# Mapping the Paediatric Quality of Life Generic Core Scales (PedsQL™) onto the Child Health Utility 9D (CHU-9D) index score for economic evaluation in children

# Short Title: Mapping PedsQL™ onto the CHU-9D index score for economic evaluation in children

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## Abstract

*Background* The paediatric Quality of life Inventory (PedsQL™ ) questionnaire is a widely used, generic instrument designed for measuring health-related quality of life (HRQoL); however, it is not preference-based and therefore not suitable for cost-utility analysis. The Child Health Utility Index-9 dimension (CHU-9D) however is a preference-based instrument that has been primarily developed to support cost-utility analysis.

*Objective* This paper presents a method for estimating CHU-9D index scores from responses to the PedsQL™ using data from a randomised controlled trial of prednisolone therapy for treatment of childhood steroid-sensitive nephrotic syndrome.

*Methods* HRQoL data was collected from children at randomisation, week 16, and months 12, 18, 24, 36 and 48. Observations on children aged 5 years and older were pooled across all data collection time-points, and were then randomised into an estimation (n=279) and validation (n=284) sample. A number of models were developed using the estimation data before internal validation. The best model was chosen using multi-stage selection criteria.

*Results* Most of the models developed accurately predicted the CHU-9D mean index score. The best performing model was a generalised linear model (MAE=0.0408; MSE=0.0035). The proportion of index scores deviating from the observed scores by <0.03 was 53%.

*Conclusions* The mapping algorithm provides an empirical tool for estimating CHU-9D index scores and for conducting cost-utility analyses within clinical studies that have only collected PedsQL™ data. It is valid for children aged 5 years or older. Caution should be exercised when using this with children younger than 5 years, older adolescents (>13 years) or patient groups with particularly poor quality of life.

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**Key Points**

PedsQL™ is a widely used tool/questionnaire for measuring health-related quality of life in children and adolescents but it is unsuitable for calculating quality-adjusted life-years (QALY), which is often required for use in economic evaluation.

CHU-9D is not as widely used as PedsQL™ but its scores can generate QALYs. One study has shown that CHU-9D scores can be produced from responses to the PedsQL™ questionnaire in 15-17-year-olds but not for younger children.

The algorithm produced in this study now permits the estimation of CHU-9D score from PedsQL™ responses in children as young as 5 years.

## Introduction

Cost-effectiveness analysis is a comparative assessment of both costs and outcomes linked to healthcare interventions. Evidence of health care benefits are often synthesised from clinical trials, public health studies or from other forms of health research. These health benefits are increasingly been captured as HRQoL (Health-related quality of life) using either ‘condition-specific’ or ‘generic’ survey instruments. Condition-specific instruments focus on health dimensions relevant to a particular disease whereas generic instruments assess core dimensions of health that are relevant to all conditions [1]. Clinical trials tend to use condition-specific instruments as a primary or secondary measure of benefit because these instruments are focused on the specific domains of quality of life that are affected by a condition and are therefore sensitive to treatment effect in these domains. On the other hand, generic instruments measure a broader HRQoL construct [2]; therefore, they allow comparisons of treatment benefit across a wide range of interventions across multiple conditions.

Generic instruments can be further classed as either ‘preference’ or ‘non-preference-based’. Preference-based generic instruments attach weights to the domains of health to reflect a stronger preference for one aspect of HRQoL over another, in order to generate a single index/score of HRQoL (also termed a utility score) [3]. In contrast, most non-preference-based instruments simply sum the scores from all the health domains and thus assume an equal weighting. Some non-preference-based instruments may apply complex weighting systems, but these weights are not preference-based. [4]. For cost-utility analysis, preference-based generic instruments are required to measure utility-based quality of life scores and unfortunately, the majority of generic instruments used in clinical trials are non-preference-based [5] and are consequently of limited use for measuring and comparing the cost-effectiveness of diverse interventions on a common scale[6, 7].

To capture both length and quality of life from treatment, Quality Adjusted Life Years (QALYs) are often applied, [8, 9] whereby cost-effectiveness is expressed as cost-per additional QALY gained. Within paediatric medicine, however, most HRQoL instruments developed for children and adolescents are non-preference-based [10] and can therefore not be used for economic evaluation [11] where QALY’s are the desired outcome. A prediction algorithm/mapping function can however be used to predict utility scores from responses to a non-preference-based instrument[5]. This algorithm reflects the statistical relationship between the preference and the non-preference-based instrument, using responses from a prior population whose responses to both instruments have been collected.

The Paediatric Quality of Life Inventory (PedsQL™) is a generic non-preference based instrument, which provides a modular approach for measuring HRQoL in healthy children and adolescents and those with acute or chronic health conditions. PedsQL™ is commonly used due to its simple computational system and its validity for a wide age range of 2 to 18-year-olds [12]. In a review of paediatric quality of life measures, PedsQL™ fulfilled basic psychometric criteria, was suitable for completion in the clinic and could be recommended for use in clinical trials [13]. It also has the advantage of having both proxy and patient-completed versions, and has additional modules measuring some disease-specific quality of life. A viable preference-based alternative to the PedsQL™ is the Child Health Utility 9D (CHU-9D), which has been specifically developed for economic evaluation in children aged 5 years and older [14]. In situations where PedsQL™ data are only available, CHU-9D utility scores can be predicted from the PedsQL™ using a mapping algorithm. Only one study has mapped the PedsQL™ onto CHU-9D [15], in which the Short Form 15-item (SF-15) version of the PedsQL™ was used in place of the standard 23-item questionnaire. Data for that study [15] were obtained from Australian older adolescents only (15-17-year-old), and the CHU-9D responses were scored using the Australian value set [16].

