of patients between these health states. In our examples, the first two pieces of  
5 information were provided in a previous paper published in MDM in 2010, which we refer to as our  
6 ‘source paper’.(2)

7 The assumption needed is about how larger number of categories (mRS states) map onto to the  
8 smaller number of states. In the first example, the smaller number of states are: dead; dependent  
9 stroke; and independent stroke. In the second example, the smaller number of states are the GOS  
10 states.

11 **1.2.2. The Modified Rankin Scale (mRS)**

12 The mRS is a commonly used measure of disability or dependence in daily activities following a  
13 stroke. It was introduced in its current form by van Swieten et al in 1988(5), and originally based on a  
14 1957 paper by J Rankin.(6) The mRS is a seven level ordinal scale, with scores ranging from 0-6  
15 inclusive, and has good inter-rater reliability.(7)

16 **1.2.3. The source paper**

17 The source paper used data from the Oxford Vascular Study (OXVASC). OXVASC is a large scale  
18 population-based cohort, initiated in 2002, involving almost 100,000 individuals registered in  
19 Oxfordshire, England.(8) The source paper used 1,283 patients from this study, recruited between  
20 April 2002 and March 2007, who had suffered either stroke or transient ischemic attack (TIA). These  
21 patients were followed-up for up to 24 months. The condition of the patients was assessed using the  
22 disease specific measure of the mRS, as well as the EuroQoL 5 Dimension (EQ-5D) tool. Based on  
23 this, the EQ-5D utilities associated with each state were estimated. (2)

24 The source paper reported that, of the 1,283 patients who had a stroke within the Oxford vascular  
25 study (OXVASC) cohort, 24.8% (319 / 1,283) were dead within 24 months. Of those who survived,  
26 mRS scores following the stroke was graded according to the modified Rankin Scale (mRS) 24  
27 months after the event in 425 patients.(2) For simplicity this 24 month state is assumed to be the  
28 patient’s long-term condition, and the patients for whom mRS outcomes were reported were  
29 assumed to be representative of those for whom the data were not collected; this is known as the  
30 missing completely at random (MCAR) assumption. (9) The ordinary least squares (OLS) based mean  
31 estimates for the utility associated with each state, combined with the standard deviations around  
32 these mean estimates, were also reported in the source paper. The numbers used from the source  
33 paper to estimate the distribution of patients in different mRS categories are presented in Table 1.

[Table 1 about here]

#### 1.2.4. Category mapping assumptions made

In each of the examples presented in this paper, different categorisation assumptions were made about how each of the mRS categories mapped onto a smaller number of categories. The mappings used are shown in Table 2. For the first example, we assumed that an independent stroke outcome corresponds to an mRS state 0, 1 or 2, and that a dependent stroke outcome corresponds to an mRS state 3, 4, and 5. Death is mRS state 6, and was assumed throughout to have a utility value of 0.

[Table 2 about here]

In the second example, we looked at the verbal descriptions of each of the mRS states, and each of the GOS states, and from this made the assumption that GOS 5 ('good recovery') corresponds to mRS states 0 or 1, that GOS 4 ('moderately disabled') corresponds to mRS states 2 or 3, and that GOS 3 ('severely disabled') corresponds to mRS states 4 or 5. GOS 2 ('persistent vegetative state') was assumed to have no utility, and so correspond, alongside GOS 1 ('dead') with mRS 6 ('dead').

#### 1.2.5. Graphical representations of the method

Figure 1 shows how the method has been applied in the first example, where the aim is to map the mRS states onto the three mutually exclusive states of 'independent stroke', 'dependent stroke' and 'dead'. Figure 2 shows the equivalent method for mapping from the mRS states to the GOS states. As the figures show, the approaches are identical apart from the final stages, where mRS state information are combined in different ways. For this reason the stages which are common to both examples will be described first. In both examples the process is repeated 10,000 times.

[Figure 1 about here]

[Figure 2 about here]

#### 1.2.6. Simulating proportions in each mRS state

The proportions in each of the mRS states at 24 months, which was assumed to be the long-term outcome, were simulated in a two-stage process using data from the source paper. In the first stage (Node 1 in both Figure 1 and Figure 2) the proportion that dies as a result of suffering a stroke is first simulated using a binomial distribution. In the second stage (Node 2a in both Figure 1 and Figure 2), the distribution of those alive in each of the six living mRS states (mRS categories 0 to 5) was simulated using a Dirichlet distribution using cell counts from the source paper at 24 months as input parameters. These simulated proportions were then stored for later use (Node 3a in both Figure 1 and Figure 2).

**1.2.7. Simulating utilities associated with each mRS state**

The source paper presents mean EQ-5D utility values and standard deviations for each mRS state. These values were used to parameterise normal distribution functions which were repeatedly sampled from to produce a large number of simulated utility distributions for each state. This process allows parameter uncertainty at this stage to be propagated through to later stages rather than disregarded.

