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The Use Of Mapping To Estimate Health State Utility Values

Running header: mapping onto HSUVs

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Abstract

Mapping functions are estimated using regression analyses and are frequently used to predict health state utility values (HSUVs) in decision analytic models. Mapping functions are used when evidence on the required preference-based measure (PBM) is not available, or where modelled values are required for a decision analytic model, for example to control for important sociodemographic variables (such as age or gender).

This article provides an overview of the latest recommendations including: pre-mapping considerations, the mapping process including data requirements for undertaking the estimation of mapping functions, regression models for estimating mapping functions, assessing performance and reporting standards for mapping studies. Examples in rheumatoid arthritis are used for illustration.

When reporting the results of mapping standards the following should be reported: a description of the dataset used (including distributions of variables used), and any analysis used to inform the selection of the model type and model specification. The regression method and specification should be justified, and as summary statistics may mask systematic bias in errors, plots comparing observed and predicted HSUVs. The final model (coefficients, error terms(s), variance and covariance) should be reported together with a worked example.

It is important to ensure that good practice is followed as any mapping function will only be as appropriate and accurate as the method used to obtain them, for example mapping should not be used if there is no overlap between the explanatory and target variables.

Key points for decision makers

- Mapping functions are generated using regression analyses
- Mapping is typically used to predict required or 'target' health state utility values (HSUVs) and are often used when the required evidence is not available or to link the target HSUV measure to other health related quality of life (HRQoL) or clinical 'source' measures.
- It is important to ensure that appropriate analysis is undertaken prior to estimating regressions, and that appropriate regression models, model specifications and datasets are used together with how and where the predicted HSUVs will be used, as this can inform the selection of the most appropriate mapping function.
- Mapping is inappropriate and will not produce accurate results if a) there is little conceptual overlap between source and target measures, b) the target or source measure is inappropriate in the population of interest, c) the estimation data has not been modelled using appropriate models and model specifications or d) the estimation sample data is unrepresentative of the target sample data it will be applied to.

1. Introduction

The practice of fitting a statistical regression model to data involving measures of health related quality of life is referred to as 'mapping' or 'cross-walking' in the literature. Mapping functions are frequently used to predict health state utility values (HSUVs) in decision analytic models. The mapping functions are obtained using regression analysis, a statistical process used to estimate relationships between variables. In its simplest form, the mapping function (sometimes referred to as an 'algorithm') obtained from the regression will take the form of:

$$y_i = \beta_{1i} + \beta_n X_{ni} + \varepsilon_\iota$$

whereby:

- y is the dependent variable (the target being predicted),
- x is the vector of explanatory variables (sometimes called independent variables or predictors),
- β_n are the coefficients obtained from the regression analysis,
- and ε is the residual (error term), with i indexing the patient

Box 1 Example of a linear function used to explore the relationship between HAQ and EQ-5D

Example 1

A simple linear function was obtained using ordinary least square regressions to provide a relationship between the Health Assessment Questionnaire (HAQ) and EQ-5D in patients with rheumatoid arthritis (Hawthorne et al, 2000). The HAQ ranges from 0 (no disability) to 3 (completely disabled) and EQ-5D ranges from 1 (full health) to -0.59 (worst possible health state). Consequently we would expect any relationship between the two measures to be negative; that is, as HAQ increases, EQ-5D decreases:

$$\mathrm{EQ} - 5\mathrm{D} = 0.86 - (0.20 \times \mathrm{HAQ})$$

The beta coefficient for HAQ (i.e. -0.20) indicates that for every unit increase in HAQ, EQ-5D reduces by 0.20 units, as expected. This relationship is statistically significant at the $p<0.05$ level.

Mapping functions are used to predict health state utility values (HSUVs) in the following cases:

- When the required preference-based measure (PBM) is not included in the dataset of interest,
- To generate HSUVs for a decision analytic model where modelled values are required, for example when sample size is small, to control for important sociodemographic characteristics e.g. age or gender, or when existing evidence is limited e.g. for severe health states

The regression analysis may be undertaken using evidence from the clinical trial of interest or may require access to a separate external dataset. Instances when external datasets are required include when the clinical trial of interest does not collect the required PBM or the evidence collected is limited in ability to inform all health states within the decision analytic model (e.g. does not include patients across the full spectrum of disease severity, or the sample size or numbers of observed clinical events are too small to subgroup for the health states in the decision analytic model) [1] . It is recommended that any mapping exercise is conducted on empirical data [2] .

This paper provides an overview of the pre-mapping considerations, the mapping process including data requirements for undertaking the estimation of mapping functions, regression models for estimating mapping functions, assessing performance and reporting standards for mapping studies. A case-study using published evidence on the relationship between a clinical measure of severity (the Health Assessment Questionnaire (HAQ)) and EQ-5D in rheumatoid arthritis is used as an exemplar throughout (see **Box 1** and the online Appendix (**Table 1)** for additional information on the rheumatoid arthritis mapping examples used).

