**Formulário de acesso a dados do Registo Nacional de Doentes Reumáticos (Reuma.pt) da SPR, 2012-2014**

## 1. Title

Mapping from the Ankylosing Spondylitis Disease Activity Score (ASDAS) to EQ5D in patients with Axial Spondyloarthritis (axSpA)

## 2. Introduction

### 2.1 Literature review

Economic evaluation, conducted in terms of cost per Quality Adjusted Life Year (QALY), strongly influences pricing and reimbursement decisions for new health technologies in many countries across the world. The calculation of QALYs requires patient outcome measures of a particular type. They must be preference-based, with the EuroQoL EQ-5D being the most widely used example.

However, whilst many clinical trials will include a battery of clinical measures and disease specific outcomes they often lack a preference-based measure. Even where they do include such a measure, this might be insufficient for the needs of the economic evaluation. For example, the trial may not be of sufficient duration to fully inform the economic analysis.

In this situation, economists regularly use an approach called "utility mapping" to bridge the gap between the available clinical evidence and that required for economic evaluation. Mapping estimates the relationship between the outcome measures found in clinical trials and the preference based measures required for economic evaluation, using some external dataset where patients have completed both.

The use of mapping is widespread across many disease areas, but has been particularly important in the assessment of technologies for patients with axial SpA.(1)

### 2.2 Previous work

Mapping has previously been used to map from the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI) to EQ5D in patients with Axial SpA.(2, 3) However, the Ankylosing Spondylitis Disease Activity Score (ASDAS) is increasingly being used in clinical studies and recommended internationally as the preferred disease activity measure in axial SpA, namely by the Assessment of Spondyloarthritis International Society (ASAS) and the European League against Rheumatism (EULAR).(4) ASDAS inactive disease (ASDAS<1.3) has also been suggested by an international task force of experts

as the preferred target in a treat-to-target approach in axial SpA.(5) Therefore, there is a pressing need for a mapping study to be performed that estimates EQ5D from ASDAS. It is also imperative that appropriate methods are used for such mapping. It has been shown that a failure to use appropriate methods leads to a systematic underestimation of the health benefits of new technologies.

Our team has led research on methods for conducting mapping studies. We led the development and publication of a Good Practice Guide in this area.(6) Our mapping study in Ankylosing Spondylitis (AS) has been used to underpin economic evaluations, for example NICE's 2016 recommendations for the use of TNF-alpha inhibitors for AS and non-radiographic SpA.

**2.3 Hypothesis**

We expect that this project will result in an accurate mapping algorithm that will enable EQ5D to be estimated using ASDAS and other characteristics. This will enable the prediction of EQ5D in data for which preference-based measures (PBM) are not collected.

**2.4 Innovation and significance**

In many countries, decisions about the use of new technologies rely on economic evaluation. This project is essential to allow such evaluations to be performed. We also know that mapping using simple methods leads to estimates of cost effectiveness that are systematically biased. The proposed project is therefore expected to have real consequences for the therapies that clinicians and patients are able to access.

Any algorithms which are produced in this analysis will also be made publicly available and could be applied to other datasets which include ASDAS but not EQ5D.

We expect that this work will lead to at least two publications in leading academic journals. One publication that demonstrates how the algorithm was calculated and will include the algorithm for others to use and one publication discussing the impacts on cost-effectiveness analysis. In addition, there is potential for other publications, including the validation of the previously estimated mapping algorithms for BASDAI and BASFI and the comparison of mapping algorithms for ASDAS and these other disease specific measures used in AS.

**3. Specific aims**

**PRIMARY AIM**

**3.1.** Create a utility mapping algorithm from ASDAS to EQ5D and make this available for use in cost-effectiveness analyses.

**SECONDARY AIMS**

**3.2.** Validate previous work that mapped from BASDAI and BASFI to EQ5D to determine how applicable previous results are to different samples of data.

**3.3.** Compare utility mappings across the different disease specific measures, including determining the impact that using different measures has on cost-effectiveness analysis.

**3.4.** Investigate the relationships between the disease specific measures and economic outcome measures in different subgroups in the sample.

## 4. Methods

### 4.1. Study design

We will perform a retrospective cohort study including all patients with axial SpA in the Reuma.pt registry.

Inclusion criteria: Patients with axial SpA included in Reuma.pt.

Exclusion criteria: Patients with missing data for the main variables analysed.

Of note, we are planning to submit a similar proposal to the SPACE (Spondyloarthritis Caught Early) Cohort, with the aim of merging data from both datasets.

### 4.2. Variables description and analysis plan

***The key variables are:***

1. ASDAS total score and all the ASDAS questions individually
2. EUROQoL EQ5D-3L (separate dimensions) - I assume this means that we will have the response to each one of the EQ5D-3L questions
3. BASDAI total score and individual questions
4. BASFI total score and individual questions

***Other variables (if available) will allow us to better characterize the population and potentially do some subgroup analysis:***

1. Patient characteristics
2. Treatment (mainly NSAIDs only or Biologics)
3. Demographic and socio-economic data
4. Classification criteria (mainly fulfilment of ASA criteria, AS or nr-axSpA)
5. CRP, ESR and HLA-B27 status
5. BASMI

6. Baseline mSASSS
7. Baseline MRI SIJ inflammation (yes/no or an MRI score)
8. Baseline MRI spine inflammation (yes/no or an MRI score)

We are requesting longitudinal data i.e. data from all visits available.