**1.2.8. Converting simulated utility values into utility multipliers**

The mRS-based HRQoL values were estimated from a subset of the OXVASC population. These values reflect both the effect of stroke on HRQoL and also the underlying HRQoL of the patient population, which they would have experienced even if they had not suffered a stroke. The effect of stroke alone on the HRQoL needs to be estimated based on these values, but the OXVASC study did not report HRQoL for a matched control group. Instead, we assumed that the mildest mRS state, mRS 0, indicated that the stroke had no long term impact on HRQoL, and so the HRQoL associated with mRS 0 represented the baseline HRQoL of the clinical population.

Having made this assumption, the effect of different degrees of severity of stroke on HRQoL can be estimated by comparing HRQoL in higher mRS states with the HRQoL in the baseline state (mRS 0). Either an additive or a multiplicative approach could be used for this comparison. In the additive approach, the HRQoL estimates from more severe states are subtracted from the baseline state, to produce *utility decrements* associated the clinical event. In the multiplicative approach, the HRQoL in more severe states was divided by that in the baseline state to produce *utility multipliers*.

The multiplicative approach was used in this paper, and so utility multipliers were produced by dividing estimates of the HRQoL in more severe states by HRQoL estimates in the mRS 0 state. The effect of making the additive assumption instead could be explored in further research.

**1.2.9. Simulating relative proportions of mRS states in each of the collapsed states**

Within the first example, illustrated in Figure 1, the independent state category (Node 4a) is comprised of a mix of the three component states mRS 0, mRS 1 and mRS 2, and the dependent state category is comprised of a mix of the three component states mRS 3, mRS 4 and mRS 5. However, neither the independent state category nor the dependent state categories are composed of equal amounts of each component state, and so an equal weighting should not be assumed. It would also be wrong to disregard parameter uncertainty due to the finite sample size on which



these estimates are based. For this reason, Dirichlet distributions were used and repeatedly resampled from. The weight of the each of the component states in the collapsed states was calculated for each Dirichlet draw. This process is illustrated graphically for a single draw from the Dirichlet distribution in Figure 3.

[Figure 3 about here]

#### **1.2.10. Producing weighted utility multiplier estimates for independent and dependent stroke categories**

Simulated distributions of the utility values associated with the independent and dependent states were produced by combining estimates of the relative proportions in each of the component states with estimates of the utility multipliers associated with each of the mRS states. The results of this process are distributions of predicted values for the utility associated with independent and dependent stroke states which take into account both uncertainty in the predicted utilities for each of the component states, and uncertainty in the true proportion of each component state within each collapsed state.

#### **1.2.11. Simulating the distribution of outcomes following an intracranial haemorrhage by GOS state**

In the first example, the same data source was used to estimate both the mean outcome associated with being in each mRS category, and the proportion of patients who are in each category. In the second example, mapping onto GOS states, a different data source was used to estimate the distribution of outcomes by GOS state following an intracranial haemorrhage. These are shown in Table 3 below, and were previously reported in Holmes et al (10).

[Table 3 about here]

#### **1.2.12. Bootstrapping means from the collapsed distributions**

The weighted utility multipliers were based on predicted values from the component distributions (mRS 0, mRS 1 and so on), whereas modellers are typically interested in using expected values, i.e. distributions representing uncertainty in the mean values. To produce estimates of the expected values, a bootstrapping procedure was used, in which the distribution of predicted values was resampled with replacement 10,000 times to produce 10,000 simulated datasets, and the mean values of each of these datasets recorded to produce a distribution of expected values.

### **1.3. Results**

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1 The following section shows first the simulated proportion and mean simulated utility in the three  
2 state example (dead, independent state, and dependent state), and then the mean simulated  
3 utilities in the GOS example.

4 **1.3.1. Results for three state simulation**

5 Table 4 below shows the mean simulated proportions in the dead, independent and dependent  
6 stroke state, together with 95% credible intervals (CrIs) as well as mean simulated utility multipliers  
7 associated with each of the states, also with 95% CrIs. The simulation suggests that approximately  
8 one quarter of patients die as a result of a stroke, around one fifth are left in a dependent state, and  
9 the remainder are left in an independent state. Being in a dependent state leads, on average, to  
10 slightly more than a halving of the patient’s quality of life, whereas being in an independent state  
11 leads to quality of life reducing by around one fifth compared with patients whose strokes had no  
12 lasting effect (mRS 0).

13 [Table 4 about here]

14 **1.3.2. Results for GOS simulation**

15 The utility multipliers associated with different GOS states, based on the simulation approach  
16 described above, are shown in Table 5.

17 [Table 5 about here]

18 **1.4. Discussion**

19 **1.4.1. Key findings**

20 This paper shows how a simulation-based approach can be used to collapse utility values from a  
21 larger to a smaller number of discrete states in a way which incorporates uncertainty at the  
22 intermediate stages. This means that the estimates produced are replicable and minimise the  
23 number and influence of modeller assumptions being made.

24 All that is required are the sample sizes and utility estimates of the uncollapsed states, and a clearly  
25 stated assumption about which of the uncollapsed states map onto each of the collapsed states.  
26 Using this approach, it is possible to make use of more recent and/or more pertinent data to inform  
27 the economic model than was previously possible using summary data alone. This is useful where  
28 one type of information of interest to modellers, such as cost or transition probabilities to other  
29 states, is presented at a coarser level of aggregation (i.e. fewer states) than another type of  
30 information of interest to modellers, such as utility scores.

