# Abstract

**Background:** Diseases often have varying levels of severity, and different systems for categorising disease severity exist. Information about the health related quality of life (HRQoL) and the costs of treating a disease may only be available reported using different categorisation systems. To be used in health economic models, mapping between the categories is required. This paper describes a method for mapping HRQoL from more (seven) to fewer (three) categories in a way which does not underplay the statistical uncertainty involved in doing so.

**Methods:** Summary data from a previous MDM paper was used alongside other sources and clearly stated assumptions in order to generate estimates of the mean HRQoL in each of the three categories which represents known uncertainty about the expected HRQoL in each of the seven states and known uncertainty about the distribution of the seven categories within each of the three categories. The approach was used to generate HRQoL multipliers, rather than just HRQoL values, in order to allow estimates of the effect of diseases to be applied to populations with different baseline HRQoL levels.

**Results:** Estimates of mean HRQoL were produced for each of the three categories incorporating the above uncertainties, so both cost and HRQoL were available to be used at the same level of aggregation within an economic model.

**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.

# Structure

## 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 is essentially 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 show two related examples where our method is useful when building and populating health economic models. Firstly, 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 recently in MDM by Modified Rankin Scale (mRS), which has seven mutually exclusive stroke severity states. (2) Secondly, 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 the 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, and 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 trying to build a model of the consequences of prescribing oral anticoagulants (OACs) in the management of atrial fibrillation (AF), OACs reduce stroke risk but can lead to intracranial haemorrhages which can cause brain injury leading to qualitatively similar types and degrees of disablement to the strokes which they are intended to prevent. It is for this reason that it was considered advantageous to use utility estimates based on the same group of patients.

## Method

### Information required

In order to use the approach described here, we need two sorts of information, and to make one assumption. The first type of information needed is the mean utilities associated with each of the larger number of health states (mRS states in this paper). The second type of information needed is the distribution of patients in each of these health states. Then, we need to be able to state an assumption about how the larger number of categories (mRS states in our examples) relate to the smaller number of categories (independent/dependent states, and GOS states, in our examples). In our examples, the first two pieces of information were provided in a previous paper published in MDM in 2010, which we refer to as our ‘source paper’.(2)

### The Modified Rankin Scale (mRS)

The mRS is a commonly used measure of disability or dependence in daily activities following a stroke. It was introduced in its current form by van Swieten et al in 1988(3), and originally based on a 1957 paper by J Rankin.(4) The mRS is a seven level ordinal scale, with scores ranging from 0-6 inclusive, and has good inter-rater reliability.(5)

### The source paper

The paper we used as a data source for our approach was published in MDM in 2010 and used data from the Oxford Vascular Study (OXVASC).(2) OXVASC is a large scale population-based cohort, initiated in 2002, involving almost 100,000 individuals registered in Oxfordshire.(6) The source paper used 1283 patients from this study, recruited between April 2002 and March 2007, who had suffered either stroke or transient ischemic attack (TIA). These patients were followed-up for up to 24 months following the stroke. The patients’ condition was assessed using the disease specific measure of the mRS, as well as the generic utility instrument EQ-5D. Based on this, the EQ-5D utilities associated with each state were estimated and reported. (2)

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

### 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 correspondences assumed are shown in Table 1 below. For the first example, we adopted the standard assumption 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 and utility multiplier value of 0.

[Table 1 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’).

### 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.

[Figure 1 about here]

[Figure 2 about here]

### 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). Table 2 shows how to do this in R.

[Table 2 about here]

### 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 produce a large number of simulated utility distributions for each state, assuming that the distributions of values for each state followed a normal distribution. This process allows parameter uncertainty at this stage to be propagated through to later stages rather than disregarded. Table 3 presents an example of this process in R.

[Table 3 about here]

### Converting simulated utility values into utility multipliers

In the economic model we developed, utility multipliers rather than utility values themselves were used, so that the multipliers could be applied to populations with different baseline utility values. Producing utility multipliers in this way means that uncertainty in both the numerator and denominator values are incorporated in the simulation. Table 4 describes this procedure in more detail.

