National EQ-5D tariffs and quality-adjusted life-year estimation: comparison of UK, US and Danish utilities in south Swedish rheumatoid arthritis patients

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ABSTRACT

Objective To study how the choice of national EQ-5D tariff may affect utility and incremental quality-adjusted life-year (QALY) estimates.

Methods South Swedish rheumatoid arthritis patients in an observational study, starting and continuing anti-tumour necrosis factor (TNF) monotherapy (n=54) or anti-TNF plus methotrexate (n=215) for 1 year during May 2002 to April 2009, were included. EQ-5D questionnaires were completed at baseline, 3, 6 and 12 months. Utilities and accumulated QALY were compared using the UK, US and Danish EQ-5D tariffs. Utilities for all 243 possible EQ-5D health states were also compared.

Results US utilities were generally higher than UK, with Danish falling in between. A substantial 1-year mean utility improvement was seen in both study groups using all tariffs (UK 0.28 vs 0.29; US 0.18 vs 0.19; Danish 0.20 vs 0.22). Adjusting for baseline differences between groups, the incremental QALY gain of combined treatment was 0.09 using the UK tariff, while 0.06 according to both US and Danish tariffs. Inter-tariff disagreement in utility and accumulated QALY varied irregularly across the range of utilities.

Conclusions Applying different national EQ-5D tariffs to the same data may result in substantially different incremental QALY estimates, crucial knowledge when interpreting cost-utility analyses. Studies using different tariffs cannot be directly compared.

The high cost of biological antirheumatic therapies makes economic priority settings ever more important. To evaluate medical interventions economically, the incremental cost per quality-adjusted life-year (QALY) of alternative interventions is often calculated in cost-utility analyses (CUA). However, QALY estimates using one of the most common utility instruments, the EuroQol 5–dimensions (EQ-5D),¹ ² potentially differ depending on which national EQ-5D tariff is applied.

QALY are calculated from utilities, usually obtained by generic instruments such as the short form 6–dimensions (SF-6D), the health utility index, or the EQ-5D. These questionnaires describe health states, which may be rescaled into utilities anchored at 1 (perfect health) and 0 (death), using health state preferences from the general population. If utility is plotted against time, the area under the curve represents accumulated QALY.

The EQ-5D rates five dimensions—mobility, self-care, usual activities, pain/discomfort and anxiety/depression—on a scale between one (no problems) and three (extreme problems), resulting in 243 (3⁵) unique health states (eg, 11232). The EQ-5D preference sets, or tariffs, most commonly used for the translation of health states into utilities emanate from valuations using the time trade-off method (TTO).³

The first TTO-based EQ-5D tariff used valuations of 42 health states from a British general population sample to model utilities for all 243 states.³ ⁴ This has since been extensively used worldwide. Applying the UK tariff to non-British study populations may, however, be problematical, because health preferences may vary between countries. Indeed, the development of other national EQ-5D tariffs has confirmed this.⁵ ⁶ Most importantly, tariffs are more or less compressed, differing considerably at the lower end. For example, the UK tariff runs to −0.59, with many states valued as worse than death (ie, <0),⁴ while the lowest US score is −0.11.⁶ The range of possible utility changes thus differs.

As shown in rheumatoid arthritis (RA), different utility instruments may also generate disparate utilities in the same patient.¹⁰ When interpreting CUA, basic knowledge of utility instruments and their tariffs may thus be important. Nonetheless, QALY remain crucial for economic evaluations, enabling priority settings across diagnoses.

The aim of the present study was to examine whether the choice of national EQ-5D tariff may affect QALY assessments. To do this, the difference in accumulated QALY over 1 year between RA patients receiving anti-tumour necrosis factor (TNF) monotherapy or anti-TNF plus methotrexate was calculated using the UK, US and Danish EQ-5D tariffs.

METHODS

Patients

More than 90% of south Swedish RA patients receiving biological agents are monitored in the South Swedish Arthritis Treatment Group (SSATG) register.¹¹ RA diagnoses are based on clinical judgement, but a previous validation showed 98% fulfillment of 1987 American College of Rheumatology criteria.¹¹ EQ-5D is validated for use in RA,¹² and has been applied in the SSATG since 2002.

To examine the potential impact on incremental QALY of applying different EQ-5D tariffs, two groups (anti-TNF monotherapy and anti-TNF plus methotrexate) of biological-naïve RA patients starting a first anti-TNF treatment (infliximab, etanercept or adalimumab) between May 2002 and April 2009,
were retrieved from the SSATG cohort. EQ-5D data at anti-TNF initiation, 3, 6 and 12 months of treatment were required for inclusion. The study was designed to illustrate potential tariff effects, not to conduct an unbiased head-to-head comparison between anti-TNF monotherapy and anti-TNF plus methotrexate. As a result of SSATG’s treatment surveillance character, no formal ethical approval was needed.

**Comparison of tariffs**
Utility scores of all 243 theoretically possible health states were plotted for each tariff against the other. Bland–Altman plots were also constructed to analyse agreement further. (For specifications of the UK, US and Danish TTO-based EQ-5D tariff equations, please refer to supplementary table S1, available online only).

