

The cost-effectiveness of tight control of inflammation in early psoriatic arthritis: Economic analysis of the TICOPA trial.

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Abstract

Objective: Treat-to-target approaches have proved to be effective in rheumatoid arthritis, but have not been studied in psoriatic arthritis (PsA). This study was undertaken to examine the cost effectiveness of tight control (TC) of inflammation in early psoriatic arthritis compared to standard care (SC).

Methods: Cost effectiveness analyses were undertaken alongside a UK-based, open-label, multicentre, randomised controlled trial. Taking the perspective of the healthcare sector, effectiveness was measured using EQ-5D-3L which allows the calculation of quality-adjusted life years (QALYs). Incremental cost effectiveness ratios (ICERs) are presented which represent the additional cost per QALY gained over a 48-week time horizon. Sensitivity analyses are presented assessing the impact of variations in the analytical approach and assumptions on the cost-effectiveness estimates.

Results: Mean cost and QALYs were higher in the TC group; £4198 vs. £2000 and 0.602 vs. 0.561. These values yielded an ICER of £53948 per QALY. Bootstrapped uncertainty analysis suggest the TC has a 0.07 probability of being cost effective at a £20,000 threshold. Stratified analysis suggest that with certain costs being controlled, an ICER of £24639 can be calculated for patients with a higher degree of disease severity.

Conclusion: A tight control strategy to treat PsA is an effective intervention in the treatment pathway, however this study does not find tight control to be cost-effective in most analyses. Reduced drug prices, targeting polyarthritis patients or reducing rheumatology visit frequencies may improve value for money metrics in future studies.

Psoriatic arthritis (PsA) is a chronic inflammatory disease with patients experiencing symptoms of both inflammatory arthritis and psoriasis. Patients suffer progressive joint damage, increasing disability and reduced life expectancy, similar to Rheumatoid Arthritis (RA) patients[1]. PsA is estimated to affect close to 1% of the general population, 7% of arthritis patients and up to 30% of patients with psoriasis [2].

There are a number of different treatment options available for patients with PsA. Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, diclofenac, celecoxib or etoricoxib are commonly prescribed to relieve pain, stiffness or swelling. If NSAIDs fail to provide relief, corticosteroids can also be prescribed. Disease-modifying anti-rheumatic drugs (DMARDs) such as leflunomide, sulfasalazine or methotrexate may be prescribed to ease symptoms and slow the progression of PsA. In recent years biological drug treatments, have been introduced for treatment of PsA ; medicines targeting tumour necrosis factor alpha, such as adalimumab, etanercept and infliximab fall into this category, as are medicines targeting interleukin 12/13, such as ustekinumab and interleukin-17, such as secukinumab [3]. The severity and chronic nature of PsA translates into high health care costs [4]. Mean annual health care costs associated with PsA patients, not treated with TNF- α inhibitors, have been estimated to be £1,446 per patient in the UK [5]. This corresponds somewhat to studies from Germany and Hungary, which estimated mean annual costs associated with PsA to be £2,875 and £1,531 respectively [5].

A UK-based study, the Tight Control of RA (TICORA), demonstrated that treat-to-target control of RA, i.e. escalation of therapy until a predefined objective target of treatment is reached, results in significantly better outcomes compared to standard care[6]. Consequently, National Institute for Health and Care Excellence (NICE) guidelines for RA treatment have recommended monthly assessments of disease activity with the aim of reaching predefined disease-activity targets. However there has been a call for stronger evidence on the efficacy and cost-effectiveness of treat-to-target (or Tight Control) strategies [7]. Until recently, the concept of Tight Control (TC) of inflammation to improve outcomes in PsA had not been investigated. Research in RA shows a strong link between actively inflamed joints, subsequent joint damage and disease progression. [8] Disease activity scores reflecting these indicators such as the DAS 28, despite being seen as predictors of clinical and radiological progression in PsA, do not take into account the unique aspects of this disease. The minimal disease activity (MDA) criteria for PsA assesses multiple domains, including patient reported outcomes, and gives a measure of the acceptability of the disease state to the patient and clinician. The MDA has been validated in multiple cohorts [9]. TICOPA (Tight Control of Psoriatic Arthritis) is a randomised, controlled trial employing MDA criteria in a TC protocol versus

standard care (SC) to treat newly diagnosed PsA patients. The results of TICOPA [10] indicate that using a TC approach significantly improves joint and skin outcomes for newly diagnosed PsA patients, with patients receiving this TC being statistically significantly more likely to achieve the American College of Rheumatology 20 (ACR20) [11] response at 48 weeks [odds ratio (OR): 1.91, 95% CI (1.03, 3.55), $p=0.0392$]. This was achieved without any suspected unexpected serious adverse events (SUSARs) or deaths, and just ten serious adverse reactions (SARs) (TC: 8, SC: 2).