[Table 4 about here]

### 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 example, there might be three mutually exclusive states A B C, and two samples of patients. In the first sample A=5, B=10, C=5, and in the second sample A=50, B=100, C=50. In both cases the proportion of the sample in each category was the same – 25%, 50%, 25% - but in the first case the smaller sample size means there is more uncertainty about the true proportion of patients in each category. This is the 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. Table 5 illustrates how to do this in R.

[Figure 3 about here]

[Table 5 about here]

### 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. Table 6 describes how this process is conducted in R. 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.

[Table 6 about here]

### 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 7 below, and were previously reported in Holmes et al (7).

[Table 7 about here]

### 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 to produce 1,000 simulated datasets, and the mean values of each of these datasets recorded.

## Results

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

### Results for three state simulation

Table 8 below shows the mean simulated proportions in the dead, independent and dependent stroke state, together with 95% predictive intervals (95% PrIs) as well as mean simulated utility multipliers associated with each of the states, also with 95% PrIs. The simulation suggests that approximately one quarter of patients die as a result of a stroke, around one fifth are left in a dependent state, and the remainder are left in an independent state. Being in a dependent state leads, on average, to slightly more than a halving of the patient’s quality of life, whereas being in an independent state leads to quality of live reducing by around one fifth.

[Table 8 about here]

### Results for GOS simulation

The utility multipliers associated with different GOS states, based on the simulation approach described above, are shown in Table 10 below.

[Table 10 about here]

### Summary

This section has shown that summary data which reports both mean utility scores associated with each of a finite number of categories, alongside the proportion of patients in each of those categories, can be used to simulate the mean utility scores associated with a smaller number of finite categories.

## Discussion

### Key findings

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

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

The approach involves making a number of assumptions, but these assumptions are clearly stated and can be developed and improved upon where additional clinical and statistical data allow it. These are discussed in more detail in the implications for research section below. In the case studies provided the approach was shown to be able to make use of the same population to inform both the utility consequences of strokes, and the utility consequences of intracranial haemorrhages which may result from prescribing oral anticoagulants to try to present strokes, allowing a model based on such data some level of greater consistency. The approach can be applied to other similar situations, provided the right form of summary data exist, which report the frequency of patients in different states, as well as the utilities associated with each state.

### Possible mechanisms and explanations for the findings

The approach illustrated here show the implications of making simple and standard assumptions about how the summary estimates presented in Rivero-Arias et al (8) relate to the individual patient data. This includes making the assumption that mean utility scores for each mRS category was normally distributed, that the distribution of patients who live can be represented with a Binomial distribution, and that the distribution of the long-term mRS states amongst those who are alive can be represented by a Dirichlet distribution. These statistical model assumptions are made in order to produce fake individual level simulations, which are a necessary intermediate stage for estimating what the mean scores and proportions would be if the patients were subdivided into a different, and smaller, number of categories. The reliability of these estimates is dependent on the appropriateness of the assumptions made. Without access to the individual level data, however, it is difficult to assess the appropriateness of the assumptions made.

### Comparison with previous published research

For our main example, our estimated utility multipliers are very similar to those presented in Dorman et al.,(9) for independent strokes but somewhat higher than those reported in that paper for dependent strokes. This is largely due to the distribution of mRS states within the Independent Stroke and Dependent Stroke categories, which for both categories of stroke are weighted towards less severe mRS states. In the case of dependent strokes (mRS 3-5), for example, only around 4% were the worst category mRS 5, which has an estimated EQ-5D score around zero, and around 75% were in the least worst category mRS 3, which has an estimated EQ-5D score over 0.5. The discrepancy may reflect improvements in the prognosis following strokes in the decade that separates the studies used. This highlights the importance of making use of more recent data where possible, given that healthcare systems change and improve. To do otherwise may be to misrepresent the costs and clinical consequences of modern treatment regimens for particular conditions.