1 The assumptions made in the approach are clearly stated and can be developed and improved upon  
2 where additional clinical and statistical data allow it. These are discussed in more detail in the  
3 implications for research section below. In the case studies provided the approach was shown to be  
4 able to make use of the same population to inform both the utility consequences of strokes, and the  
5 utility consequences of intracranial haemorrhages which may result from prescribing OACs to  
6 prevent strokes, allowing a model based on such data greater consistency. The approach can be  
7 applied to other similar situations, provided the right form of summary data exist, which report the  
8 frequency of patients in different states, as well as the utilities associated with each state.

#### 9 **1.4.2. Possible mechanisms and explanations for the findings**

10 The approach illustrated here show the implications of making simple and standard assumptions  
11 about how the summary estimates presented in Rivero-Arias et al (11) relate to the individual  
12 patient data. This includes making the assumptions that mean utility scores for each mRS category  
13 was normally distributed, that the distribution of patients who live can be represented with a  
14 Binomial distribution, and that the distribution of the long-term mRS states amongst those who are  
15 alive can be represented by a Dirichlet distribution. These statistical model assumptions are made in  
16 order to produce hypothetical individual level simulations, which is a necessary intermediate stage  
17 for estimating the mean scores and proportions if the patients were subdivided into a different, and  
18 smaller, number of categories. The reliability of these estimates is dependent on the  
19 appropriateness of the assumptions made. Without access to the individual level data, however, it is  
20 difficult to assess the appropriateness of the assumptions made.

#### 21 **1.4.3. Comparison with previous published research**

22 For our first example, our estimated utility multipliers are very similar to those presented in Dorman  
23 et al.,(12) for independent strokes but somewhat higher than those reported in that paper for  
24 dependent strokes. This is largely due to the distribution of mRS states within the Independent  
25 Stroke and Dependent Stroke categories, which for both categories of stroke are weighted towards  
26 less severe mRS states. In the case of dependent strokes (mRS 3-5), for example, only around 4%  
27 were the worst category (mRS 5), which has an estimated EQ-5D multiplier near zero, while three-  
28 quarters were in the least worst category (mRS 3), which has an estimated EQ-5D multiplier over 0.5.

29 The way our estimates differ from those in Dornan et al (12) may reflect improvements in the  
30 prognosis following strokes in the decade that separates the studies used. This highlights the  
31 importance of making use of more recent data where possible, given that healthcare systems change  
32 and improve. To do otherwise may be to misrepresent the costs and clinical consequences of  
33 modern treatment regimens for particular conditions.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**1.4.4. Limitations**

The approach described here is designed to allow better use of existing summary data, in the absence of true individual level data. It does this by creating hypothetical individual level data as an intermediate stage. The approach is necessarily limited by the need to make assumptions about the statistical relationship between the summary data available and the individual level data. For example, we assumed that the mean EQ-5D estimates for each mRS followed a normal distribution, which is bounded between negative and positive infinity. EQ-5D utility scores show a negative lower bound whose value depends on the valuation tariff used and an upper ceiling (1.00) by construction, and so a statistical distribution where these bounds are applied may be more appropriate. We also know that EQ-5D data are only poorly approximated by the normal distribution, as the distribution of EQ-5D is typically known to be ‘multimodal’. This represents a more general limitation common to a range of modelling approaches, (13) rather than something specific to this approach.

Without access to the individual level data the appropriateness of the statistical assumptions made, such as the choice of stochastic distributions, cannot be assessed. The dependence of the reconstructed summary estimates on the choice of statistical distributions can be assessed, however, by using different statistical models and comparing the results. As the R code is presented in the online appendix, it is convenient for readers to assess the dependence of the estimates on modelling assumptions themselves, and assess the impact of alternative choices of statistical distributions which use the same summary data.

In addition to assumptions about the choice of statistical distribution, this method involves making two further types of qualitative assumption. Firstly, we made the assumption of perfect mapping (‘deterministic bijection’) between health states based on descriptions of states. Secondly, we made the assumption in the second example that a persistent vegetative state has mean utility equal to death, whereas it may be that the utility associated with this state is different to this, and possibly negative (‘worse than death’).

The first type of assumption, the perfect mapping, should represent the best assumption of the economic modeller based on clinical knowledge. Where other clinical evidence and opinion exists which suggests alternative mapping arrangements should be considered, the effect of making these assumptions on the modelling results and utility/cost estimates should be explored and presented where possible as sensitivity analyses.

A further assumption made was that the 24 month state reported in the Rivero-Arias paper was the patient’s permanent state, and the patients for whom mRS outcomes were reported were assumed to be representative of those for whom the data were not collected. Additionally, we assumed that

all patients who died of strokes died instantly, which will underestimate both the costs and utilities associated with this event.