This study mapped responses from the 23-item generic core scale version of the PedsQL™ onto CHU-9D index scores in children aged 5 to 13 years who were participants in a randomised control trial of different steroid regimes in childhood steroid-sensitive nephrotic syndrome [17].

## Methods

### Data

The data for this study was obtained from the PREDNOS study, a UK-based double-blind placebo controlled randomised controlled trial (RCT) designed to evaluate the clinical and cost-effectiveness of an extended steroid (prednisolone) treatment over 16 weeks compared with the standard 8-week treatment regimen in children with steroid-sensitive nephrotic syndrome. Participants were recruited from general hospitals and tertiary paediatric nephrology units across the UK, and were followed-up for at least 24 months up to a maximum of 48 months; the study closed when the last participant had completed 24 months of follow-up.

In accordance with the study protocol, the proxy-reported version of the PedsQL™ and the CHU-9D were used to collect HRQoL data at baseline, week 16, and at months 12, 24, 36 and 48 for children in both study arms. PedsQL™ was completed for children across all age groups (2 to 18 years) using the appropriate age-specific module, whilst the CHU-9D was completed for children who were 5 years and older [17]. In order to optimise the sample size, data on children who had completed both instruments across all the time-points were considered relevant for the mapping exercise. The sample was split into either an estimation or a validation sample. The estimation sample was used to develop the models while the validation sample was used for internal cross-validation of the mapping models.

Two approaches were available for selecting the estimation and the validation sample. The first was to randomise children at baseline into either the estimation or validation sample, and then account for the panel nature of the data in the regression equations. This approach results in a dataset that ensures all observations from individual children are either contained within the estimation or the validation sample and never within both. This, however, also results in the variation being reduced, as fewer children are contained within each sample. Therefore, an alternative approach was chosen for this mapping study whereby the entire sample of time-variant observations were randomised into either the estimation or the validation sample; and a clustering variable included to account for having multiple observations from the same child. A preliminary analysis was conducted to explore the impact of having the same participants, but different observations, in the estimation and validation sample on the predicted CHU-9D index score. See supplementary appendix. Randomising the entire sample into estimation and a validation sample limits the issue overfitting when selecting the final model. A 3:1 split between has been used [18]. Here, 50% of the entire sample was randomised to the validation sample in an attempt to rigorously avoid overfitting. The estimation and validation samples contained only observations with valid CHU-9D and PedsQL™ index scores, that is after excluding missing items.

### Outcome measures

The CHU-9D was initially designed for children aged 7 to 11 years; however, further research has now extended its use to children as young as 5 years [19-21] and to adolescents up to age 17 years [22]. The use of the instrument in 5-year-olds is currently being trialled [23]. The self-reported and proxy-reported versions of the CHU-9D questionnaire each consist of nine dimensions: sad, worried, annoyed, tired, sleep, pain, school, routine, and activity. Each dimension contains five severity levels, resulting in a possible 1,953,125 unique health states associated with the measure. Responses from the CHU-9D instrument were transformed into quality of life (utility) weights derived from a UK general population sample using an algorithm developed by Stevens et al. [14]. Applying these weights produces a utility value set of between 0.33 (worst health state) and 1 (best health state), and a utility score of zero denotes death on the CHU-9D scale.

The PedsQL™ generic core scale is a well-validated non-preference-based measure developed for toddlers, school-age children and adolescents. The self-reported version of the questionnaire has been validated in 5 to 18-year-olds while the parent or proxy-reported version is valid for use in 2 to 18-year-olds [12, 24]. Both versions of the instrument have the same number of items across the four sub-scales or domains of health for each age-specific module: For toddlers (2-4 years), young children (5-7 years), older children (8-12 years) and adolescents (13-18 years). The number of items within the health domain varies for some modules. The physical functioning (PF) domain has eight items, and both the emotional functioning (EF) and the social functioning (SF) domains have five items each. School functioning (FU) has five items for all age groups except toddlers where there are three items. Similar to the CHU-9D instrument, responses to each of the twenty-three items are on a five-point scale of increasing severity from 0 to 4: never a problem; almost never a problem; sometimes a problem; often a problem; and almost always a problem. Responses are then reverse scored and linearly transformed (0=100, 1=75, 2=50, 3=25 and 4=0). The total PedsQL™ score is the mean of the transformed score from all items answered. The total score is expressed on a 0 to 100 scale with 100 reflecting best possible health state.

### Analysis

Characteristics of participants in the study were summarised as means and standard deviation for continuous variables, and frequency (%) for categorical variables. The conceptual overlap between the two instruments across the whole sample were explored using Spearman correlation coefficients.

The prediction mapping exercise regressed the CHU-9D utility scores (dependent variable) against the PedsQL™ total, sub-scale or item scores (independent variables) to generate an algorithm that could then be subsequently used to predict the CHU-9D values. In order to select the model with a good prediction accuracy, three ‘functional forms’ or estimators were explored since it was not pragmatic to compare all mapping functions that are available. The estimators were chosen based on their perceived theoretical advantage and their performance in previous mapping studies.

The first was the ordinary least squares (OLS) regression with predicted utility scores censored at the value of 1. Whilst the OLS regression minimises the sum of squared errors, and represents the most common method within mapping studies [18] it has been shown not to cope well with multi-modal distributions [25] and does not always predict a perfect health. Despite its limitation, the OLS often gives good prediction accuracy in mapping.