### 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 fake 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 of course bounded between negative and positive infinity. We know that in fact 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, rather than something specific to this approach. (10)

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 appendix, it is convenient for interested readers to assess the dependence of the estimates on modelling assumptions themselves, and suggest 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, or 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 or bijection assumption, should represent the best assumption of the economic modeller based on clinical knowledge, and where other clinical evidence and opinion exists which suggests alternative mapping arrangements should be considered or used instead, the effect of making these assumptions on the modelling results and utility/cost estimates should be explored and presented where possible.

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.

### 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 bijection assumptions to make.

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. (9,11,12)

### Conclusions

The implications for clinical practice of this research are subtle, but have the potential to be significant. The choice of cost and utility estimates in cost effectiveness models affects the results they produce, which in turn has the potential to affect the decisions made by healthcare reimbursement agencies like NICE, and so the range and quality of the healthcare experienced by patients. An implication of this model for cost-effectiveness models is that, if the modeller chooses to accept the limitations of the method used to produce them, a newer set of utility multiplier estimates are available to modellers using mathematical models which involve strokes and different stroke categories as health states. The approach described also could be adapted to other datasets in other clinical areas. The validity and attractiveness of this approach in comparison to the alternatives needs further investigation and consideration.

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# Tables

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **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 | GOS 4: Moderately disabled |
| 3 | Moderate Disability | Moderate disability requiring some help but able to walk without assistance. | Dependent stroke |
| 4 | Moderately Severe Disability | Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance. | GOS 3: Severely disabled |
| 5 | Severe Disability | Severe disability; bedridden, incontinent, and requiring constant nursing care and attention. |
| 6 | Dead | Dead | Dead | GOS 1: Dead;  GOS 2: Vegetative state |

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

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| --- |
| 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. |

Table Example code for simulating proportions in each mRS state

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| 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. |

Table Example code for producing random draws from a normal distribution.

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| --- |
| 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. |

Table Example code for converting from utility values to utility multipliers

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| --- |
| 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. |

Table Description of how to simulate uncertainty in the distribution of component states in each collapsed state

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| --- |
| 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 Description of how to produce weighted utility multiplier estimates for independent and dependent stroke categories

|  |  |  |
| --- | --- | --- |
| **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 Probability of GOS categories following non-fatal intracranial haemorrhage

|  |  |  |
| --- | --- | --- |
| Aggregate health State | Proportion  Mean (95% PrIs) | Utility Multiplier  Mean (95% PrIs) |
| 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 Mean simulated proportions dead, or in dependent state or independent state following a stroke, together with 95% predictive intervals

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

Table Cell counts used from source paper to populate the Dirichlet distribution in this simulation

|  |  |
| --- | --- |
| **State** | **Utility Multiplier**  **Mean (95% PrIs)** |
| 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 Mean utility multipliers associated with different GOS states