The TICOPA trial [10] did report headline within-trial cost-effectiveness results indicating that, while TC conferred incremental quality-adjusted life year (QALY) benefits, it was not cost-effective at the NICE willingness-to-pay (WTP) threshold of £20,000 having an incremental cost effectiveness ratio (ICER) of £50,723. This paper reports in-depth cost-effectiveness analyses of the TICOPA study with extensive sensitivity and sub-group analyses to help identify the drivers of the cost-effectiveness results.

Methods

Patients

The TICOPA trial focused on newly diagnosed (<24 months symptom duration) adult patients with PsA who had not received DMARDs. The primary objective of TICOPA was to evaluate the efficacy of TC (4 weekly review with treatment escalated until MDA achieved) compared to SC (12 weekly review with no set protocol), using the American College of Rheumatology 20% response (ACR20) as primary endpoint at the 48 weeks post-randomisation. Key secondary outcomes included ACR50 and ACR70, Psoriasis Area Severity Index 75% (PASI75) [12], along with cost-effectiveness over 48 weeks. Each patient was followed from baseline to the end of the 48-week data collection period. EQ-5D-3L and cost effectiveness data was collected prospectively at baseline, 12, 24 and 48 weeks using a combination of patient-reported sources and nurse/doctor reported information. Full details of the TICOPA trial are reported in the trial protocol [13] and main results paper [10].

Perspective

The primary economic analysis was a within-trial cost-utility analysis undertaken from the perspective of the Health and Personal Social Services provider, in order to inform health policy relating to the use of this intervention in the UK National Health Service (NHS).

Costs

Patient self-reported questionnaires were used to collect resource use data and covered health service utilisation, measuring both face-to-face contact and contact via telephone or email. The questionnaires requested information on hospital (e.g. hospital visits and stays) and community-

based (e.g. GP, nurse, physiotherapist contact) care. In addition, research nurses had consent to access patients' clinical records providing information on visits and medication use. This clinical information was combined with the patient-reported resource use. Each component of resource use was identified and costs (UK £) derived from market prices and national estimates. Unit costs of health services were obtained from national sources including the PSSRU Costs of Health and Social Care 2012[14] and the Department of Health's National Schedule of Reference Costs[15] (See supplementary material: Table 1). All costs are adjusted to 2013 prices [16].

Market prices for medications were assigned using the British National Formulary (BNF)[17], (See supplementary material: Table 2). The Patient Resource measure asks patients not to include visits to the Rheumatology clinic. We assumed that patients adhered to this and costed 12 visits (at £128 per visit) to the clinic for the TC group and 4 visits for the control group that were integral to intervention receipt (as per protocol). This assumption was tested in sensitivity analyses.

Outcomes

In line with the NICE reference case, the primary outcome for the economic evaluation was the QALY and associated ICER [18]. QALYs are a composite measure of Health-Related Quality of Life (HRQoL) and length of life. They represent a quality-weighted survival value where one QALY is the equivalent of one year of full health. Participant HRQoL was assessed at baseline, 12, 24 and 48 week periods using the EQ-5D-3L preference-based measure[19]. The EQ-5D has been shown to be valid in PsA [20]. Participant EQ-5D responses were converted to health-state utility values using the UK tariff [21] and QALYs were calculated using an area under the curve approach.

Cost-effectiveness analyses

In line with the clinical efficacy analysis, an intention-to-treat (ITT) analysis was the primary method for analysing and summarising the health economic trial data. The trial analysis was a cost-utility analysis comparing TC and SC over the 48 week trial duration. No discounting was necessary given the time period of data collection (< 1 year).