**Comparison using SSATG data**
Utilities for the study population were calculated according to the UK, US and Danish tariffs, and Bland–Altman plots were constructed to study inter-tariff agreement of accumulated QALY. The 1-year difference in mean accumulated QALY between the anti-TNF monotherapy and anti-TNF plus methotrexate groups was calculated for each tariff, adjusting for baseline utility, disease duration and TNF inhibitor used by multiple regression. Covariates were chosen based on Spearman correlation and clinical relevance. Due to multicollinearity between utility, health assessment questionnaire scores and disease activity score in 28 joints, the latter variables were controlled for in separate sensitivity analyses.

**RESULTS**
Complete EQ-5D data were available for 54 subjects initiating anti-TNF monotherapy and for 215 receiving methotrexate concomitantly. Comparing the groups, patients starting anti-TNF monotherapy displayed longer disease duration, more previous disease-modifying antirheumatic drugs, less infliximab use and somewhat higher disease activity and disability at baseline (see supplementary table S2, available online only).

**Comparison of tariffs**
Figure 1 plots utilities for all 243 EQ-5D health states. While full health universally translates into 1, the worst possible state (33 333) corresponds to −0.62, −0.59 and −0.11, respectively, for the Danish, UK and US tariffs. US utilities are generally higher than UK and Danish, with mean differences of 0.23 and 0.08, respectively. Disagreement gradually increases with lower utilities. While showing better agreement at the lower spectrum, Danish utilities are again generally higher than UK, with a mean difference of 0.15.

**Comparison using SSATG data**
A rapid and sustained mean utility improvement was seen in both treatment groups. Mean utilities, utility change and accumulated QALY according to each tariff are presented in table 1, as are differences between means of the intervention arms. Agreement in 1-year accumulated QALY between the UK and the US and Danish tariffs, respectively, decreased with lower accumulated QALY levels, while disagreement between the US and Danish tariffs was less systematic (figure 2A). Figure 2B displays the 1-year development of mean utility by each tariff.

Comparing mean accumulated QALY of the intervention arms, a difference of 0.09, favouring combined treatment, was found using the UK tariff, while applying the US or Danish tariffs both resulted in smaller incremental QALY estimates of 0.06.

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**Figure 1** UK, US and Danish EQ-5D utility scores of all 243 theoretically possible health states plotted for comparison. (A) Regular scatter plots. Solid lines represent total agreement. (B) Bland–Altman plots: for each health state, the difference between the two utility scores (y-axis) is plotted against their mean (x-axis). Solid lines represent total agreement. DK, Danish; MTX, methotrexate; QALY, quality-adjusted life-year; TNF, tumour necrosis factor.
DISCUSSION
The current study demonstrates how different national EQ-5D tariffs may affect incremental QALY assessments. Applying the UK tariff, the incremental QALY gain of combined treatment was approximately 1.5 times that found with the US or Danish tariffs.

While our results are attributable to known differences between tariffs, we believe this issue to be important to emphasise to rheumatologists. Previous comparisons of tariffs\textsuperscript{5}\textsuperscript{14}\textsuperscript{18} found both methodological issues and country-specific differences in health perception to explain disparities. The mean interval between all 29,403 theoretically possible health state pairs is 0.25 for US and 0.35 for UK utilities\textsuperscript{16} and analogous to our results, applying either tariff resulted in different conclusions in a study of Parkinson's disease.\textsuperscript{17}

The generalisability of our findings can be appreciated from figure 1 and 2A. Inter-tariff disagreement in utility varies irregularly across the range of health states (figure 1). Accumulated

Table 1 Utilities and accumulated QALY according to the UK, US and Danish EQ-5D tariffs

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<thead>
<tr>
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<th>UK</th>
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<th>US</th>
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<th>Danish</th>
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<tbody>
<tr>
<td></td>
<td>Anti-TNF monotherapy</td>
<td>Anti-TNF plus methotrexate</td>
<td>Anti-TNF monotherapy</td>
<td>Anti-TNF plus methotrexate</td>
<td>Anti-TNF monotherapy</td>
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<td>Utility</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>0.35 (0.27 to 0.43)</td>
<td>0.41 (0.37 to 0.46)</td>
<td>0.55 (0.49 to 0.60)</td>
<td>0.59 (0.56 to 0.62)</td>
<td>0.50 (0.44 to 0.56)</td>
<td>0.54 (0.50 to 0.57)</td>
</tr>
<tr>
<td>12 Months</td>
<td>0.63 (0.56 to 0.70)</td>
<td>0.71 (0.68 to 0.74)</td>
<td>0.73 (0.68 to 0.78)</td>
<td>0.78 (0.76 to 0.80)</td>
<td>0.70 (0.64 to 0.75)</td>
<td>0.75 (0.73 to 0.79)</td>
</tr>
<tr>
<td>Utility change</td>
<td>0.28 (0.19 to 0.38)</td>
<td>0.29 (0.25 to 0.34)</td>
<td>0.19 (0.11 to 0.26)</td>
<td>0.19 (0.16 to 0.22)</td>
<td>0.20 (0.12 to 0.27)</td>
<td>0.22 (0.18 to 0.25)</td>
</tr>
<tr>
<td>Accumulated QALY</td>
<td>0.57 (0.51 to 0.62)</td>
<td>0.67 (0.65 to 0.70)</td>
<td>0.69 (0.65 to 0.73)</td>
<td>0.76 (0.74 to 0.78)</td>
<td>0.66 (0.62 to 0.70)</td>
<td>0.73 (0.71 to 0.75)</td>
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Differences between groups