There are also potential issues of generalisability when applying estimates based on a sample of the OXVASC study population to other patient populations, especially if adapting models based on these estimates to other countries. This is always the case for disease-specific utility and cost data of this type.

#### **1.4.5. Research recommendations**

A range of further research directions are possible based on this approach. The most important of these is to attempt to verify the accuracy of this approach using individual patient data, where the 'true' answers are already known. The comparison presented in this paper was unable to do that because the results were based on different studies. Research should also be conducted to try to identify the most appropriate way of applying this form of approach to a range of clinical areas, including the most appropriate choice of distributions and mapping assumptions to make. Research could also be conducted to estimate

The main purpose of the approach described here is to make sure that decision models are based on all pertinent available information, and are not limited by lack of clear interoperability between costs and utility summaries. The effectiveness of this approach should be judged on whether it offers an improvement on current practice, rather than whether it produced the most accurate summary estimates theoretically possible.

In the clinical area considered in the case study, it may also be valuable to see how the model could be applied to summary data which report either mean cost or utility data using the Barthel index, which is also commonly used in this area. (12,14,15)

#### **1.4.6. Conclusions**

The comparison with the estimates reported in Dornan et al (12) revealed differences in estimates which appear clinically plausible and to reflect improvements in stroke care which have occurred over the two decades that separate the results used by Dornan et al from those from OXVASC. As such it appears that the method described here was able to provide updated estimates of the HRQoL effects of suffering either a dependent or independent stroke. The higher HRQoL estimates for dependent strokes produced by this method, which is based on much more recent data, may therefore be more appropriate than previous estimates for use in contemporary health economic modelling.

1 As the mRS and GOS are both measures of disablement rather than classifications of the causes of  
2 such disablement, the decision to group certain mRS categories into GOS categories also seems  
3 appropriate as it means data from the same patient population is used to inform both the potential  
4 HRQoL consequences of strokes, and of intracranial haemorrhages which can be caused on rare  
5 occasions by the OACs intended to prevent strokes. Using the same patient population means that  
6 estimated differences in consequences could not be the result of different baseline characteristics in  
7 the populations. The approach described also could be adapted to other datasets in other clinical  
8 areas. The validity and attractiveness of this approach in comparison to the alternatives needs  
9 further investigation and consideration.

For Peer Review

## 2. References

1. Chuang L-H, Whitehead SJ. Mapping for economic evaluation. *Br. Med. Bull.* [Internet]. 2012 Jan [cited 2012 Dec 4];101:1–15. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22209743>
2. Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez R. Mapping the Modified Rankin Scale (mRS) Measurement into the Generic EuroQol (EQ-5D) Health Outcome. *Med. Decis. Mak.* [Internet]. 2010;30(3):341–54. Available from: <Go to ISI>://000277892800009
3. Simpson EL, Stevenson MD, Scope A, Poku E, Minton J, Evans P. Echocardiography in newly diagnosed atrial fibrillation patients: a systematic review and economic evaluation. *Health Technol. Assess.* (Rockv). 17.
4. Minton JW, Stevenson MD, Simpson E, Lip GYH. When is it cost effective to use transthoracic echocardiography to aid the decision to prescribe oral anticoagulants in patients with newly diagnosed atrial fibrillation? An economic evaluation. *PLoS One*.
5. Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* [Internet]. 1988 May 1 [cited 2012 Mar 18];19(5):604–7. Available from: <http://stroke.ahajournals.org/cgi/doi/10.1161/01.STR.19.5.604>
6. RANKIN J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. *Scott. Med. J.* [Internet]. 1957 May [cited 2012 Apr 4];2(5):200–15. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/13432835>
7. Wilson JTL, Hareendran A, Hendry A, Potter J, Bone I, Muir KW. Reliability of the modified Rankin Scale across multiple raters: benefits of a structured interview. *Stroke.* [Internet]. 2005 Apr [cited 2012 Apr 4];36(4):777–81. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15718510>
8. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet* [Internet]. 2004 Jun 12 [cited 2012 Sep 28];363(9425):1925–33. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15194251>
9. Heitjan DF, Basu S. Distinguishing “Missing at Random” and “Missing Completely at Random.” *Am. Stat.* [Internet]. 1996 Aug [cited 2013 Jun 30];50(3):207. Available from: <http://www.jstor.org/stable/2684656?origin=crossref>
10. Holmes MW, Goodacre S, Stevenson MD, Pandor A, Pickering A. The cost-effectiveness of diagnostic management strategies for adults with minor head injury. *Injury* [Internet]. (0). Available from: <http://www.sciencedirect.com/science/article/pii/S0020138311003573>
11. Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez R. Mapping the Modified Rankin Scale (mRS) Measurement into the Generic EuroQol (EQ-5D)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Health Outcome. Med. Decis. Mak. [Internet]. 2010;30(3):341–54. Available from: <Go to ISI>://000277892800009

12. Dorman P, Dennis M, Sandercock P. Are the modified “simple questions” a valid and reliable measure of health related quality of life after stroke? J. Neurol. Neurosurg. Psychiatry [Internet]. 2000;69(4):487–93. Available from: <http://jnnp.bmj.com/content/69/4/487.abstract>

13. Mann R, Gilbody S, Richards D. Putting the “Q” in depression QALYs: a comparison of utility measurement using EQ-5D and SF-6D health related quality of life measures. Soc. Psychiatry Psychiatr. Epidemiol. [Internet]. 2009 Jul [cited 2012 Dec 4];44(7):569–78. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19011721>

14. Lin H-J, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, et al. Stroke Severity in Atrial Fibrillation: The Framingham Study. Stroke [Internet]. 1996;27(10):1760–4. Available from: <http://stroke.ahajournals.org/content/27/10/1760.abstract>

15. Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, et al. A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS. Health Technol. Assess. (Rockv). 2002;6(26).