# Figures

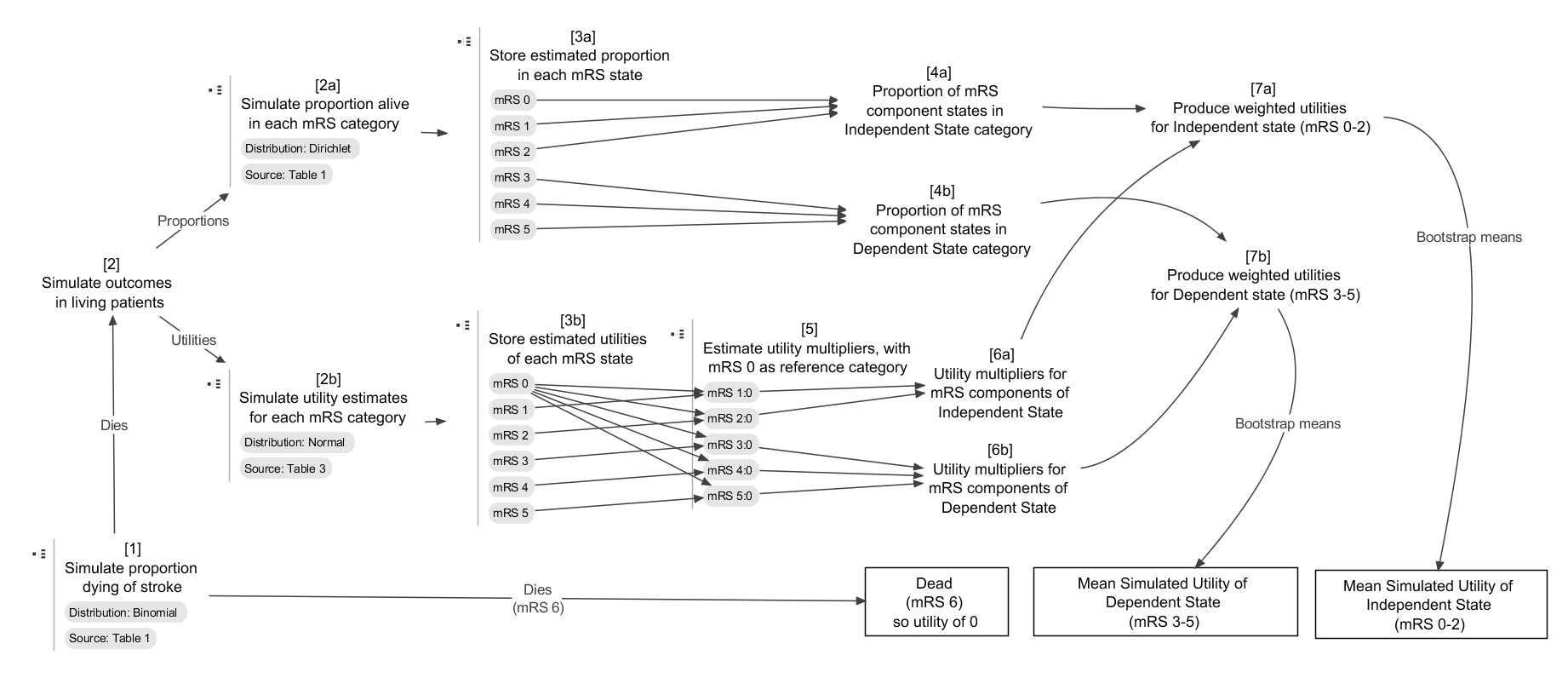


Figure Graphical representation of approach for mapping from mRS states to dependent stroke and independent stroke states. (Sources refer to sources in Rivero-Arias).