To assess uncertainty, resampling was conducted to produce 10000 bootstrapped estimates of the incremental costs and benefits. The bootstrapping approach is a non-parametric method that treats the original sample as though it was the population and draws multiple random samples from the original. The cost-effectiveness plane is a scatter plot plotting the bootstrapped ICERs to illustrate the uncertainty surrounding the cost-effectiveness estimates.

A cost effectiveness acceptability curve (CEAC) was constructed illustrating the probability that each intervention would be cost-effective given a range of willingness-to-pay (WTP) thresholds per

incremental QALY [22, 23]. The NICE WTP per incremental QALY threshold (Lambda [λ] =£20000) was used to define cost-effectiveness. Additional analyses considered an upper WTP λ of £30000. Estimates of trial-arm net monetary benefit (NMB) from the bootstrapped results were generated to enable CEAC creation. NMB was derived thus:

$$NMB = (\lambda * QALYs) - Costs$$

Net benefit was also generated on an individual patient level to allow net benefit regression modelling; this was employed to allow parametric analysis of the costs and benefits of the intervention [24]. Whether the treatment arm is a significant predictor of net benefit or not was determined, controlling for any baseline sample heterogeneity and baseline differences between groups. Secondary cost-effectiveness analyses were conducted using the other outcomes of the trial as the effects of interest; ACR20, ACR50, ACR70 and PASI75 where the resulting ICERs relate to a patient achieving the targeted response.

Missing Data

Multiple imputation was employed to account for missing cost and EQ-5D data in our primary analysis. This approach is recommended for economic analyses conducted alongside clinical trials as it reflects the uncertainty inherent in replacing missing data. [25] Predictive mean matching techniques were used as the key variables of cost and QALYs are continuous[26].

Sensitivity Analyses

Following discussions with clinicians a variation on this analysis was conducted whereby consultation costs were assumed to be equivalent across arms. **This was felt to be a plausible scenario given that those patients receiving TC would, after reaching target, no longer attend every 4 weeks but reduce the frequency of their visits.** A complete-case analysis, based on 114 patients with complete cost and QALY data at all timepoints is also reported. A threshold analysis was conducted to estimate the outcomes and costs required for this particular intervention to be deemed cost-effective. In the event of a potential reduction in the cost of medications (for example due to the introduction of biosimilars), sensitivity analyses were performed by subtracting 25% and 50% of all medication costs and assessing the subsequent ICERs.

Stratified analyses

Stratified medicine, which aims to identify and treat patients who have the greatest potential to benefit from a specific treatment, is regarded as imperative to the progress of healthcare according

to the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) [27]. A stratified analysis was performed based on two classes of severity: (i) Oligoarthritis which is arthritis affecting up to four joints simultaneously; and (ii) Polyarthritis which affects five or more simultaneously.

All analyses were conducted using MS Excel® (Microsoft, Seattle, WA, USA) and STATA® version 12 (STATA Corp., College Station, TX, USA).

Results

In total, 164 patients, from eight secondary care rheumatology centres in the UK, were asked to complete health economics questionnaires between May 28, 2008 and March 21, 2012. After excluding those with either missing resource use or EQ-5D data, complete case analysis included 60 patients and 54 patients in the TC and SC arms, respectively. Missing data in general was low, with no resource use item >5% missing. The rate of missingness for EQ-5D data did not exceed this to any great extent. (For full missing data see supplementary: Table 3). Following multiple imputation of cost and EQ-5D data this allowed a total sample of 80 patients in each arm. Four patients did not complete the baseline questionnaires, therefore were not included in imputations. Data from 160 patients was included in the base case analysis. The sample characteristics are presented in Table 1.

Table 1: Baseline Characteristics

Costs

With the exception of Rheumatology appointments and medications, both arms in the trial showed a gradual decline in resource use as treatment progressed. As can be seen from Table 2, TC patients on average required fewer community based health and social services and needed fewer hospital based services than SC patients. Excluding Rheumatology visits and medications, the mean resource use cost for TC patients was £614 per patient, with SC costing a mean of £937 per patient (Table 2). Medication costs however were much higher for the TC patients: mean of £1981 per patient compared with £529 per SC patient, due mainly to a higher usage of TNF- α inhibitors in the TC arm. Rheumatology appointment costs, as expected, were much greater for those patients in the TC arm of the trial. These visits amounted to a mean cost of £1602 compared with £534 for SC patients.