2 Pre-mapping considerations

Prior to commencing mapping it is important to consider where the mapping functions will be applied. When the function is to be used in a decision model it is important to identify:

- The required PBM (generally informed by the requirements of the reimbursement agency);
- The health state definitions for the decision analytic model (e.g. health states representing discrete clinical events, health states defined by a clinical measure(s) of severity);
- The distribution of patient characteristics (e.g. age, condition, and condition severity range);
- The intervention and comparator(s) under evaluation (are these likely to have an independent effect on health related quality of life (HRQoL)), and the decision analytic model structure (cohort, individual patient simulation).

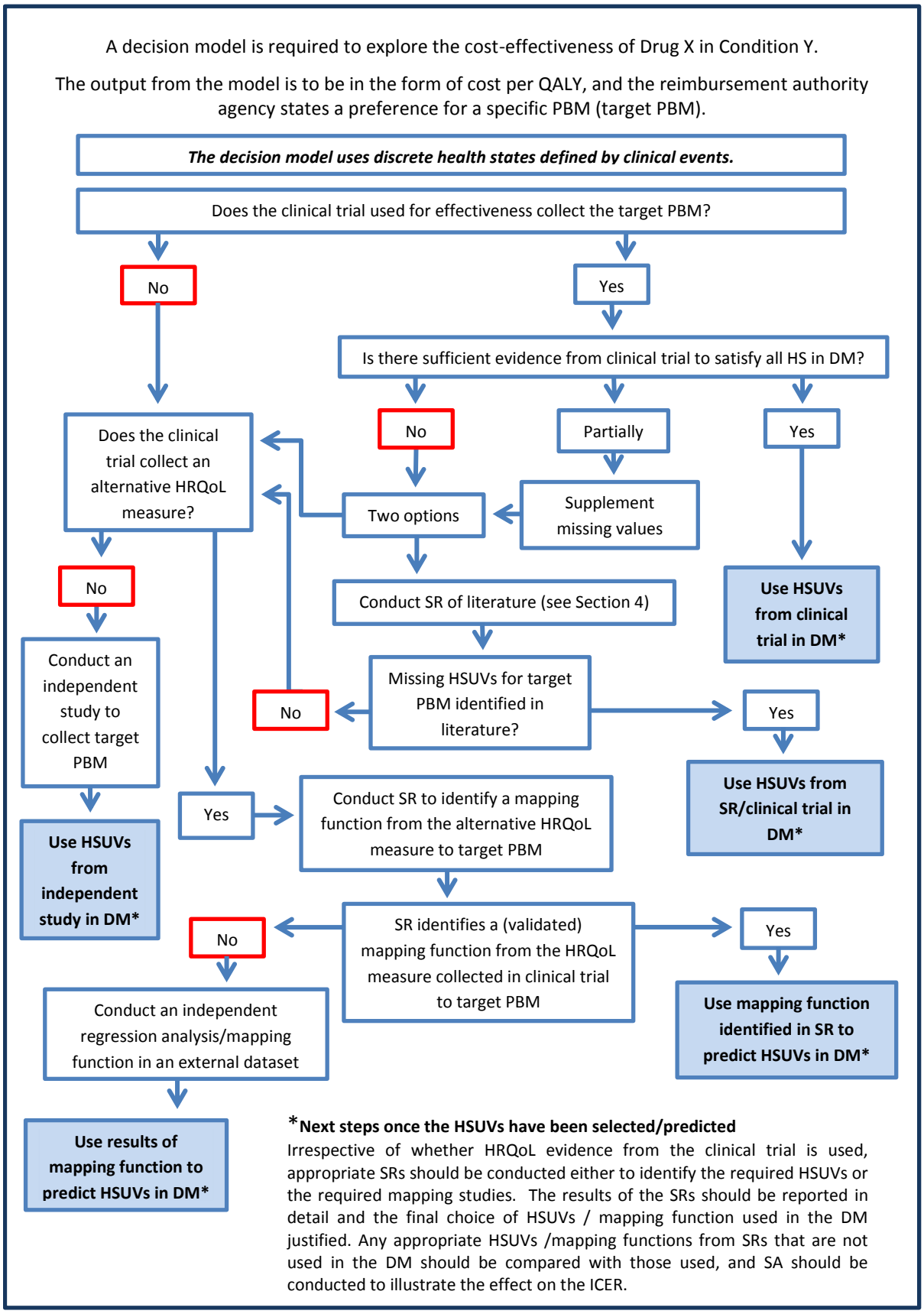
Figure 1a and **Figure 1b** outline the process used to identify if a mapping function is required to predict the HSUVs for a decision model. The first example, **Figure 1a**, has discrete health states which are defined using clinical events, such as fractures in osteoarthritis. The second example, **Figure 1b**, has a series of continuous health states defined by a clinical variable that represents the effectiveness of the treatment under evaluation and also describes the severity of the disease, such as the HAQ used in rheumatoid arthritis. In the latter models, it is particularly important that any mapping function predicts accurate HSUVs across the full spectrum of disease severity used within

the decision analytic model. Of course, if the required PBM and clinical variable are collected in the clinical trial of interest, and the sample is sufficiently large across the full spectrum of disease severity, it is possible to use a series of discrete HSUVs subgrouped by disease severity. Any sampling in probabilistic sensitivity analyses should take into account the relationship to ensure there are no anomalies in sampled values.