The generalised linear model (GLM) [26] chosen as the second functional form chosen because it accommodates skewness and heteroscedasticity in the estimation sample. The GLM requires specification of a distribution ‘family’ that captures the relationship between the mean and variance, and a link function between the linear part and the mean. The Modified Park test was applied to identify the preferred ‘family’ based on the lowest χ2 value, and the Hosmer-Lemeshow and Pearson correlation tests [27, 28] were used to select the link function, defined as fitting well if both tests yielded non-significant p-values. The third form chosen for the prediction function was the Tobit model, a censored regression that accommodates both the lower and upper limit utility scores[29]. Tobit models have been suggested for mapping despite concerns about inconsistencies in the presence of non-normality and heteroscedasticity [30].

As well as the three functional forms chosen, other models have been used for mapping such as the beta-binomial estimator and finite mixture models used to accommodate skewed distributions [15]. However, neither of these models have been shown to be better than GLM or OLS when predicting utility value at near perfect health state [31, 32]. Furthermore, the MM-estimator [33] has the potential to cope with heteroscedasticity and the undesired effect of outliers within the estimation sample, and has been shown to have the lowest predictive error in a previous paper that mapped PedsQL™ onto CHU-9D in an older population [15]. Unfortunately however, the MM-estimator does not permit the use of cluster variables, which are required given the nature of this mapping sample. In addition, there are alternatives to the Tobit estimator for handling ceiling effects such as the multivariable fractional polynomials (MFP) and the censored least absolute deviation (CLAD) but again, neither of these estimators have been convincingly shown to be better than OLS [34].

In summary, six model-specifications (covariates) were developed based on the OLS, Tobit and the GLM ‘functional forms’, thus generating eighteen models in total.

Modes specification/covariates

Model-1 PedsQL™ total scale score

Model-2 Model-1, age, and sex

Model-3 PedsQL™ sub-scale scores

Model-4 Model-3, age and sex

Model-5 PedsQL™ sub-scale score square terms and interaction terms

Model-6 Model-5, age and sex

The PREDNOS data is a longitudinal dataset that can be viewed as having a two-stage structure, where the data collection time-points (level 1 units) are nested within subjects/patients (level 2 unit). A random-intercept mixed-effect model is often used to account for multilevel hierarchical data structures, but was not considered appropriate in our mapping context because the relationship between CHU-9D and PedsQL™ should be the same regardless of when the questionnaire was administered. In practice neither CHU-9D utility score nor PedsQL™ total score computation depend upon follow-up time-points within studies. Therefore, the PREDNOS data was considered to have only one hierarchical level, which is at the patient-level. The within-patient correlation was taken into account by including the ‘clustering’ option for each of the eighteen model specifications.

e.g. Model-1 specification:

 regress ***[CHU-9D score]*** ***[PedsQL™ score]***, vce (cluster, ***[patient ID]*** )

Where ***[patient ID]*** was a unique patient identifier.

### Assessing model performance

The following selection criteria were applied to shortlist the models.

Step 1: The models were assessed on the exactness of their mean prediction in the estimation sample [35]. Models that accurately predicted the mean CHU-9D score up to one-ten thousandth of a QALY were shortlisted for the next step.

Step 2: One model from each functional form were selected based on their combined prediction accuracy in the estimation and validation sample. The indicators of prediction accuracy were the mean absolute error (MAE) and the mean square error (MSE). The MAE is the mean absolute difference between the observed and the predicted values, while MSE is the mean squared difference between the observed and the predicted CHU-9D utility score. Larger MAE and MSE indicate poorer fit and vice versa. MAE was prioritised over MSE as the primary criteria because it has been shown to be less sensitive to outliers [36], which are often found with utility data.

Step 3: To assess and compare the shortlisted models from step 2, a series of assessments were applied. First, the distribution of the predicted and the observed CHU-9D scores were plotted to examine how well the predicted scores matched the observed. Second, the proportion of predictions deviating from observed values by <0.03, 0.05 and <0.1 were calculated as a representation of how often the models produce reliable predictions. Lastly, the MAEs were presented for different CHU-9D ranges to assess how well the models perform at the top and lower ranges of index scores. All analysis described above follows the ‘Mapping onto Preference-based measures reporting Standards’ (MAPS) [37]. The Akaike information criterion (AIC), Bayesian information criterion (BIC) and R-square for selected models were presented for the final model but these were not used as model-selection criteria. The purpose of a mapping function is to predict utility values, not on explanatory power or fit of the function.

## Results

### Sample characteristics

There were 643 observations across the five data collection time-points from children who were aged 5 years or older presenting with first episode steroid sensitive nephrotic syndrome. These observations were randomised into group A (n=321) and B (n=322). The longitudinal nature of the study meant that the number of missing items in the two groups varied across the data collection time-points. After removing observations where either CHU-9D or PedsQL™ index score could not be computed, the remaining 279 observations with pairs of valid PedsQL™ and CHU-9D index scores in the first group formed the estimation sample, while the 284 observations in the second group formed the validation sample. The estimation and validation samples constituted the total mapping sample (N=563).