The Ankylosing Spondylitis Disease Activity Score (ASDAS) contains 4 dimensions which score patients between 0 and 10, with 10 being the most severe state. In addition, it includes the patients C- reactive protein (CRP) measured in mg per litre.
EQ5D-3L covers 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and each dimension has 3 response levels (no problems, some problems, extreme problems). It is designed for self-completion, has a low response burden and is applicable to a range of diseases and treatments. EQ-5D-3L has a distinctive distribution which includes a multimodal distribution bounded between -0.594 and 0.883, as well as a mass of observations at 1, representing full health. These properties are difficult to estimate using standard statistical techniques.

For the reasons outlined above, we will use methods developed recently in the literature specifically for utility mapping. We will use two different mixture models, both of which were developed specifically for utility mapping. Mixture models have been proven to outperform standard linear regressions and other commonly used techniques for mapping.(7-9) They use multiple components, allowing the model to be very flexible and reflect the multimodal nature of the outcome measures to be estimated. The two models outlined below also prevent predictions outside the feasible range: less than -0.594, above 1 as well as the unfeasible gap between full health and the next feasible health state at 0.883.

The first mixture model we will use is an adjusted limited dependent variable mixture model (ALDVMM) implemented using the publicly available Stata command 'aldvmm'.(8) This model has previously been used to map from BASDAI and BASFI to EQ5D(2), as well as a range of other empirical examples(2, 8, 10, 11). The ALDVMM is a bespoke model developed specifically for utility mapping and the Stata function includes a number of user-specified options to tailor the method to the target utility instrument and country specific tariff of interest. This includes specifying the next feasible value after full health. This "truncation point" allows the creation of the typical gap seen in PBMs just below full health. There is the option to specify no truncation and therefore allow each component of the mixture model to

be fully continuous up to the highest feasible value of 1 for full health. The method has previously been described in detail(7). In brief, ALDVMM is a mixture of adjusted, normal distributions for use when the dependent variable is limited above at 1 (full health) and below, in this case at -0.594. As well as estimating the model with different numbers of components, we will also estimated it with and without truncation.

The second mixture model is a beta-based mixture model (betamix) implemented using the user-written Stata command 'betamix'. This model has previously been used to map from the Asthma Quality of Life Questionnaire (AQLQ) to EQ5D-5L in patients with asthma. The same as ALDVMM, the betamix command allows the user to specify the characteristics of the preference-based measures (PBMs) of interest, including the upper and lower limits of the PBM, whether or not there is a gap between full health and the next feasible health state and the number of components in the mixture model. In addition, betamix allows the user to specify whether there are probability masses at certain parts of the distribution, allowing estimation to account for the relatively large number of values at 1, and potentially a spike in values at the next feasible health state and the worst possible health state. In brief, betamix is a two-part model. Part one is a multinomial logit model which determines whether an observation belongs to one of the specified probability masses or the main distribution estimated by the mixture model. The second part of the model is the mixture model which consists of a mixture of beta distributions. This mixture model is transformed from the specified boundary values on to a (0,1) interval for the purposes of estimation before being transformed back to the original boundaries for interpretation. As well as estimating the model with different numbers of components, we will also estimate it with and without truncation, and with and without probability masses at different parts of the distribution: full health, the next feasible state and worse possible health.

We will estimate the two models described here with a number of different user-specified options, including different numbers of mixture components, with and without a gap immediately below full health and for the betamix only, the inclusion of different probability masses. In order to determine the most appropriate specification for each model, we will use a number of model selection criteria. The preferred model will be chosen using the root mean squared error (RMSE), absolute error and Akaike and Bayesian Information Critera (AIC and BIC, respectively) as well as visual representations of the model fit to help determine the best fitting model.

As well as the main analysis mapping ASDAS to EQ5D, we will also use the Reuma.pt data to validate the results from Wailoo et al (2015) which mapped from BASDAI and BASFI to EQ5D-3L.(2) As well as verifying the previous mapping algorithms this will also allow us to compare the mapping algorithms to determine whether they produce similar EQ5D values in patients. We will determine which of the measures can help to predict EQ5D most accurately, therefore informing cost-effectiveness analysis more accurately.

#### 4.2.4 Sample size

There is no specific power calculation for this type of study. The higher the number of patients the more robust will be the models that we are able to build. Therefore we are requesting data from all Reuma.pt patients with a diagnosis of axSpA (non-radiographic and radiographic axSpA).

## 5. Limitations and expected results

**Expected results:**

We expect that this study will result in a usable utility mapping algorithm for use in cost-effectiveness analysis, allowing EQ5D to be estimated from the ASDAS measure in patients with Axial SpA. We expect to see differences in this relationship in patients with different characteristics. We expect that our results will validate previously created mapping algorithms to estimate EQ5D from both BASDAI and BASFI. Finally, we expect to see an improved accuracy in cost-effectiveness analysis when using these mapping algorithms compare to estimated EQ5D using other methods.