If evidence from the required PBM is not available in the clinical trial of interest, then there are two options. The first, and typically preferred option, is to conduct a systematic review of the literature to identify HSUVs using the required PBM, see [3] for guidance on this. The second option if another HRQoL measure is available in the clinical trial of interest, is to conduct a systematic review of the mapping literature to identify validated and appropriate mapping studies (mapping from the HRQoL measure included in the study to the required PBM) [3]. Where no validated and appropriate mapping functions are identified, an external dataset that includes evidence from both the HRQoL measure included in the clinical trial and the required PBM can be used to generate a new mapping function. If no other HRQoL measure has been included then an independent study may need to be undertaken to collect the target PBM. Where the required PBM has been included but there is insufficient evidence to subgroup for all the health states in the decision analytic model, then a systematic review to identify HSUVs is recommended. Identified HSUVs can then be used in the decision model and if none are found, new mapping studies or new data collection of the target PBM may be required.

A database of all existing published functions mapping to EQ-5D is available, and recommended for consideration http://www.herc.ox.ac.uk/downloads/mappingdatabase. (Note: this summarises the sample, model type, measures used, and whether the mapping function is externally validated) [4].

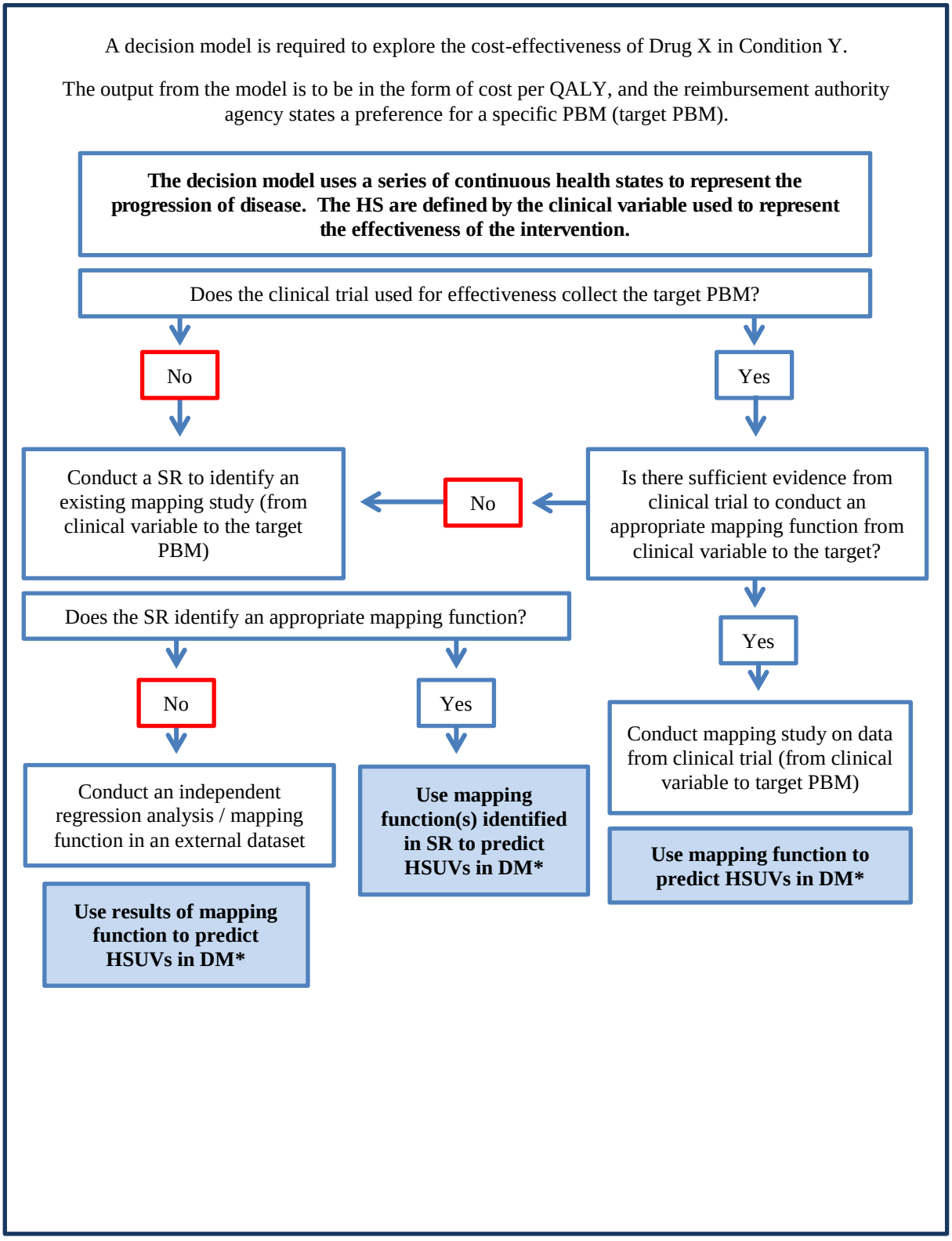
Figure 1a Steps to identifying appropriate HSUVs to inform decision models using discrete health states defined by clinical events



DM: decision model; **HS:** health states in DM; **ICER**: incremental cost-effectiveness ratio; **PBM:** preference-based measures; **HSUV:** health state utility values; **SR:** systematic review; **SA:** sensitivity analysis

irrespective of whether HRQoL evidence from the clinical trial is used, appropriate SRs should be conducted to identify appropriate mapping studies. The results of the SRs should be reported in detail and the final choice of mapping function used in the DM justified. Any appropriate mapping functions from SRs that are not used in the DM should be compared with those used, and SA should be conducted to illustrate the effect on the ICER of using these alternatives.