### 3. Tables

mRS Category	Frequency	Proportion of total	Collapsed category	Proportion of collapsed category
mRS 0	61	0.144	Independent	0.194
mRS 1	143	0.336	State	0.454
mRS 2	111	0.261		0.352
mRS 3	82	0.193	Dependent	0.745
mRS 4	24	0.056	State	0.218
mRS 5	4	0.009		0.036

Table 1 Cell counts used from source paper to populate the Dirichlet distribution in this simulation. The Dirichlet distribution was therefore  $Dirichlet(\theta)$  where  $\theta = \{61, 143, 111, 82, 24, 4\}$

mRS Score	Category	Description	Reduced Category	Glasgow Outcome Scale State
0	No Symptoms	No symptoms at all.	Independent stroke	GOS 5: Good Recovery
1	No Significant Disability	No significant disability despite symptoms; able to perform all usual duties and activities.		
2	Slight Disability	Slight disability; unable to perform all normal activities but able to look after own affairs without assistance		Dependent stroke
3	Moderate Disability	Moderate disability requiring some help but able to walk without assistance.	GOS 3: Severely disabled	
4	Moderately Severe Disability	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.		
5	Severe Disability	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention.	Dead	GOS 1: Dead; GOS 2: Vegetative state
6	Dead	Dead		

Table 2 The modified Rankin Score (mRS) categories, and assumed mapping between mRS states and reduced stroke categories and Glasgow Outcome Scale (GOS) states

Event category	Dirichlet distribution value	Central estimate (95% CrIs)
GOS 2	115.5	0.116 (0.097 to 0.136)
GOS 3	140	0.140 (0.119 to 0.162)
GOS 4	79.3	0.079 (0.063 to 0.097)
GOS 5	665.1	0.665 (0.636 to 0.694)

Table 3 Probability of GOS categories following non-fatal intracranial haemorrhage. The Dirichlet distribution was therefore  $\text{Dirichlet}(\theta)$  where  $\theta = \{115.5, 140, 79.3, 665.1\}$ . The central estimates are the medians of the simulated values, presented to three decimal places. Note: because of the number of decimal places the central estimates are displayed to, and because the sum of the elements in  $\theta$  is 999.9 rather than 1000, the central estimates shown are not exactly  $\theta_i/1000$ .

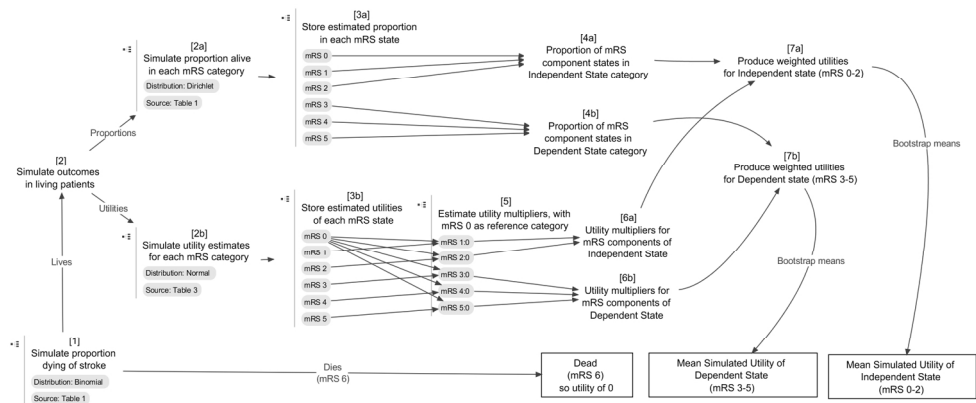
Aggregate health State	Proportion	Utility Multiplier
	Mean (95% CrIs)	Mean (95% CrIs)
Dead	0.249 (0.225 to 0.273)	0
Independent	0.557 (0.520 to 0.592)	0.823 (0.821 to 0.826)
Dependent	0.194 (0.164 to 0.228)	0.483 (0.478 to 0.487)

Table 4 Mean simulated proportions dead, or in dependent state or independent state following a stroke, together with 95% credible intervals (CrIs)

For Peer Review

State	Utility Multiplier Mean (95% CrIs)
GOS 1: Dead Or GOS 2: Vegetative State	0
GOS 3: Severely Disabled	0.226 ( 0.221 to 0.231)
GOS 4: Moderately Disabled	0.642 (0.638 to 0.645)
GOS 5: Good Recovery	0.895 (0.892 to 0.898)

Table 5 Mean utility multipliers associated with different GOS states. CrIs: Credible intervals. GOS: Glasgow Outcome Scale. See Table 2 for estimated proportions in GOS 2 to GOS 5 following an intracranial haemorrhage.