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|  Table Demographic characteristics of estimation and validation sample by data collection time-point |
|  | **Baseline** | **4 months** | **12 months** | **24 months** | **36 months** | **48 months** |
| **Estimation sample** | n=55 | n=47 | n=58 | n=54 | n=39 | n=26 |
| **Gender** |   |   |   |   |   |   |
|  Male, n (%) | 35 (63.6) | 33 (70.2) | 36 (62.1) | 32 (59.2) | 23 (58.9) | 18 (69.2) |
| **Age, year** |   |   |   |   |   |   |
|  Mean (SD) | 7 (2.1) | 7.6 (2.1) | 7.4 (2.1) | 7.2 (1.9) | 7.3 (1.9) | 8.1 (2.0) |
|  Median (IQR) | 6 (3) | 7 (4) | 7 (3) | 7 (2) | 7 (3) | 8 (3) |
|  Range | 5, 12 | 5, 12 | 5, 12 | 5, 12 | 5, 12 | 5, 12 |
| **CHU-9D** |   |   |   |   |   |   |
|  Mean (SD) | 0.940 (0.063) | 0.929 (0.103) | 0.941 (0.080) | 0.950 (0.068) | 0.922 (0.081) | 0.937 (0.077) |
|  Median (IQR) | 0.952 (0.106) | 0.952 (0.100) | 0.952 (0.081) | 0.968 (0.073) | 0.931 (0.108) | 0.967 (0.107) |
|  Range | 0.786, 1.000 | 0.534, 1.000 | 0.509, 1.000 | 0.68, 1.000 | 0.702, 1.000 | 0.697, 1.000 |
| **PedsQL™**  |   |   |   |   |   |   |
|  Mean (SD) | 77.11 (16.16) | 82.4 (16.8) | 81.94 (15.91) | 84.24 (14.31) | 78.49 (20.58) | 80.85 (17.72) |
|  Median (IQR) | 79.35 (28.26) | 89.13 (29.35) | 87.5 (20.65) | 88.04 (18.48) | 82.61 (30.43) | 82.61 (29.35) |
|  Range | 40.22, 100.00 | 45.65, 100.00 | 41.3, 100.00 | 43.48, 100.00 | 31.52, 100.00 | 39.13, 100.00 |
|   |   |   |   |   |   |   |
| **Validation sample** | n= 36 | n= 46 | n= 50 | n= 70 | n= 56 | n= 26 |
| **Gender** |   |   |   |   |   |   |
|  Male, n (%) | 25 (69.4) | 30 (65.2) | 32 (64.0) | 44 (62.9) | 29 (51.8) | 15 (57.7) |
| **Age** |   |   |   |   |   |   |
|  Mean (SD) | 6.9 (1.8) | 7.1 (1.9) | 7.3 (2.0) | 7.6 (2.2) | 7.4 (2.2) | 8 (1.9) |
|  Median (IQR) | 7 (3) | 7 (2) | 7 (3) | 7 (3) | 7 (3) | 8 (2) |
|  Range | 5, 11 | 5, 12 | 5, 12 | 5, 12 | 5, 13 | 5, 13 |
| **CHU-9D** |   |   |   |   |   |   |
|  Mean (SD) | 0.924 (0.081) | 0.945 (0.067) | 0.941 (0.075) | 0.938 (0.076) | 0.951 (0.067) | 0.945 (0.06) |
|  Median (IQR) | 0.952 (0.1) | 0.96 (0.079) | 0.96 (0.081) | 0.952 (0.102) | 0.967 (0.071) | 0.959 (0.097) |
|  Range | 0.711, 1 | 0.69, 1 | 0.739, 1 | 0.65, 1 | 0.712, 1 | 0.828, 1 |
| **PedsQL™**  |   |   |   |   |   |   |
|  Mean (SD) | 75.88 (16.91) | 81.35 (14.53) | 78.28 (19.01) | 80.6 (17.25) | 83.13 (19.11) | 81.68 (20.3) |
|  Median (IQR) | 77.72 (27.36) | 83.7 (18.48) | 83.7 (28.26) | 86.96 (27.17) | 91.85 (27.17) | 90.76 (20.65) |
|  Range | 42.39, 97.83 | 41.3, 100 | 21.74, 100 | 33.7, 100 | 40.22, 100 | 29.35, 100 |

CHU-9D, child health utility index-9 dimension; PedsQL; PedsQL, paediatric Quality of life generic core scale

The randomisation yielded a balanced distribution of demographic characteristics between the estimation and the validation sample (Table 1). The mean CHU-9D utility score was 0.93742 (SD = 0.07897) and 0.94094 (SD = 0.07173) for all observations within the estimation and validation sample respectively. The mean PedsQL™ score was 80.93 (SD = 16.76) within the estimation sample and 80.31 (SD = 17.79) within the validation sample. Within each sample, the mean PedsQL™ total score was lower than the mean CHU-9D utility score when both scores were standardised on a 100-point scale. Although both HRQoL measures were negatively skewed (Fig. 1), the ceiling effect was more prominent with the CHU-9D. Level 1 or “no problem” always had the highest proportion of responses. For more details on the CHU-9D responses please refer to the online supplementary material.

Fig. Kernel density plots of CHU-9D utilities and PedsQL™ total scores for the estimation and validation data

There was a moderate statistical correlation between the CHU-9D utility scores and PedsQL™ total scores (Spearman’s rho=0.530; *p*<0.0001). The correlation between CHU-9D utility score and physical, emotional, school and social functioning were 0.438, 0.585, 0.377 and 0.422 respectively. The Spearman correlation coefficient between the CHU-9D dimensions and PedsQL™ subscale scores/functions ranged from -0.0672 and -0.4523. All correlations were statistically significant (*p*<0.0001).