Figure 1b Steps to identifying appropriate HSUVs to inform decision models using continuous health states to represent the progression of disease



DM: decision model; **HS:** health states in DM; ICER: incremental cost-effectiveness ratio; **PBM:** preference-based measures; **HSUV:** health state utility values; **SR:** systematic review; **SA:** sensitivity analysis

3 Overview of the mapping process

Mapping involves four key stages:

1. Identifying an appropriate estimation dataset .
2. Applying regression techniques to find the best-fit statistical relationship between the measures (either mapping to the index score or the classification system of the target PBM). This stage includes the refinement of the model specifications, the selection of the model type, and assessing the model performance.
3. Applying the regression results to the study dataset of interest to predict HSUVs.
4. Assessing/validating the regression results (through a thorough comparison of predicted and observed HSUVs, comparison with any evidence in the literature, and applying the mapping function in a second dataset which satisfies all the conditions of Step 1. (NB: It is rare that the latter is conducted due to lack of availability of appropriate evidence.)

It is worth noting that regression results can be applied to aggregate values rather than individual levels to produce predictions, such as using summary data published in a paper [14].

3.1 Data requirements for undertaking mapping

The use of a published appropriate mapping function requires access to individual patient level evidence on the explanatory variables used in the mapping function. Where an external estimation dataset is used, all explanatory variables should be in both datasets. The clinical and demographic characteristics, and the distribution of the explanatory variables, should also be similar in both datasets as the statistical relationship may differ at different severities of health [5]. Primary data collection is required if no appropriate estimation dataset exists. There are a number of basic analyses that should be conducted prior to estimating a mapping function (Box 2) [1].

Box 2 Summary of recommendations before estimating mapping functions

Required application of the mapping function

- Determine the range of health states that require utility estimates for the cost-effectiveness model and any important covariates
- Ensure the patient characteristics in the dataset used to estimate the mapping function match those of the proposed cost-effectiveness model, in particular the extremes of disease severity in chronic conditions, or time since event for acute clinical events. If more than one dataset is available, their characteristics should be compared to justify the final dataset choice
- Determine whether a mapping function obtained using statistical regression methods is required, or if mean values from subgroups of patients will suffice

Relationships between explanatory and independent variables

- Examine the characteristics (dispersion, distribution, atypical values etc) of both the explanatory and dependent variables, including the level of overlap or relationship between the variables
- Identify whether the relationship between the explanatory and dependent variables is likely to be influenced by any intervention the patient will receive

Source: Adapted from Wailoo et al, 2017 [1]

3.2 Explanatory and target PBM variables

The vast majority of mapping functions tend to use HSUVs (i.e. the preference-based index used to estimate quality adjusted life-years (QALYs)) as the dependent variable. For the UK EQ-5D-3L measure this would be the HSUVs which range from one (representing no problem on any of the five dimensions) to -0.59 (representing extreme problems on all five dimensions). The usefulness of

functions obtained using the preference-based index as the dependent variable is constrained to the setting of the preference-weights used. For example, a function obtained using the UK EQ-5D-3L preference weights cannot be used to generate EQ-5D-3L HSUVs suitable for the Netherlands (which have their own set of preference-weights for the EQ-5D).

An approach that can be used to predict HSUVs for alternative sets of preference-weights is known as 'response mapping' [6]. Again using the EQ-5D-3L as an example, response mapping uses logistic regressions (one regression for each dimension) and the responses to the dimension questions (as opposed to the preference-based index) as the dependent variables [7]. The predicted values from the logistic models (five models predicting the probability of scoring 1, 2 or 3 on the five dimensions) are then used together with the required preference weights for each of these responses to predict the associated EQ-5D HSUV. Interested readers are pointed to Ara, Kearns & Brazier [7] for a worked example.

The choice of both the dependent and explanatory variables will be informed by the evidence available in the datasets used for mapping, and where the mapping function will be applied. For example if the mapping function is to be used in a decision analytic model that will be adapted to inform policy decisions in multinational settings, response mapping avoids the need to obtain different mapping functions for each required set of preference weights.

Prior knowledge as well as standard techniques should be used to examine the relationship between the explanatory and dependent variables to inform choice of model specification including the inclusion of interaction or squared terms (example provided in **Box 3**).