Graphical representation of approach for mapping from mRS states to dependent stroke and independent stroke states. (Sources refer to sources in Rivero-Arias).  
649x280mm (72 x 72 DPI)

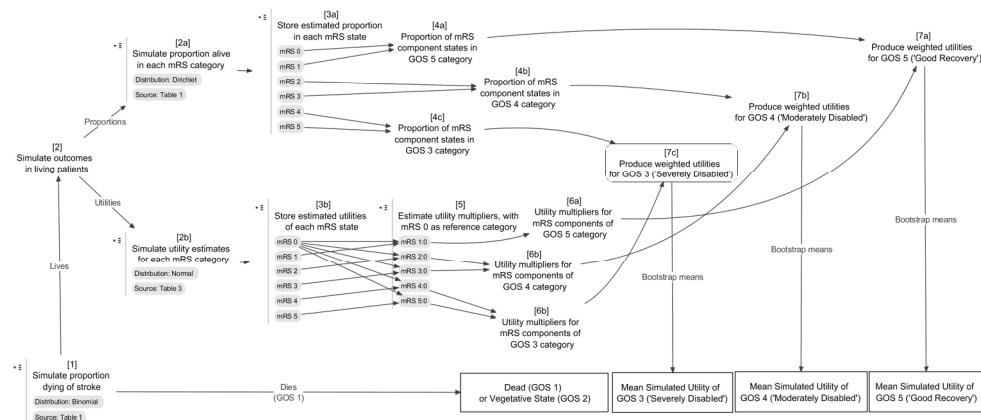


Figure 2 Graphical representation of approach for mapping from mRS states to GOS states  
714x319mm (72 x 72 DPI)

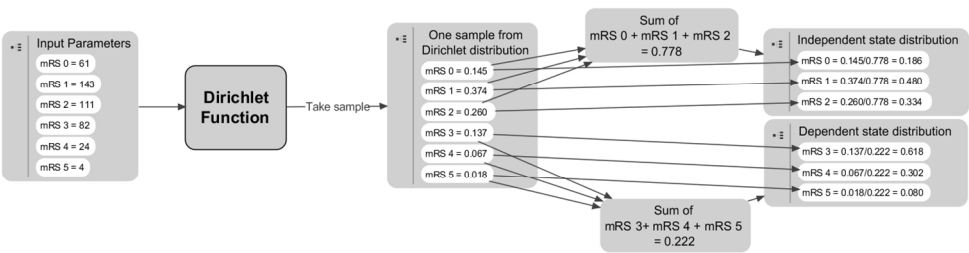


Figure 3 Weighting the component states in the collapsed states (dependent state, independent state) based on a draw from the Dirichlet distribution  
517x143mm (72 x 72 DPI)



## 1.1. Appendix

### Simulating proportions in each mRS state

The R code for doing this is:

```
mRS_followingStroke <- rdirichlet(N.PSA, c(61, 143, 111, 82, 24, 4))
```

Where N.PSA and c(61, 143, 111, 82, 24, 4) are both arguments to the rdirichlet function. N.PSA provides the number of samples used in probabilistic sensitivity analysis (PSA), and c(61, 143, 111, 82, 24, 4) providing the parameter values for the Dirichlet function. These parameter values are taken directly from the source paper.

### Producing random draws from a normal distribution

The R code for doing this for the mRS 3 state is:

```
s3 <- rnorm(N.PSA, .545, .277)
```

Where 0.545 is the mean utility reported in the source paper for this mRS state, and 0.277 is the standard deviation report. The simulated values for the other mRS states are produced similarly.

### Converting from utility values to utility multipliers

To turn the utility simulations into utility multipliers (indicated in node 5 of both Figure 1 and Figure 2) we assumed that mRS 0 ('no symptoms') represented full health. The multipliers for mRS states 1-5 were therefore produced by dividing simulated values from the more severe category by simulated values from the mRS 0 distribution. The R command for producing the utility multiplier associated with mRS 3, for example, is simply:

```
mult.s3 <- s3/s0
```

This produces a vector of length N.PSA, because both s3 and s0 are also vectors of length N.PSA. The multipliers associated with the other mRS states are produced similarly.

### Simulating uncertainty in the distribution of the component states in each of the collapsed state

The R code for doing this for each draw from the Dirichlet distribution for the Independent state category is shown below:

```
Stroke.Ind <- mRS_followingStroke[,1:3]
Stroke.Ind.sums <- apply(Stroke.Ind, 1, sum)
Stroke.Ind <- apply(Stroke.Ind, 2, function (x) x / Stroke.Ind.sums)
```

The approach for the Dependent stroke category is similar, but uses columns 4, 5 and 6 of the object

mRS\_followingStroke, instead of columns 1, 2 and 3.