### Performance and validation

Table 2 summarises the performance measures for all the model specifications, for both the estimation and the validation sample. Within the estimation sample, the models were able to reasonably predict the mean CHU9D value (0.93742; SD = 0.07898). Of the eighteen models, twelve were able to predict the precise mean value by up to one-ten-thousandth of a utility value, and were therefore shortlisted for the next selection process. The exceptions were the six Tobit models. Within the validation sample however, the models were less able to predict the mean CHU-9D score (0.94094; SD = 0.07174). The GLM\_2 had the lowest mean predicted value (0.93409) while Tobit\_3 had the highest mean predicted value (0.96575) giving a difference between the observed and predicted mean values of 0.0069 and 0.0245, respectively. These differences were below the threshold of 0.03 - generally considered to be a minimally important difference [38, 39]. A further observation was that some OLS models and all the Tobit models had maximum predicted values beyond the upper limit of the CHU-9D utility scale (0.33 to 1.00). However, none of the models predicted a utility value below the lower limit of the CHU-9D utility scale.

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| Table Performance of PedsQL™ to CHU-9D index score models in the estimation and validation samples |  |
|  | **Estimation Sample** |  | **Validation sample** | **Average MAE across samples** |
| **Mean** | **Min** | **Max** | **MSE** | **MAE** | **AIC** | **BIC** |  | **Mean** | **Min** | **Max** | **MSE** | **MAE** |
| **Observed** | **0.93742 (0.07898)** | **0.50940** | **1.00000** |  |  |  |  |  | **0.94094 (0.07174)** | **0.65000** | **1.00000** |  |  |  |
| GLM\_1 | 0.93742 (0.04433) | 0.74143 | 0.97345 | 0.00466 | 0.04789 | 98.12 | 105.38 |   | 0.93462 (0.05026) | 0.66582 | 0.97345 | 0.00366 | 0.04525 | 0.04657 |
| GLM\_2 | 0.93742 (0.04535) | 0.72021 | 0.98126 | 0.00446 | 0.04704 | 101.78 | 116.30 |   | 0.93409 (0.05250) | 0.66769 | 0.98006 | 0.00372 | 0.04579 | 0.04642 |
| GLM\_3 | 0.93742 (0.04978) | 0.72956 | 0.98071 | 0.00403 | 0.04313 | 101.91 | 120.06 |   | 0.93936 (0.05009) | 0.64983 | 0.97949 | 0.00326 | 0.04046 | 0.04180 |
| GLM\_4 | 0.93742 (0.05019) | 0.73330 | 0.98309 | 0.00393 | 0.04254 | 105.77 | 131.19 |   | 0.93907 (0.05061) | 0.65902 | 0.98256 | 0.00324 | 0.04060 | 0.04157 |
| GLM\_5 | 0.93742 (0.05176) | 0.65715 | 0.98975 | 0.00356 | 0.04109 | 112.75 | 152.70 |   | 0.93756 (0.05431) | 0.71233 | 0.98512 | 0.00344 | 0.04172 | *0.04141* |
| GLM\_6 | 0.93742 (0.05193) | 0.66093 | 0.98935 | 0.00353 | 0.04078 | 116.70 | 163.90 |   | 0.93761 (0.05476) | 0.70516 | 0.98550 | 0.00345 | 0.04182 | *0.04130* |
| OLS\_1 | 0.93742 (0.04266) | 0.81166 | 0.98597 | 0.00440 | 0.04595 | -718.03 | -710.77 |   | 0.93586 (0.04530) | 0.78676 | 0.98597 | 0.00348 | 0.04429 | 0.04512 |
| OLS\_2 | 0.93742 (0.04338) | 0.80481 | 1.00366 | 0.00434 | 0.04575 | -717.97 | -703.44 |   | 0.93579 (0.04651) | 0.78818 | 1.00054 | 0.00348 | 0.04460 | 0.04518 |
| OLS\_3 | 0.93742 (0.04732) | 0.81207 | 0.99522 | 0.00398 | 0.04245 | -739.82 | -721.67 |   | 0.93902 (0.04632) | 0.78872 | 0.99389 | 0.00310 | 0.03981 | *0.04113* |
| OLS\_4 | 0.93742 (0.04762) | 0.81562 | 1.00483 | 0.00396 | 0.04236 | -737.82 | -712.40 |   | 0.93884 (0.04693) | 0.79050 | 1.00305 | 0.00310 | 0.03989 | *0.04113* |
| OLS\_5 | 0.93742 (0.04924) | 0.76241 | 1.01474 | 0.00380 | 0.04218 | -741.10 | -701.16 |   | 0.93777 (0.05063) | 0.77988 | 1.01377 | 0.00327 | 0.04050 | 0.04134 |
| OLS\_6 | 0.93742 (0.04935) | 0.76394 | 1.01301 | 0.00379 | 0.04219 | -737.88 | -690.67 |   | 0.93778 (0.05071) | 0.77576 | 1.01234 | 0.00326 | 0.04052 | 0.04136 |
| Tobit\_1 | 0.96369 (0.05818) | 0.79220 | 1.02990 | 0.00533 | 0.05285 | -185.28 | -174.39 |   | 0.96156 (0.06177) | 0.75824 | 1.02990 | 0.00428 | 0.05003 | 0.05144 |
| Tobit\_2 | 0.96348 (0.05855) | 0.78748 | 1.04827 | 0.00526 | 0.05242 | -183.12 | -164.97 |   | 0.96136 (0.06271) | 0.75878 | 1.04466 | 0.00431 | 0.05063 | 0.05153 |
| Tobit\_3 | 0.96319 (0.06452) | 0.79299 | 1.04910 | 0.00496 | 0.05195 | -205.65 | -183.86 |   | 0.96575 (0.06269) | 0.76089 | 1.04170 | 0.00405 | 0.04816 | 0.05006 |
| Tobit\_4 | 0.96307 (0.06456) | 0.79396 | 1.05047 | 0.00492 | 0.05159 | -202.25 | -173.20 |   | 0.96549 (0.06296) | 0.76257 | 1.04897 | 0.00403 | 0.04806 | 0.04983 |
| Tobit\_5 | 0.96304 (0.06735) | 0.74322 | 1.07926 | 0.00482 | 0.05284 | -205.81 | -162.23 |   | 0.96387 (0.06842) | 0.76384 | 1.04872 | 0.00434 | 0.05107 | 0.05196 |
| Tobit\_6 | 0.96300 (0.06734) | 0.74480 | 1.07843 | 0.00481 | 0.05270 | -201.93 | -151.09 |   | 0.96385 (0.06838) | 0.76169 | 1.05209 | 0.00433 | 0.05099 | 0.05185 |