Box 3 An example where additional explanatory variables are included when exploring the relationship between HAQ and EQ-5D in Rheumatoid Arthritis (RA)

Example 2

The HAQ does not include any information on pain levels, but EQ-5D has a pain dimension. Hurst and colleagues explored the effect of including additional explanatory variables (including a measure of pain) [8]:

$$\text{EQ} - 5\text{D} = 1.12 + (-0.188 \times \text{HAQ}) + (-0.008 \times \text{HAD} - \text{mood}) + (-0.003 \times \text{Pain} - \text{VA scale}) + (-0.068 \times \text{disease activity})$$

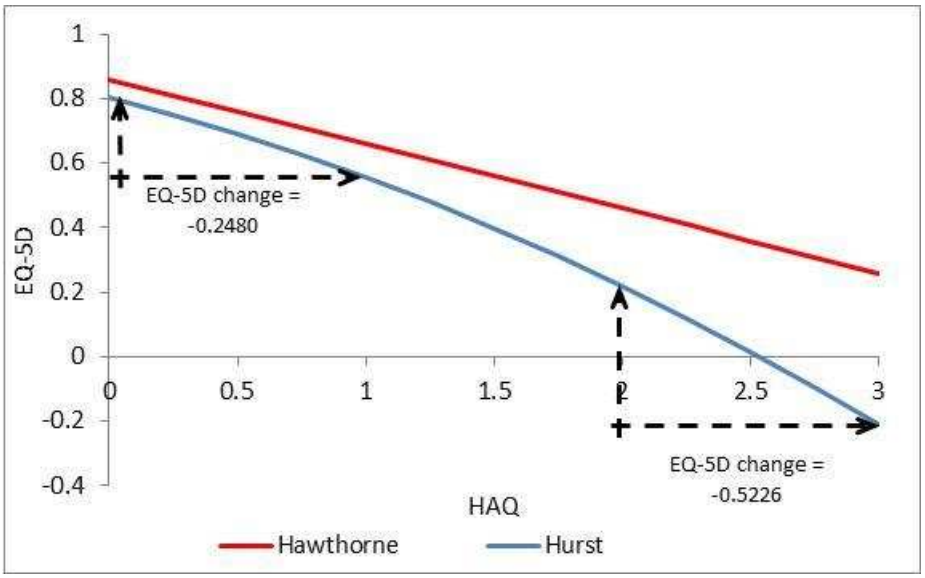
The beta coefficient for pain-VA scale (-0.003) was statistically significant at the $p<0.05$ level, and illustrates that as pain increases, EQ-5D decreases, as expected.

Relationships between measures are not always linear, and the possibility of a curved relationship between EQ-5D and HAQ was explored through the inclusion of a squared term in the analyses used to inform a Rheumatoid Arthritis model [9].

$$\text{EQ} - 5\text{D} = 0.804 - 0.203 \times \text{HAQ} - 0.045 \times \text{HAQ}^2$$

The beta coefficient for HAQ squared was statistically significant. It is clear from the figure below that the relationship between EQ-5D and HAQ now changes across the indices, with a greater magnitude per unit change at more severe levels. Consequently a change in HAQ from 3 to 2 produces a greater change in EQ-5D (EQ-5D change = -0.5226) than a change in HAQ from 1 to 0 (EQ-5D change = -0.2480) See Figure 2.

Figure 2: Plot illustrating magnitude of change in EQ-5D associated with one unit change in HAQ



It is important that both the required PBM and any measure of HRQoL used as an explanatory variable (e.g. an alternative generic preference-based measure (GPBM) or condition specific measure (CSM)) are valid for use in the population where they are being applied. If either measure is not appropriate (i.e. not relevant or insensitive) for the condition of interest, then mapping between the measures is also inappropriate [10]. It is also important that there is conceptual (i.e. they are measuring similar concepts or dimensions as shown using a comparison of the conceptual domains of each measure) and empirical (i.e. they are correlated) overlap between the dependent and explanatory measures. The mapping function will not produce accurate predictions of HSUVs if there is little overlap, and the model may suffer from omitted variable bias. Evidence shows that this is more likely when mapping from condition-specific measures to GPBMs. One example where there was little overlap was mapping the overactive bladder questionnaire onto the SF-6D [10], potentially suggesting that the generic measure was insensitive in this patient group. If this occurs a better solution may be to consider a condition-specific preference-based measure.

Sample size considerations also apply, for example item-level dummy models for explanatory measures with many items may not be appropriate in small datasets. In addition sample characteristics are also important, for example a dataset with few responses in severe health is unlikely to enable the estimation of accurate mapping functions for severe health. Summary

statistics and distributions of the dependent and explanatory variables used in the mapping should be reported.

3.3 Regression models

A range of different statistical models can be used to estimate mapping functions, and the literature exploring different approaches is increasing each year. The most appropriate model for use will depend on the measures involved, the distribution of the dependent variable, the relationship between the dependent and explanatory variables, any interactions between the variables, and the evidence available in the datasets used. Plots of the dependent variable are particularly useful as they indicate the distribution of the data which is informative for selection of the regression method. **Box 4** provides a checklist for the steps to take when designing and choosing a model to estimate the mapping function (see Appendix **Box 1** , and papers by Hernandez and colleagues [11;12] for additional information and empirical examples).

When a HRQoL measure is used as an explanatory variable, mapping can be performed by modelling from the total score, the dimension scores, the item scores, or the item responses [10].