Table 2: Costs and QALYs by treatment arm

EQ-5D and QALYs

Mean changes in EQ-5D from baseline to 48 weeks were 0.218 (0.301) and 0.097 (0.341) for TC and SC, respectively (For full EQ-5D data see supplementary: Table 4). Table 2 above provides a summary of EQ-5D generated QALYs calculated for each treatment arm at each time interval. As there were no deaths in the trial QALYs were dependent on utility values rather than survival. A between group t-test showed that total QALYs were statistically significantly different ($p=0.0186$), indicating significantly greater improvements in TC than SC over time.

Cost-utility analyses

Costs and QALYs are included in Table 2. The mean cost per patient in the TC arm was £4198 compared with £2000 for the SC arm; the large difference stemming from increased Rheumatology visits and medication costs. Mean QALYs were 0.602 and 0.561 for TC and SC, respectively. Thus TC incurred much higher (over double) costs than SC but conferred small additional QALYs. The QALYs and costs yielded a deterministic ICER of £53948 per QALY. Bootstrapped uncertainty analysis produced a mean simulation ICER of £50723. As can be seen in Figure 1, the majority of iterations lie in the northeast quadrant (TC more effective, yet more costly), with some lying in the northwest (TC less effective and more costly).

Figure 1: Cost Effectiveness Plane

Figure 2 below represents the CEAC; this reflects the probability of cost-effectiveness across a range of WTP values. Bootstrapped uncertainty analysis suggested that TC had only a 7.3% probability of being cost-effective at the £20000 threshold; this probability rises to 22.3% if the threshold was £30000. It is evident that TC is unlikely to be considered cost-effective using the current WTP threshold of £20000 per QALY gained.

Figure 2: Cost-effectiveness acceptability curve: Tight Control vs Standard care

Sensitivity Analyses

Results from a complete-case analysis, based on 114 patients with complete cost and EQ-5D data yielded a deterministic ICER of £80392 per QALY. Bootstrapped uncertainty analysis produced a mean simulation ICER of £74952 - again, higher than imputed probabilistic results and the NICE WTP threshold.

Overall, the mean health care costs associated with treatment for PsA and associated healthcare use by patients was higher in the TC arm than in the SC arm for all analyses. When visit costs were made equal between arms (i.e. appointments on a 12-weekly basis in both arms) the bootstrapped ICER is £26909 with a 36.33% chance of being cost-effective, hence TC remains above the NICE WTP threshold. When a threshold of £30000 is used this figure is 52.7%. Table 3 shows the results assessing the sensitivity of cost-effectiveness to different approaches and analysis inputs. A potential 50% reduction in the cost of medications does not bring the ICER below NICE WTP threshold. A threshold analysis was conducted to estimate the outcomes and costs required for TC to be deemed cost effective (ICER<£20000) (Table 3). Either a reduction of TC costs by 37% or an increase in TC QALYs of 68% would be required for the TC strategy to become cost-effective over the time horizon considered. To illustrate, with incremental QALYs remaining at 0.041, incremental costs must reduce to £819.96 or, if incremental costs remain at £2198, then incremental QALYs must increase to over 0.110 to achieve cost-effectiveness.

The results of the NMB regression, on 160 patients, indicate that treatment arm is not a significant predictor of NMB. However disease severity was a statistically significant predictor (see supplementary material: Table 5) with polyarthritis patients having lower NMB values. The interaction between treatment arm and severity was insignificant ($p=0.963$). Stratified analysis, where patients were classified by the severity of their symptoms into subgroups, was also performed (see supplementary material: Table 6). TC was more expensive and more efficacious for both groups of patients, yielding an ICER of £138796 and £43703 for oligoarthritis and polyarthritis patients, respectively. However, when consultation costs were assumed to be equivalent across both TC and SC arms this reduces the ICER for the more severe patients to £24639; much closer to the NICE WTP threshold.

In order to account for baseline differences in age, gender and quality of life between treatment groups, adjusted QALYs were calculated. This resulted in higher QALYs for patients in the TC arm and lower QALYs for those in SC; mean adjusted QALYs were 0.6067 and 0.5561 for TC and SC respectively. A between group t-test showed that these were statistically significantly different ($p < 0.0001$), again indicating significantly greater improvements in TC than SC over time. However despite the increased QALY difference following the adjustment for baseline differences, the calculated ICER of £43463 remains higher than the current WTP threshold (see supplementary material: Table 6).