AIC= Akaike information criterion ; BIC= Bayesian information criterion; Min = Minimum value ; Max= Maximum value

A model had the best prediction accuracy for its functional form if it had the lowest MAE across the estimation and validation sample.

All Tobit models were excluded from further analysis after the first selection criteria. For step two, GLM 6 and OLS 3 had the ‘best’ performance in terms of MAE in the estimation and validation sample for their respective functional forms, and were therefore selected for a final comparison – ‘step 3’. GLM 6 performed better than OLS 3 in the estimation sample but the reverse was observed in the validation sample. Table 3 contains the model performance results. For the final models in step 3, the distribution of the predicted score was also examined (Fig. 2). GLM 6 had a wide range of predicted CHU-9D scores compared to OLS 3 (Fig. 2).

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| Table 3 Model performance of the two best-fitting models |
|   | **Estimation Sample** | **Validation Sample** |
|   | **Observed** | **GLM\_6** | **OLS\_3** | **Observed** | **GLM\_6** | **OLS\_3** |
| Mean | 0.937419 | 0.937419 | 0.937419 | 0.940941 | 0.937612 | 0.939018 |
| SD | 0.078978 | 0.051926 | 0.047318 | 0.071737 | 0.054762 | 0.046323 |
| CV | 0.084251 | 0.055393 | 0.050477 | 0.076240 | 0.058406 | 0.049331 |
| Min | 0.509400 | 0.660930 | 0.812068 | 0.650000 | 0.705160 | 0.788717 |
| P25 | 0.907600 | 0.910639 | 0.900076 | 0.912300 | 0.914908 | 0.905183 |
| P50 | 0.952100 | 0.957229 | 0.946303 | 0.952100 | 0.958496 | 0.950063 |
| P75 | 1.000000 | 0.978902 | 0.980433 | 1.000000 | 0.977276 | 0.977413 |
| Max | 1.000000 | 0.989350 | 0.995221 | 1.000000 | 0.985504 | 0.993891 |
| MSE | - | 0.00353 | 0.00398 | - | 0.00345 | 0.00310 |
| MAE | - | 0.04078 | 0.04245 | - | 0.04182 | 0.03981 |
| <0.03 AE (%) | - | 53.40% | 51.61% | - | 55.89% | 53.17% |
| <0.05 AE (%) | - | 72.04% | 70.25% | - | 73.23% | 70.77% |
| <0.10 AE (%) | - | 92.27% | 90.32% | - | 91.20% | 93.31% |

SD = Standard deviation, CV = Coefficient of variation, Min = Minimum value, P25 = 25th percentile, P50 = 50th percentile, P75 = 75th percentile, Max = Maximum value, MSE = Mean squared error, MAE = Mean absolute error, <0.05 AE (%) = percentage with absolute error below 0.05, <0.10 AE (%) = percentage with absolute error below 0.10

Approximately 56% of the predicted values from GLM 6 in the validation sample had absolute errors lower than the minimally important difference value of 0.03, the corresponding values for the OLS 3 was 53%. GLM 6 remained the preferred model specification when the error threshold was extended to 0.05.

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| --- |
|   Table Distribution of errors by observed CHU-9D range |
| CHU-9D range |   | GLM\_6 | OLS\_3 |
|   |   | MSE | MAE | MSE | MAE |
| **Estimation** |   |   |   |   |   |
| 0.5 ≤ value < 0.6 | n=3 | 0.09443 | 0.30095 | 0.11168 | 0.33058 |
| 0.6 ≤ value < 0.7 | n=6 | 0.01873 | 0.12096 | 0.02823 | 0.16497 |
| 0.7 ≤ value < 0.8 | n=11 | 0.00726 | 0.07674 | 0.00988 | 0.09602 |
| 0.8 ≤ value < 0.9 | n=49 | 0.00301 | 0.04441 | 0.00259 | 0.04034 |
| 0.9 ≤ value < 1.0 | n=111 | 0.00154 | 0.02853 | 0.00155 | 0.03015 |
| Full health | n=102 | 0.00242 | 0.03847 | 0.00279 | 0.03899 |
| **Validation** |   |   |   |   |   |
| 0.6 ≤ value < 0.7 | n=3 | 0.05502 | 0.23049 | 0.05277 | 0.22693 |
| 0.7 ≤ value < 0.8 | n=12 | 0.01185 | 0.09583 | 0.01376 | 0.10958 |
| 0.8 ≤ value < 0.9 | n=47 | 0.00468 | 0.05691 | 0.00329 | 0.04316 |
| 0.9 ≤ value < 1.0 | n=115 | 0.00187 | 0.03057 | 0.00131 | 0.02942 |
| Full health | n=107 | 0.00223 | 0.03593 | 0.00237 | 0.03643 |