Box 4 Recommendations for estimating mapping functions

Summary of statistical modelling recommendations

1. Assess range and distribution of utility score (summary statistics and plot) or dimensions of explanatory variable (target PBM)
2. Use the simplest regression models possible that satisfy associated assumptions considering the distribution of the target# utility score or dimensions3. Select explanatory variables using theory and observed relationships. Include all variables considered important as omission can risk mis-specification and biased estimates.
3. Select the final model using good practice techniques for all regression analyses, including performance and model fit (see Table 2).

[#] *the target utility is the dependent variable*

Source: Adapted from: Wailoo et al, 2017 [1]

While linear ordinary least squares (OLS) is the simplest approach and is frequently used as a starting point, this may be inappropriate for the distribution of the preferred PBM. Much of the literature has focussed upon mapping to EQ-5D and models obtained using OLS regressions have a tendency to under-predict at the top and over-predict at the bottom of the index [10]. The EQ-5D-3L distribution poses particular challenges as the data are typically bimodal or trimodal, with a large proportion of responses at one (full health), and peaks for moderate health states and severe health states. Tobit and censored least absolute deviation (CLAD) models have been used as a way of dealing with the large proportion of responses at one, though these do not always offer an improvement in predictive accuracy [5]. Although the latent class mixture model, censored mixture model and multinomial logit model have all been used to model the trimodal distribution more appropriately, these models can prove difficult to estimate on smaller samples. When mapping between HRQoL measures, while the accuracy of the predicted values will be governed by the degree of content overlap to some degree, a mis-specified model will not produce the most accurate predictions.

3.4 Selecting and applying mapping functions

Published appropriate mapping functions are potentially the preferred first option but it is important to review these thoroughly and justify the final choice through comparing the characteristics of the dataset used in the regression analyses to those where the function will be applied, and the reported predictive ability of the function [5]. Particular consideration should be given to potential errors if the function is to be used to predict values beyond the limits of any of the variables used in the regression analyses (this relates to both the dependent and explanatory variables). If there is sufficient evidence for the preferred PBM in the clinical study used to inform the effectiveness of the

intervention in a decision model, it may be appropriate to estimate a mapping function using the evidence from the clinical study, but this will depend on why mapping is required, the quality of the evidence, and the availability of alternative external datasets.

For de-novo studies, the selection of the final mapping function in terms of regression model, dependent and explanatory variables, will depend on performance. Alongside predictive ability (the difference between observed and predicted HSUVs reported as mean error, root mean square error or mean absolute errors), other information such as goodness of fit, information criterion and whether regression methods assumptions are met should also be reported (see **Table 1** for an explanation of statistics).

Table 1 Overview of standard statistics used in mapping

Model fit	
R^2	R-squared describes the proportion of the variation in the dependent variable explained by the explanatory variables (not recommended for comparisons across models estimated on the same data as the statistic can vary according to the number of explanatory variables)
Adj R^2	Adjusted R-squared describes the proportion of the variation in the dependent variable explained by the explanatory variables and adjusts this for the number of explanatory variables included in the model (enabling comparisons across models estimated on the same data with different explanatory variables included)
AIC	Akaike Information Criteria is a measure of the quality of a regression model within a dataset, where a lower value indicates a better model
BIC	Schwarz Information Criteria is a measure of the quality of a regression model within a dataset, where a lower value indicates a better model, and this incorporates a penalty for the inclusion of a larger number of explanatory variables
Predictive abilities	
Errors	The difference in observed and predicted values. Provide an indication of predictive ability but mean errors can mask systematic errors e.g. across the distribution. Typically MAE is reported and further reported for subsets of the data e.g. according to disease severity, range of the explanatory variable(s) or range of the dependent variable
MAE	Mean Absolute Error
RMSE	Root Mean Squared Error
Other	
Correlation	Examines the association between dependent and explanatory variables to determine overlap

The recommended mapping function should be reported together with the statistics needed to undertake univariate and probabilistic sensitivity analyses (confidence intervals or standard errors around the betas, and the variance covariance matrix (a standard output from the regression analysis in many statistical software packages)). The error term distribution is also important to reflect individual level variability in HSUVs. If a published mapping function is used, and the required statistics are not available to explore the variance in the predicted HSUVs, a threshold analysis can be conducted to determine the HSUVs required to ensure the results from the decision model would be considered cost-effective.

An important consideration when performing mapping functions is whether the results are to be used in a cohort model or an individual level simulation. The former will require mean HSUVs which generally tend to be in the central area of a PBM's range, while the latter is far more likely to require a much wider range of HSUVs. This is particularly important when assessing the predictive ability of the mapping function, including when sampling for probabilistic sensitivity analyses.

4. Reporting standards for mapping studies

A summary of recommendations for reporting mapping studies from a recent ISPOR task force is provided in **Box 5** and additional details are available from the MAPS statement) [13]. It is good practice to fully describe the dataset used to estimate the mapping function, including the distribution (e.g. range, mean, standard deviation) of all variables used in the regression, and any analysis used to inform the selection of the model type and model specification (see Hernandez Alava et al [12] for a worked example). The regression method and specification should be justified, and sufficient information should be provided to enable the reader to determine whether these are appropriate. Mean errors can mask systematic bias in the errors across the range of predicted HSUVs and it has been suggested that errors in subgroups such as EQ-5D range (EQ-5D < 0, 0-0.25, 0.25-0.5, 0.5-0.75, 0.75-1) should also be reported [5].