Table 3: Sensitivity Analyses

Cost-effectiveness analysis

Cost-effectiveness analyses using the TICOPA trial end-points as measures of effect were conducted for 160 patients. The most effective treatment was TC, with 17.8% more patients achieving ACR20 compared to SC. This resulted in an ICER of £13502 per percentage increase in ACR20 response over the 48-week period. The proportion of patients achieving ACR50 was 26.2% higher in the TC arm with a lower ICER of £8358 per percentage increase in ACR50 response. As can be seen from Table 4, a lower rate of success and higher ICER were observed per patient achieving ACR70 over the 48-week period. In relation to psoriasis activity (PASI75), again the most effective treatment was TC, with 25% more patients achieving a PASI75 score. This resulted in an ICER of £8776 per patient meeting this target.

Table 4: Cost-effectiveness Analysis

Discussion

This paper is the first study to assess the cost-effectiveness of tight control versus standard care in the treatment of early psoriatic arthritis. The results indicate that the probability of TC being cost-effective was 7.03% when using a WTP per QALY gain threshold of £20000. The higher use of high cost of TNF- α inhibitors appears to be a key factor in the magnitude of TC arm costs. Sensitivity analyses showed that reducing medication costs (which included the biologic drugs used in TC) by

50% does not bring the ICER below £20000. The price of the anti-TNFs have not changed over time; although price reductions for treatments such as Methothrexate, Sulfasalazine and Leflunomide, have occurred since the analyses the sensitivity analyses showed little impact on cost-effectiveness results. Tight control in this study required eight extra visits to the clinic for assessment which also drove up costs in the TC arm. Self-assessments by patients or tele-care approaches may reduce these costs but the sensitivity analyses suggest that this would not be sufficient to make TC cost-effective unless a higher WTP threshold is employed.

There was little difference in QALYs gained between both arms. Both the TC and SC arms experienced increases in mean EQ-5D throughout the trial period, with SC being slightly higher at the 12-week timepoint only. The baseline and 48-week EQ-5D means across both arms of 0.51 and 0.67 used in this analysis appear typical and are in line with previous studies results [20, 28]. The EQ-5D includes items on pain and mobility which we might expect to capture the major symptoms and functional impairment associated with PsA. It also includes an item on depression and anxiety which should capture some of the psychological impact related to the illness but it is possible issues such as the impact on self-esteem and confidence are important omissions from the measure. The EQ-5D measure has been shown previously to be a useful tool of clinical status in PsA, however it may not be sensitive for minor skin symptoms [20]. The small difference in QALYs also relates to the fact that neither treatment had survival benefits and because benefits were only measured over a period of 48 weeks. We chose not to model the costs and benefits of the interventions over a longer time horizon as there is insufficient evidence that either treatment would have substantive impact after the trial period. [10] However, should the greater improvement in quality of life experienced by the TC group persist, then modelling this benefit forward would improve cost-effectiveness metrics in TC's favour.

The NICE reference case (2013)[18] indicates that costs borne by patients may be accounted for in cost-effectiveness studies. In this study, however, we used a health and social services rather than societal perspective and thus patient out-of-pocket costs were not accounted for. The TC arm included a higher number of consultations leading to increased travel time and time off work for these patients. Should these costs be included it is expected that the cost difference between TC and SC would increase.

The results of a stratified analysis suggest that TC is more beneficial for polyarthritis patients. Furthermore, when the number of planned rheumatology visits were reduced, the ICER for these patients moved much closer to the lower NICE WTP threshold. Future studies concentrating on tight

control of PsA for polyarthritis patients might be of interest and longer term follow-up of patients is required to determine whether the additional benefits experienced by TC are maintained.

Conclusion

A tight control strategy to treat PsA is an effective intervention in the treatment pathway, but carries much higher costs. While this study did not find tight control to be cost-effective in most analyses, reduced drug prices, targeting polyarthritis patients or reducing rheumatology visit frequencies may improve value for money metrics in future studies.