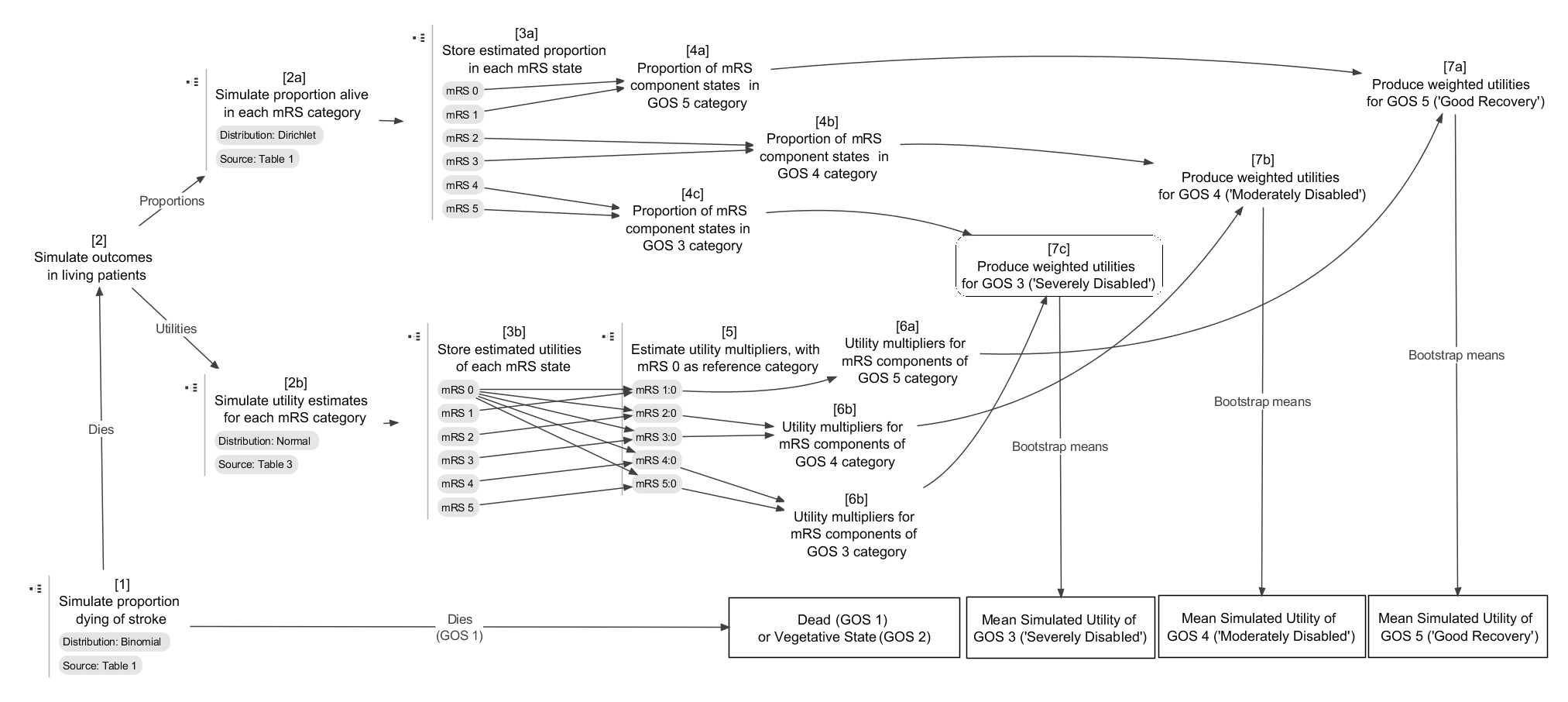


Figure Graphical representation of approach for mapping from mRS states to GOS states

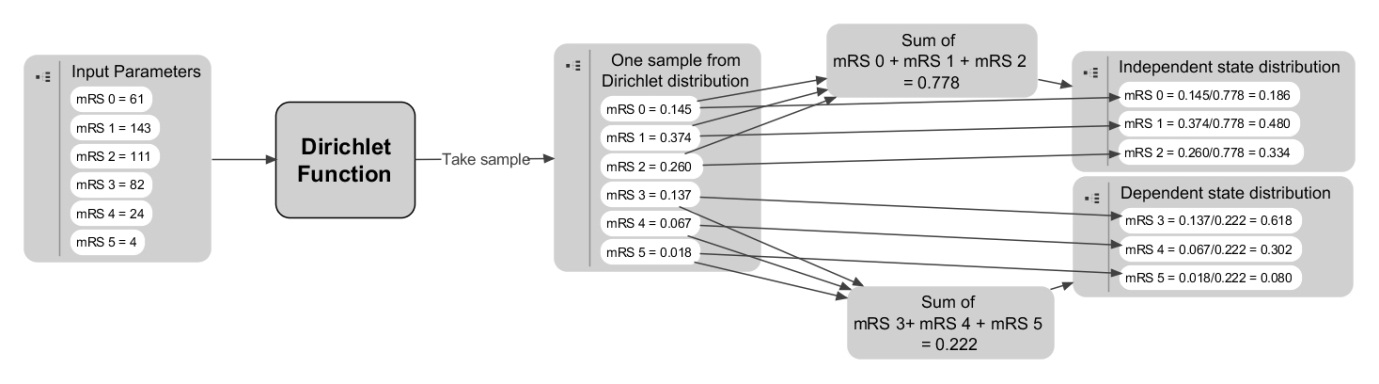


Figure Weighting the component states in the collapsed states (dependent state, independent state) based on a draw from the Dirichlet distribution