Plots comparing observed and predicted mean HSUVs are particularly useful as they indicate how well the model fits the data and indicate any areas where the error in the predictions may be larger, such as more severe health states (see **Figure 5** in Hernandez Alava et al[11] where the observed and predicted EQ-5D scores are plotted across the range of observed HAQ scores). Providing further details on the size of the errors is recommended, reporting errors either by severity categories using a clinical variable or across the range of the PBM (see **Table 5** in Hernandez Alava et al[11] which

provides mean errors in the HSUVs predicted using the alternative functions sub-grouped by HAQ score).

Of prime importance is that the output clearly describes how to use the mapping algorithm to predict HSUVs in another dataset. Further validation of performance of mapping functions is recommended where this is possible, ideally in an independent sample where predicted and observed HSUVs can be compared to indicate the accuracy of the predictions. However, this is not routinely expected due to the frequent lack of suitable datasets.

Box 5 Recommendations of reporting standards for mapping studies

Summary of reporting standards recommendations

Summary of dataset

1. Describe the characteristics of all candidate datasets including any relevant differences
2. Describe the dataset selected including study characteristics, patient recruitment, patient characteristics including disease severity, at baseline and follow-up. In longitudinal datasets, where possible missing responses should be analysed and any identified pattern described.
3. Summarise and plot the distribution of the target utility measure.
4. Describe the estimated models including their appropriateness in the dataset given the data properties and distribution.
5. Describe the selection of explanatory variables including the theory and observed relationships used to inform selection.
6. Describe model performance and fit. Provide information on errors presented in terms of disease severity (subgrouped by the clinical outcome measure(s) where possible or the target utility measure), using a table or plot. Describe model selection including any tests or judgements used in the process.
7. Provide details of the final model including: coefficient values, error term(s) distributions(s), variances and covariances.
8. Provide model syntax, an excel program or a worked example that enables readers to use the final model to produce mapped predictions in another dataset. Describe parameter uncertainty in the final model and the suitability of the model in terms of future sampling in cost-effectiveness probabilistic sensitivity analysis to determine whether predicted values lie within the feasible utility range for the PBM.

Source: Adapted from Wailoo et al, 2017 [1]

5. Strengths and limitations of mapping

Mapping allows appropriate HSUVs to be generated for use in decision models including extrapolation, inclusion of important covariates that may affect the HSUVs and where they are completely missing. In the case where validated mapping functions based on appropriate data are available, then mapping can provide a quick and easy way to generate HSUVs. It also provides a pragmatic solution to generating the HSUVs required in a decision model where appropriate data is available..

However, mapping will introduce additional uncertainty to the analysis, and should be considered as a second-best solution compared to directly collected HSUVs [5]. Published mapping functions may not report all the recommended information that is required to judge whether or not the recommended mapping functions are appropriate for use. Furthermore, datasets that are used are often based on a pragmatic choice e.g. an existing trial, which may be limited in application across other studies of interest, meaning that the accuracy of the mapped results may be reduced. In addition many existing studies are limited in their sample size, for example if they are collected using an existing trial, and where larger datasets are available these are often general population datasets that have limited data for more severe states. Some studies have found that the size of the error increases for more severe states [18], due to both a combination of limited data availability in these states and limitations of the models used to estimate the mapping functions. However, it has been found that this limitation may have limited impact on the accuracy of economic evaluations using mapped values as these focus on the *differences* in QALYs over time or across groups rather than the levels [14]).

The accuracy of mapping functions is also affected by the overlap between the target and explanatory variables, and explanatory variables that are clinical or from a condition-specific measure may have little or limited overlap with the target utility measure, for example the overlap may be limited to only a subset of the dimensions of the preference-based measure. Some condition-specific measures can also fail to capture all co-morbidities and side-effects, and hence this will impact on the ability of the condition-specific measure to predict the target utility measure.
Mapping is inappropriate and will not produce accurate results if a) there is little conceptual overlap between source and target measures, b) the target or source measure is inappropriate in the population of interest, c) the estimation data has not been modelled using appropriate models and model specifications or d) the estimation sample data is unrepresentative of the target sample data it will be applied to.

6. Summary

This article has outlined the process when using either existing published or new mapping functions. It covers considerations relating to where the HSUVs will be used and how the mapping functions should be generated, including data requirements, regression methods/models. Common issues and existing recommendations are summarised together with a checklist for minimum reporting standards. Mapping is of increasing interest as it enables appropriate HSUVs to be estimated for use in decision models. It is important to ensure that good practice is followed as any mapping results will only be as appropriate and accurate as the method used to obtain them.

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Author contributions

RA wrote the manuscript. DR reviewed the literature and contributed to the manuscript. CM contributed to the manuscript.

Compliance with Ethical Standards

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APPENDIX

Box A1 Sources used in the RA case-study

The introduction of biological drugs for the treatment of inflammatory arthritis instigated an abundance of economic evaluations exploring the cost-effectiveness of these interventions in patients with rheumatoid arthritis, the most common form of inflammatory arthritis. The health assessment questionnaire disability index (HAQ) was invariably used to represent the effectiveness of interventions in clinical trials. The HAQ covers eight categories of function including dressing, eating, walking, hygiene, reach, grip and usual activities and is scored on a summary scale from 0 (no disability) to 3 (completely disabled). Although scored in increments of 0.125 the HAQ is generally treated as a continuous variable.