**Limitations include:**

Depending on the number of missing data, the robustness of our models may be affected.

## 6. Timeline

We propose to start this project as soon as we receive the data and will complete within a maximum of one year. We are seeking external (academic) funding which, if successful, will allow the work to be completed more quickly.

## 7. Research team and institutions

- Pedro Machado: University College London, London, UK
- Pedro David Carvalho: Centro Hospitalar e Universitário do Algarve, Faro, Portugal
- Laura Gray: University of Sheffield, Sheffield, UK

- Allan Wailoo: University of Sheffield, Sheffield, UK
- Dr Monica Hernandez: University of Sheffield, Sheffield, UK

**Statistical analysis**

Laura Gray will be responsible for statistical analysis in this project. Laura studied BSc Economics and Statistics at the School and Mathematics and Statistics at the University of Sheffield and obtained her undergraduate degree in 2009. She completed her MSc in Financial Economics at the Department of Economics, University of Sheffield in 2010. In 2016, she completed her PhD in the Econometrics of Obesity in the School of Health and Related Research (ScHARR) also at the University of Sheffield (title of thesis: "A Public Health Approach to Childhood Obesity: the Role of Econometrics"). Since 2014 she has worked as a research associate in the Health Economics and Decision Science section of the School of Health and Related Research (ScHARR) at the University of Sheffield. She has worked on a number of projects that have involved utility mapping using mixture models.

Dr Pedro Machado (University College London) and Dr Pedro Carvalho (Faro, Portugal) will provide clinical advice and guidance relating to axial spondyloarthritis. They will liaise with and support Dr Gray while preparing/cleaning the database, as they already have experience working with Reuma.pt data and have previously published articles using this dataset.

Prof Allan Wailoo (University of Sheffield) will provide advice relating to previous work on BASDAI and BASFI, as well as how the mapping algorithm can be used in future cost-effectiveness analysis. He is a Professor of Health Economics & Director of NICE Decision Support Unit.

Dr Monica Hernandez (University of Sheffield) will provide advice relating to the technical statistical techniques used in the project and the interpretation of the results. She is a Senior Research Fellow in Econometrics.

**Co-authors**

All clinicians who actively work on this project will be co-authors, according to the rules defined by the Scientific and Coordinator Commission of Reuma.pt and taking in account the proportion of included patients (Reuma.pt).

**8. Funding and conflicts of interest**

The research team declares no conflicts of interest.

We are seeking external (academic) funding, which, if successful, will allow the work to be completed more quickly (as the research team will be able to allocate more time to the project).

**References**


1. Corbett M, Soares M, Jhuti G, Rice S, Spackman E, Sideris E, et al. Tumour necrosis factor-α inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systematic review and economic evaluation. Health Technol Assess. 2016;20(9):1-334, v-vi.
2. Wailoo A, Hernández M, Philips C, Brophy S, Siebert S. Modeling Health State Utility Values in Ankylosing Spondylitis: Comparisons of Direct and Indirect Methods. Value Health. 2015;18(4):425-31.
3. Mlcoch T, Sedova L, Stolfa J, Urbanova M, Suchy D, Smrzova A, et al. Mapping the relationship between clinical and quality-of-life outcomes in patients with ankylosing spondylitis. Expert Rev Pharmacoecon Outcomes Res. 2017;17(2):203-11.
4. van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017;76(6):978-91.
5. Smolen JS, Schöls M, Braun J, Dougados M, FitzGerald O, Gladman DD, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis. 2018;77(1):3-17.
6. Wailoo AJ, Hernandez-Alava M, Manca A, Mejia A, Ray J, Crawford B, et al. Mapping to Estimate Health-State Utility from Non-Preference-Based Outcome Measures: An ISPOR Good Practices for Outcomes Research Task Force Report. Value Health. 2017;20(1):18-27.
7. Hernández Alava M, Wailoo AJ, Ara R. Tails from the peak district: adjusted limited dependent variable mixture models of EQ-5D questionnaire health state utility values. Value Health. 2012;15(3):550-61.
8. M HA. Fitting adjusted limited dependent variable mixture models to EQ-5D. In: AJ W, editor. Stata J. 2015. p. 737–50.
9. Coca Perraillon M, Shih YC, Thisted RA. Predicting the EQ-5D-3L Preference Index from the SF-12 Health Survey in a National US Sample: A Finite Mixture Approach. Med Decis Making. 2015;35(7):888-901.
10. Wailoo A, Hernandez Alava M, Escobar Martinez A. Modelling the relationship between the WOMAC Osteoarthritis Index and EQ-5D. Health Qual Life Outcomes. 2014;12:37.
11. Ward Fuller G, Hernandez M, Pallot D, Lecky F, Stevenson M, Gabbe B. Health State Preference Weights for the Glasgow Outcome Scale Following Traumatic Brain Injury: A Systematic Review and Mapping Study. Value Health. 2017;20(1):141-51.