**Producing weighted utility multiplier estimates for independent and dependent stroke categories**

For the Independent state the R code for doing this is as follows:

```
Stroke.Ind.utils <- Stroke.Ind[,1] * 1 + Stroke.Ind[,2] *  
mult.s1 + Stroke.Ind[,3] * mult.s2
```

Here Stroke.Ind[,1] refers to the first column, the weight of mRS 0, and Stroke.Ind[,1] refers to column 2, the corresponding weights of mRS 1. The object mult.s1 is a vector of estimates of the utility multiplier of mRS 1 compared with mRS 0, and mult.s1 is a vector of estimates of the utility multiplier of mRS 2 compared with mRS 0. As the reference utility value is mRS 0, the utility multiplier associated with mRS 0 is just 1. The weighted utility multiplier estimates associated with Dependent strokes are calculated similarly.

Table 6 Example R code required for the procedures described in this paper

R code	Comments
<pre>Bootstrapper &lt;- function(inputs, simulates = 10000){   X.mean &lt;- vector("numeric", simulates)   N.inputs &lt;- length(inputs)   for (i in 1:simulates) {X.mean[i] &lt;- mean(inputs[sample(1:N.inputs, replace=T)])}   return(X.mean) }</pre>	<p>This is code for a bespoke function in R for finding the bootstrapped means of a vector of numbers. Other bootstrapping functions exist, but this function is easy to make.</p> <p>The function defaults to running 10,000 bootstraps of the dataset. This can be adjusted by specifying a different ‘simulates’ argument.</p>
<pre>Require(MCMCpack)</pre>	<p>Loads a library containing the rdirichlet() function used later.</p>
<pre>N.PSA &lt;- 10000</pre>	<p>Specify that PSA involves 10,000 sets of draws</p>
<pre>Dead_nonDead &lt;- rbinom(N.PSA, 1283, (319/1283)) / 1283</pre>	<p><b><u>NODE 1</u></b></p> <p>Specifies that the object Dead_nonDead should be created containing 10,000 draws from a binomial distribution.</p> <p>The binomial distribution is parameterized with two numbers from table 1 of Rivero-Arias. ‘319’ is the number dead following stroke. ‘1283’ is the sample size of relevant individuals. The outputs from rbinom are all divided by 1283 to produce proportions rather than frequencies.</p>
<pre>mRS_followingStroke &lt;- rdirichlet(N.PSA, c(61, 143, 111, 82, 24, 4))</pre>	<p><b><u>NODE 2a + NODE 3A</u></b></p> <p>This creates a matrix containing the output of 10,000 draws from a dirichlet distribution populated by the values from table 1 of the</p>

```

DepInd_followingStroke <-
cbind(apply(mRS_followingStroke[,1:3], 1,
sum), apply(mRS_followingStroke[,4:6], 1,
sum))

```

```

DeadDepInd_followingStroke <-
cbind(Dead_nonDead, (1 - Dead_nonDead) *
DepInd_followingStroke[,1], (1-
Dead_nonDead) *
DepInd_followingStroke[,2])

```

```

colnames(DeadDepInd_followingStroke) <-
c("Dead", "Independent", "Dependent")

```

```

s0 <- rnorm(N.PSA, .959, .074)
s1 <- rnorm(N.PSA, .812, .181)
s2 <- rnorm(N.PSA, .656, .218)
s3 <- rnorm(N.PSA, .545, .277)
s4 <- rnorm(N.PSA, .248, .281)
s5 <- rnorm(N.PSA, .020, .046)

```

```

mult.s1 <- s1/s0
mult.s2 <- s2/s0
mult.s3 <- s3/s0
mult.s4 <- s4/s0
mult.s5 <- s5/s0

```

```

Stroke.Ind <- mRS_followingStroke[,1:3]
Stroke.Dep <- mRS_followingStroke[,4:6]

```

```

Stroke.Dep.sums <- apply(Stroke.Dep, 1,
sum)
Stroke.Ind.sums <- apply(Stroke.Ind, 1,
sum)

```

```

Stroke.Dep <- apply(Stroke.Dep, 2,
function (x) x / Stroke.Dep.sums)
Stroke.Ind <- apply(Stroke.Ind, 2,
function (x) x / Stroke.Ind.sums)

```

Rivero-Arias paper showing distribution of modified Rankin Scale stroke outcomes at 24 months.

#### **NODE 4a + NODE 4b**

This converts six columns of mRS\_followingStroke into two columns, giving the sums of 'independent' and 'dependent' strokes respectively. The two calls to the apply function take the first three and last three columns of the mRS\_followingStroke dataframe, and output the sums of each row.

This combines estimates of the proportion alive following a stroke, Dead\_nonDead, with the proportion of those alive in either dependent or independent states, DepInd\_followingStroke. The output is a three column matrix giving 1) proportion alive; 2) proportion in independent state; 3) proportion in dependent state.

This command labels the columns of the previously created matrix to be easier to interpret.