The HAQ measure was used to represent the benefits of treatments, and to define health states and progression of the condition within the decision analytic models. As preference-based measures (PBM) were not typically collected in the clinical trials, it was necessary to obtain the required HSUVs from alternative sources. Due to the definitions of health states within the decision models, in the majority of cases, a continuous relationship between HAQ and a PBM was required.

Almost all early publications reported simple linear relationships obtained using ordinary least square (OL) regressions, and frequently used just the HAQ as an explanatory variable (although some included additional explanatory variables such as age, gender, pain, or disease activity) (see Pennington & Davis [15] for the impact of different mapping algorithms from HAQ to EQ-5D in patients with RA within the same cost-effectiveness model). As biologics are indicated for patients at the more severe end of the disease spectrum, the HAQ could progress to the most extreme level (i.e. HAQ = 3) in decision analytic models. Functions obtained using OLS regressions tend to overestimate HSUVs at the bottom end of the PBM and underestimate HSUVs at the top of the PBM, consequently, these functions would underestimate the potential benefits of treatment.

Hernández and colleagues explored alternative models in a large dataset and the interested reader can find details of the research and decision making process for the final model in their publications [11;12;15].

Table A1 Alternative models reported in the sources used in the case-study examples

Author, year, model	Function obtained from regressions
Hawthorne et al, 2000 [16] **Linear OLS**	$\text{EQ} - 5\text{D} = 0.86 - (0.20 \times \text{HAQ})$
Marra et al, 2007 [17] **Linear OLS**	$\text{EQ} - 5\text{D} = 0.72 - 0.20 \times \text{HAQ} + 0.25 \times \frac{\text{Age}}{100}$
NICE, 2010 [9] **Linear OLS**	$\text{EQ} - 5\text{D} = 0.804 - 0.203 \times \text{HAQ} - 0.045 \times \text{HAQ}^2$
Hurst et al, 1997 [8] **Linear OLS**	$\text{EQ} - 5\text{D} = 1.12 + (-0.188 \times \text{HAQ}) + (-0.008 \times \text{HAD} - \text{mood}) + (-0.003 \times \text{Pain} - \text{VA scale}) + (-0.068 \times \text{disease activity})$
Hernandez Alava et al, 2012; 2013 [11;12] **Linear OLS**	$\text{EQ} - 5\text{D} = 0.941 - 0.084 \times \text{HAQ} - 0.045 \times \text{HAQ}^2 - 0.478 \times \frac{\text{VASpain}}{100} + 0.019 \times \frac{\text{Age} - 54.32}{10} + 0.005 \times \left(\frac{\text{Age} - 54.32}{10}\right)^2 - 0.046 \times \text{male} + 0.028 + 0.010$
Hernandez Alava et al, 2012; 2013 [11;12] **Tobit**	$\text{EQ} - 5\text{D} = \text{minimum}\{y, 1\}$ where $y = 1.013 - 0.165 \times \text{HAQ} - 0.022 \times \text{HAQ}^2 - 0.499 \times \frac{\text{VASpain}}{100} + 0.018 \times \frac{\text{Age} - 54.32}{10} + 0.007 \times \left(\frac{\text{Age} - 54.32}{10}\right)^2 - 0.047 \times \text{male} + 0.032 + 0.012$
Hernandez Alava et al, 2012; 2013 [11;12] **adjusted censored mixture model**	$\text{EQ} - 5\text{D} = \begin{cases} 1 \text{ if } y > 0.883 \\ y \text{ otherwise} \end{cases}$ where $y = a \times \frac{j}{j+k+l} + b \times \frac{k}{j+k+l} + c \times \frac{l}{j+k+l}$ $a = 0.343 - 0.062 \times \text{HAQ} - 0.295 \times \frac{\text{VASpain}}{100} + 0.007 \times \frac{\text{Age} - 54.32}{10} + 0.004 \times \left(\frac{\text{Age} - 54.32}{10}\right)^2 - 0.012 \times \text{male} + 0.015 + 0.002$ $b = 0.990 - 0.245 \times \text{HAQ} - 0.068 \times \text{HAQ}^2 - 0.105 \times \frac{\text{VASpain}}{100} + 0.007 \times \frac{\text{Age} - 54.32}{10} + 0.004 \times \left(\frac{\text{Age} - 54.32}{10}\right)^2 - 0.012 \times \text{male} + 0.006 + 0.002$ $c = 0.806 - 0.160 \times \text{HAQ} - 0.025 \times \text{HAQ}^2 - 0.056 \times \frac{\text{VASpain}}{100} + 0.007 \times \frac{\text{Age} - 54.32}{10} + 0.004 \times \left(\frac{\text{Age} - 54.32}{10}\right)^2 - 0.012 \times \text{male} + 0.003 + 0.002$

EQ-5D – EuroQol five-dimensional questionnaire; **HAQ** – Health Assessment Questionnaire