Although the prediction accuracy of the mean scores were similar in both models, the accuracy level was not uniform across the CHU-9D utility range as shown in Table 4. The number of observations with utility score <0.7 was small, therefore, the comparison between the best two models were restricted to observations with higher utility values. GLM 6 was superior to OLS 3 in the estimation sample, however in the validation sample there were diverging results. OLS 3 had a better prediction accuracy when utility values were higher than 0.8 but less than full health, whilst the GLM 6 was superior at predicting full health and utility values between 0.7 and 0.8. So, although OLS 3 had a better prediction accuracy in the validation sample overall, it was found to be only marginally better than GLM 6.

Fig. Distribution of the observed CHU-9D score, GLM 6 and OLS 3 predicted CHU-9D score in the estimation and validation sample

In summary, relative to GLM 6, OLS 3 lacked the ability to predict the wider range of CHU-9D values (0.7 to 1), and a higher proportion of its predicted values had absolute errors above the minimally important difference. Furthermore, it was less able to predict full health, which is particularly important for utility data that tends to have ceiling effects. Taking all these factors into account, the GLM6 model was selected as the preferred model for mapping from PedsQL™ to CHU-9D. Table 5 shows the coefficients for generating deterministic and probabilistic utility predictions using the GLM 6 model. Coefficients for OLS 3 have also been presented in situations where this might be desired. Using GLM 6 as an example, the CHU-9D utility score can be calculated from the following coefficients:

$$CHU-9D utility score=0.7135215+\left.\left(PedsQL PF\right)^{2} \left(1.62\*10^{-4}\right)\right.+\left.\left(PedsQL EF\right)^{2} \left(4.77\*10^{-4}\right)\right.- \left.\left(PedsQL SF\right)^{2} \left(4.0\*10^{-5}\right)\right.- \left.\left(PedsQL FU\right)^{2} \left(1.646\*10^{-4}\right)\right.- \left.\left(PedsQL PF\right)\left(PedsQL EF\right)\left(1.10\*10^{-4}\right)\right.- \left.\left(PedsQL PF\right)\left(PedsQL SF\right)\left(1.14\*10^{-4}\right)\right.+ \left.\left(PedsQL PF\right)\left(PedsQL FU\right)\left(3.7\*10^{-5}\right)\right.- \left.\left(PedsQL EF\right)\left(PedsQL SF\right)\left(2.46\*10^{-4}\right)\right.- \left.\left(PedsQL EF\right)\left(PedsQL FU\right)\left(1.16\*10^{-4}\right)\right. + \left.\left(PedsQL SF\right)\left(PedsQL FU\right)\left(4.36\*10^{-4}\right)\right.+ Age \left(2.79\*10^{-2}\right)- \left(5.46\*10^{-4}\right) if female$$

|  |  |
| --- | --- |
|  Table Coefficients for the two best-fitting models |  |
|  | **GLM 6** | **OLS 3** |
|  | **Coefficient** | **SE** | **Coefficient** | **SE** |
| PedsQL™ PF Squared | 0.000162 | 0.000103 |  |  |
| PedsQL™ EF Squared | 0.000477\*\*\* | 0.000127 |  |  |
| PedsQL™ SF Squared | -0.000040 | 0.000145 |  |  |
| PedsQL™ FU Squared | -0.0001646 | 0.000101 |  |  |
| PedsQL™ PF × EF | -0.000110 | 0.000147 |  |  |
| PedsQL™ PF × SF | -0.000114 | 0.000173 |  |  |
| PedsQL™ PF × FU | 0.000037 | 0.000143 |  |  |
| PedsQL™ EF × SF | -0.000246 | 0.000209 |  |  |
| PedsQL™ EF × FU | -0.000116 | 0.000167 |  |  |
| PedsQL™ SF × FU | 0.000436\*\*\* | 0.000130 |  |  |
| PedsQL™ PF |  |  | 0.0007133\*  | 0.000297 |
| PedsQL™ EF |  |  | 0.0016477\*\*\* | 0.000228 |
| PedsQL™ SF |  |  | -0.00011 | 0.000383 |
| PedsQL™ FU |  |  | 0.000261 | 0.000276 |
| Age | 0.0279345 | 0.039717 |  |  |
| Sex | -0.0546336 | 0.146341 |  |  |
| Constant | 0.7135215 | 0.399623  | 0.7422337\*\*\* | 0.028841  |

SE = Standard error

PF = Physical functioning, EF= Emotional functioning, SF = Social functioning, FU = School functioning

*\*P < 0.05, \*\*P <0.01, \*\*\*P <0.001*

## Discussion

Whilst complying with current guidance for conducting and reporting mapping analyses [37], the results of this analysis show that CHU-9D utility scores can be estimated from PedsQL™ subscale scores with sufficient accuracy. A total of eighteen models were explored: Six model specifications, each with three functional forms. All the models produced reasonably similar predictions of the mean utility scores. The preferred algorithm for mapping PedsQL™ onto CHU-9D was selected using a three-stage elimination process. The GLM and OLS models outperformed the Tobit models in terms of MAE, with GLM 6 and OLS 3 being shortlisted for the third and final selection process. GLM 6 was chosen as the preferred mapping model because it was able to predict a wider range of CHU-9D utility scores and had a higher proportion of predicted values deviating from the observed values by less than 0.03.