<table>
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<tr>
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<th>Unadjusted</th>
<th>Adjusted*</th>
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<tbody>
<tr>
<td>Utility change</td>
<td>0.01 (−0.09 to 0.11)</td>
<td>0.06 (−0.01 to 0.13)</td>
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<tr>
<td>Accumulated QALY</td>
<td>0.11 (0.05 to 0.16)</td>
<td>0.09 (0.04 to 0.13)</td>
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Figures given are mean (95% CI); anti-TNF monotherapy n=54, anti-TNF plus methotrexate n=215.

*Adjusted for baseline differences in EQ-5D utility, disease duration and TNF inhibitor used (infliximab, etanercept or adalimumab). Adjusting for baseline differences in disease activity score in 28 joints or health assessment questionnaire scores instead of EQ-5D utility rendered similar results (data not shown).

QALY, quality-adjusted life year; TNF, tumour necrosis factor.

Figure 2 (A) Bland–Altman plots: for each patient (n=269; rheumatoid arthritis (RA) patients treated with either anti-tumour necrosis factor (TNF) monotherapy or anti-TNF plus methotrexate) the difference between the two EQ-5D tariffs in accumulated quality-adjusted life-years (QALY) during 1 year (y-axis) is plotted against their mean (x-axis). Solid lines represent total agreement. (B) Development of mean utility (with 95% CI) in RA patients continuing anti-TNF monotherapy (lower lines) or anti-TNF plus methotrexate (upper lines) for 1 year, according to the UK, US and Danish EQ-5D tariffs. Areas under the curves represent mean accumulated QALY, and the differences between areas are the incremental QALY of combined therapy. *Adjusted for baseline differences in EQ-5D utility, disease duration and TNF inhibitor used (infliximab, etanercept or adalimumab). DK, Danish.
QALY thus also differ more or less between tariffs, depending on the initial and achieved utility (figure 2A). When comparing mean accumulated QALY of two interventions, if a change of tariff affects the intervention arms by different magnitude, the result will change accordingly. Compared with the current analysis, greater difference between UK and US or Danish results would be expected if instead comparing active treatment with placebo, assuming the latter to result in lower accumulated QALY for which differences are more pronounced (figure 2A).

EQ-5D is among the most widely accepted utility instruments. If tariff-related disparities reflect true country-specific differences in health perception, national tariffs are crucial. More national tariffs are currently available for EQ-5D than for any other utility instrument, and while displaying a certain ceiling effect, EQ-5D appears to discriminate better than comparable instruments between worse conditions and across levels of global health.10

The present study was designed to assess tariff effects on QALY estimates. Intervention arms and inclusion criteria (introducing selection bias by requiring full EQ-5D data and excluding anti-TNF discontinuers) were chosen for illustrative purposes, not to conduct an unbiased head-to-head comparison of treatments. The observational setting entails inherent limitations,19 including baseline disparities between groups, missing data and potential channelling bias. Patients on combined therapy were already receiving methotrexate at baseline, which probably explains some differences. Linear regression was applied to adjust for this, but residual confounding cannot be ruled out. Utility improvement in a larger sample of south Swedish RA patients commencing anti-TNF therapy has previously been described using the UK tariff.20

In conclusion, applying different national EQ-5D tariffs to the same data may result in substantially different incremental QALY estimates, crucial knowledge when interpreting CUA. Evaluations using different tariffs cannot be directly compared. Which EQ-5D tariff is best suited for Swedish conditions remains unknown, and we look forward to the development of a Swedish EQ-5D tariff.

Acknowledgements The authors are indebted to all colleagues and staff in the SSATG.

Funding The study was funded by unrestricted grants from Region Skåne, Lund University Hospital, the Swedish Research Council, the Faculty of Medicine at Lund University, Österlund and Kock Foundations, the Swedish Rheumatism Association and King Gustav V 80-year fund.

Competing interests L-EK has received a speaker’s fee from Wyeth, PG from Wyeth, Abbott and Schering-Plough. The remaining authors declare no conflict of interest.

Provenance and peer review Not commissioned; externally peer reviewed.

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National EQ-5D tariffs and quality-adjusted life-year estimation: comparison of UK, US and Danish utilities in south Swedish rheumatoid arthritis patients


Ann Rheum Dis 2011 70: 2163-2166 originally published online August 22, 2011
doi: 10.1136/ard.2011.153437