#### **NODE 2b + NODE 3b**

These commands use data from table 3 (the 24 months column) from Rivero-Arias to produce 10,000 draws from Normal distributions parameterized with the means and standard deviation values from the paper. s0 is the estimated utility following an mRS 0 outcome, s1 is the estimated utility following an mRS 1 outcome, and so on.

#### **NODE 5 + NODE 6a + NODE 7a**

These convert the draws of estimates associated with each of the mRS states into utility multipliers for each of states mRS 1 to 5, where mRS 0 is the reference category.

#### **NODE 4a + NODE 4b**

These commands calculate the relative distribution of mRS states among those within either the 'dependent' (mRS 3-5) in 'independent' (mRS 0-2) stroke categories. This allows weighted averages of utilities from mRS specific utility multipliers to be produced later.

<pre>Stroke.Ind.utils &lt;- Stroke.Ind[,1] * 1 + Stroke.Ind[,2] * mult.s1 + Stroke.Ind[,3] * mult.s2  Stroke.Dep.utils &lt;- Stroke.Dep[,1] * mult.s3 + Stroke.Dep[,2] * mult.s4 + Stroke.Dep[,3] * mult.s5  Stroke.Ind.utils.mean &lt;- Bootstrapper(Stroke.Ind.utils) Stroke.Dep.utils.mean &lt;- Bootstrapper(Stroke.Dep.utils)</pre>	<p><b><u>NODE 7a</u></b> This produces an estimate of the utility multiplier associated with an independent stroke using a weighted average of utility multipliers associated with mRS 0, mRS 1 and mRS 2</p> <p><b><u>NODE 7b</u></b> This produces an estimate of the utility multiplier associated with a dependent stroke using a weighted average of utility multipliers associated with mRS states 3, 4 and 5.</p> <p><b><u>BOOTSTRAPPING</u></b> These commands run the bootstrapping function created earlier to produce 10,000 bootstrapped estimates of the centre of the distributions Stroke.Dep.utils and Stroke.Ind.utils.</p>
R code	Comments
<pre>GOS_5 &lt;- mRS_followingStroke[,1:2] GOS_4 &lt;- mRS_followingStroke[,3:4] GOS_3 &lt;- mRS_followingStroke[,5:6]  GOS_5.sums &lt;- apply(GOS_5, 1, sum) GOS_4.sums &lt;- apply(GOS_4, 1, sum) GOS_3.sums &lt;- apply(GOS_3, 1, sum)  GOS_5 &lt;- apply(GOS_5, 2, function (x) x / GOS_5.sums) GOS_4 &lt;- apply(GOS_4, 2, function (x) x / GOS_4.sums) GOS_3 &lt;- apply(GOS_3, 2, function (x) x / GOS_3.sums)  GOS_5.utils &lt;- GOS_5[,1] * 1 + GOS_5[,2] * mult.s1 GOS_4.utils &lt;- GOS_4[,1] * mult.s2 + GOS_4[,2] * mult.s3 GOS_3.utils &lt;- GOS_3[,1] * mult.s4 + GOS_3[,2] * mult.s5  n.bootstraps &lt;- 10000</pre>	<p>Approach for mapping from mRS to GOS</p> <p>Assuming code above has all been run (so mRS estimates and so on have all been calculated)</p> <p><b><u>NODE 4a + NOD 4b + NODE 4c</u></b> These commands the Dirichlet derived cell counts into GOS 5 (columns 1 and 2), GOS 4 (columns 3 and 4), and GOS 3 (columns 5 and 6).</p> <p>These commands calculate the sums across the rows of the newly created variables GOS_5, GOS_4, and GOS_3</p> <p>These commands convert the cell counts into proportions.</p> <p><b><u>NODE 6a + NODE 6b + NODE 6c + NODE 7a + NODE 7b + NODE 7c</u></b> These commands calculate a weighted utility multiplier value for each row in GOS_5, GOS_4 and GOS_3 given the relative proportion of each of the component states.</p> <p><b><u>BOOTSTRAPPING</u></b> <i>These commands show how to perform bootstrapping without use of the Bootstrapper</i></p>

<pre>GOS_5.mean &lt;- vector("numeric", n.bootstraps) GOS_4.mean &lt;- vector("numeric", n.bootstraps) GOS_3.mean &lt;- vector("numeric", n.bootstraps)  for (i in 1:n.bootstraps){ GOS_5.mean[i] &lt;- mean(GOS_5.utils[sample(1:N.PSA, n.bootstraps, replace=T)]) GOS_4.mean[i] &lt;- mean(GOS_4.utils[sample(1:N.PSA, n.bootstraps, replace=T)]) GOS_3.mean[i] &lt;- mean(GOS_3.utils[sample(1:N.PSA, n.bootstraps, replace=T)]) }</pre>	<p><i>function developed earlier</i></p> <p>Sets the number of bootstrap replicates to 10,000</p> <p>Creates three empty vectors for storing bootstrapped estimates of the means</p> <p>Produces 10,000 bootstrapped estimates of the means of GOS_5, GOS_4 and GOS_3</p>
---	---

Table 7 Description of full R script used to perform the analyses