## Appendix

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| **R code** | **Comments** |
| Bootstrapper <- function(inputs, simulates = 10000){  X.mean <- vector("numeric", simulates)  N.inputs <- length(inputs)  for (i in 1:simulates) {X.mean[i] <- mean(inputs[sample(1:N.inputs, replace=T)])}  return(X.mean)  }  Require(MCMCpack)  N.PSA <- 10000  Dead\_nonDead <- rbinom(N.PSA, 1283, (319/1283)) / 1283  mRS\_followingStroke <- rdirichlet(N.PSA, c(61, 143, 111, 82, 24, 4))  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)  Stroke.Ind.utils <- Stroke.Ind[,1] \* 1 + Stroke.Ind[,2] \* mult.s1 + Stroke.Ind[,3] \* mult.s2  Stroke.Dep.utils <- Stroke.Dep[,1] \* mult.s3 + Stroke.Dep[,2] \* mult.s4 + Stroke.Dep[,3] \* mult.s5  Stroke.Ind.utils.mean <- Bootstrapper(Stroke.Ind.utils)  Stroke.Dep.utils.mean <- Bootstrapper(Stroke.Dep.utils) | 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.  The function defaults to running 10,000 bootstraps of the dataset. This can be adjusted by specifying a different ‘simulates’ argument.  Loads a library containing the rdirichlet() function used later.  Specify that PSA involves 10,000 sets of draws  **NODE 1**  Specifies that the object Dead\_nonDead should be created containing 10,000 draws from a binomial distribution.  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.  **NODE 2a + NODE 3A**  This creates a matrix containing the output of 10,000 draws from a dirichlet distribution populated by the values from table 1 of the 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.  **NODE 7a**  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  **NODE 7b**  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.  **BOOTSTRAPPING**  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. |
| **R code** | **Comments** |
| GOS\_5 <- mRS\_followingStroke[,1:2]  GOS\_4 <- mRS\_followingStroke[,3:4]  GOS\_3 <- mRS\_followingStroke[,5:6]  GOS\_5.sums <- apply(GOS\_5, 1, sum)  GOS\_4.sums <- apply(GOS\_4, 1, sum)  GOS\_3.sums <- apply(GOS\_3, 1, sum)  GOS\_5 <- apply(GOS\_5, 2, function (x) x / GOS\_5.sums)  GOS\_4 <- apply(GOS\_4, 2, function (x) x / GOS\_4.sums)  GOS\_3 <- apply(GOS\_3, 2, function (x) x / GOS\_3.sums)  GOS\_5.utils <- GOS\_5[,1] \* 1 + GOS\_5[,2] \* mult.s1  GOS\_4.utils <- GOS\_4[,1] \* mult.s2 + GOS\_4[,2] \* mult.s3  GOS\_3.utils <- GOS\_3[,1] \* mult.s4 + GOS\_3[,2] \* mult.s5  n.bootstraps <- 10000  GOS\_5.mean <- vector("numeric", n.bootstraps)  GOS\_4.mean <- vector("numeric", n.bootstraps)  GOS\_3.mean <- vector("numeric", n.bootstraps)  for (i in 1:n.bootstraps){  GOS\_5.mean[i] <- mean(GOS\_5.utils[sample(1:N.PSA, n.bootstraps, replace=T)])  GOS\_4.mean[i] <- mean(GOS\_4.utils[sample(1:N.PSA, n.bootstraps, replace=T)])  GOS\_3.mean[i] <- mean(GOS\_3.utils[sample(1:N.PSA, n.bootstraps, replace=T)])  } | Approach for mapping from mRS to GOS  Assuming code above has all been run (so mRS estimates and so on have all been calculated)  **NODE 4a + NOD 4b + NODE 4c**  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).  These commands calculate the sums across the rows of the newly created variables GOS\_5, GOS\_4, and GOS\_3  These commands convert the cell counts into proportions.  **NODE 6a + NODE 6b + NODE 6c + NODE 7a + NODE 7b + NODE 7c**  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.  **BOOTSTRAPPING**  *These commands show how to perform bootstrapping without use of the Bootstrapper function developed earlier*  Sets the number of bootstrap replicates to 10,000  Creates three empty vectors for storing bootstrapped estimates of the means  Produces 10,000 bootstrapped estimates of the means of GOS\_5, GOS\_4 and GOS\_3 |