The GLM 6 model predicted the CHU-9D utility scores with more accuracy when compared to other similar published studies (MAE=0.04078; MSE=0.00353). For example, in one study that looked at the relationship between the CHU-9D and the SDQ – Strengths and Difficulties Questionnaire behavioural questionnaire– the MSE was 0.124[40, 41] ,while another study that estimated CHU-9D utility scores from the KIDSCREEN questionnaire had an MAE = 0.095 [42]. The GLM 6 produced from this analysis also performed better than a previous model that had predicted EQ‑5D‑Y (EuroQoL-youth version) utility scores from PedsQL™ (MAE=0.115) [35]. Furthermore, Mpundu-Kaambwa and colleagues [15] mapped the PedsQL™ onto the CHU-9D (MAE=0.1169 ;MSE=0.0213) using an Australian value set and data derived from 15-17-year-olds. The mapping algorithm reported here has been derived from more observations, has a wider age range and used a UK value set.

Despite these strengths, there are some limitations. The sample size was small compared to other mapping studies [5] thereby limiting the ability to robustly demonstrate the relationship between CHU-9D and PedsQL™. A larger sample size may have reduced the prediction error of the model. Response-mapping is an alternative to mapping summary scores whereby the domain scores from each instrument are mapped. However, a recent review [5] concluded that this more complex approach did not offer anything superior over and above a simpler mapping of summary scores, a finding which has been supported by a recent applied study that mapped from PedsQL™ onto CHU-9D [15]. For these reasons, this mapping exercise was focused on summary score mapping only. Another caveat was the ceiling effect. A wider spectrum of health profiles was lacking as a considerable number of children had perfect or near perfect health, with none having utility scores below 0.5 in the estimation sample. This was reflected in the distribution of scores across the five response levels for each of the CHU-9D domains and each PedsQL™ subscale score. The implication is caution is advised if using the algorithm for a less healthy paediatric population. Additionally, the age range of the sample reflected the natural history of the condition with few older adolescents. Future research can focus on refining this mapping algorithm should data for children with more severe health states across a wider age range become available.

A final methodological concern was the proxy-completion of both HRQoL instruments in this study given that self-completion is the gold standard approach for measuring HRQoL, at least in adults [43, 44]. Proxy-reported responses are not directly interchangeable because of proxy biases [45]. However, for some very young children the use of proxies is unavoidable.

Mapping is not a substitute for direct utility estimation. It is therefore advised that, where possible, preference-based outcomes be collected for the measurement of cost-effectiveness. However, if direct estimation is not feasible, the algorithm presented provides a valuable and scientifically robust approach to predicting CHU-9D utility values. The standard errors for the coefficients have been reported making it possible for future users of the algorithm to account for the uncertainty around the predicted values. A final note is that it cannot be stressed strongly enough that the algorithm presented should be viewed as an interim solution. External validation using data from another study will provide the most robust evidence of the usefulness of this algorithm.

## Conclusion

 This study builds on a previous study that mapped PedsQL™ onto CHU-9D scores within a sample of 15-17-year-olds using the Australian value set [15]. Our findings shows that CHU9D scores can be estimated from PedsQL™ generic core scale values with good prediction accuracy. The CHU-9D index score for this study was derived using the UK value set. This algorithm can therefore be used to generate QALYs for evaluating the cost-effectiveness of interventions targeting children. Future research should consider validating this algorithm further in children with lower CHU-9D utility index scores than those observed in the PREDNOS study.

## NOTES

**Data availability**

The data for this analysis was from the PREDNOS study and it is not yet available because the study results have not been published. At the discretion of the funder (NIHR) of the study, the data may become publicly available at a later date. The methods section of the paper explains the randomisation and regression analysis underpinning this study. STATA do files are however available from the corresponding author on request.

**Compliance with Ethical Standards**

The study was approved by the North West GM Central Research Ethics Committee Ref: 12/NW/0766

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**Author contributions**

**Tosin Lambe (TL)** Conducted the mapping analysis and wrote the paper. **Emma Frew (EF)** Developed the mapping protocol, supervised the mapping analysis, and wrote the paper. **Natalie J Ives (NJI)**supervised on the statistical aspects of the study and edited the paper. **Rebecca L Woolley (RLW)** supervised on the statistical aspects and edited the paper. **Carole Cummins (CC)** Major input into the trial design that generated the data for this mapping study, and edited the paper. **Elizabeth A Brettell (EAB)** Overall co-ordination, management and oversight of the PREDNOS study that generated the data for this mapping paper and edited the paper. **Emma N Barsoum (ENB)** Co-ordination of the PREDNOS trial, significant input into the study set up, monitoring and ensuring execution of the PREDNOS study that generated data for this mapping paper. Edited this paper. **Professor Nicholas JA Webb (NJAW)** Chief Investigator of the PREDNOS study, led the protocol design, recruited participants and edited this mapping paper.

**Conflict of Interest**

 **NJAW** has served on Advisory Boards within the past five years for Abbvie, Alexion, AMAG, Astellas, Raptor, Takeda and UCB. These have been related to the design and conduct of early phase trials in childhood kidney disease. None has been related to the treatment of corticosteroid sensitive nephrotic syndrome. TL, EF, NJI, RLW, EAB, ENB, CC, NJI declare no conflict of interest.

**Informed consent**

Written informed consent was obtained from parents/guardians of participants and written assent was obtained from participants of appropriate age.

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**List of trial co-investigators:**

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