References

1. Gladman, D.D. and V.T. Farewell, *Progression in psoriatic arthritis: role of time varying clinical indicators*. Journal of Rheumatology, 1999. **26**(11): p. 2409-13.
2. Gladman, D.D., et al., *Psoriatic arthritis: epidemiology, clinical features, course, and outcome*. Annals of the Rheumatic Diseases, 2005. **64 Suppl 2**: p. ii14-7.
3. UK, A.R. *What treatments are there for psoriatic arthritis?* 2014 26th May]; Available from: <http://www.arthritisresearchuk.org/arthritis-information/conditions/psoriatic-arthritis/treatments.aspx>.
4. Bojke, L., et al., *Modelling the cost-effectiveness of biologic treatments for psoriatic arthritis*. Rheumatology, 2011. **50 Suppl 4**: p. iv39-iv47.
5. Poole, C.D., et al., *Estimation of health care costs as a function of disease severity in people with psoriatic arthritis in the UK*. Rheumatology, 2010. **49**(10): p. 1949-56.
6. Grigor, C., et al., *Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): A single-blind randomised controlled trial*. Lancet, 2004. **364**(9430): p. 263-269.
7. Scott, I.C., A. Wailoo, and D.L. Scott, *Payers' views on treating-to-target in rheumatoid arthritis: an English perspective*. Clinical & Experimental Rheumatology, 2012. **30**(4 Suppl 73): p. S85-90.
8. Conaghan, P.G., et al., *Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis*. Arthritis & Rheumatism, 2003. **48**(1): p. 64-71.
9. Coates, L.C., J. Fransen, and P.S. Helliwell, *Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment*. Annals of the Rheumatic Diseases, 2010. **69**(1): p. 48-53.
10. Coates, L.C., et al., *Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial*. The Lancet, 2015.
11. Felson, D.T., et al., *The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials*. Arthritis & Rheumatism, 1993. **36**(6): p. 729-40.
12. Feldman, S.R. and G.G. Krueger, *Psoriasis assessment tools in clinical trials*. Annals of the Rheumatic Diseases, 2005. **64 Suppl 2**: p. ii65-8; discussion ii69-73.
13. Coates, L.C., et al., *The TICOPA protocol (Tight Control of Psoriatic Arthritis): a randomised controlled trial to compare intensive management versus standard care in early psoriatic arthritis*. BMC Musculoskeletal Disorders, 2013. **14**: p. 101.
14. Curtis, L., *Unit Costs of Health and Social Care 2012*. 2012, Personal Social Services Research Unit: Kent.
15. *National schedule of reference costs year 2011-2012 NHS Trusts PCT combined*. Department of Health.
16. CCEMG - EPPI-Centre Cost Converter. 2013 15th February 2014]; Available from: www.eppi.ioe.ac.uk/costconversion/.
17. (BNF), B.N.F., *Drug costs from the BNF. 67th edition*. 2013, British Medical Association and The Royal Pharmaceutical Society of Great Britain: London.
18. NICE, *guide to the methods of technology appraisal*. 2013, National Institute for Health and Care Excellence.
19. EuroQol, G., *EuroQol--a new facility for the measurement of health-related quality of life*. Health Policy, 1990. **16**(3): p. 199-208.
20. Brodsky, V., et al., *Comparison of the Psoriatic Arthritis Quality of Life (PsAQoL) questionnaire, the functional status (HAQ) and utility (EQ-5D) measures in psoriatic arthritis:*

- results from a cross-sectional survey.* Scandinavian Journal of Rheumatology, 2010. **39**(4): p. 303-9.
21. Dolan, P., *Modeling valuations for EuroQol health states.* Med Care, 1997. **35**(11): p. 1095-108.
 22. Fenwick, E., K. Claxton, and M. Sculpher, *Representing uncertainty: the role of cost-effectiveness acceptability curves.* Health Economics, 2001. **10**(8): p. 779-87.
 23. Fenwick, E., B.J. O'Brien, and A. Briggs, *Cost-effectiveness acceptability curves--facts, fallacies and frequently asked questions.* Health Economics, 2004. **13**(5): p. 405-15.
 24. Hoch, J.S., A.H. Briggs, and A.R. Willan, *Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis.* Health Economics, 2002. **11**(5): p. 415-30.
 25. Ramsey, S., et al., *Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report.* Value in Health, 2005. **8**(5): p. 521-33.
 26. Faria, R., et al., *A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials.* Pharmacoeconomics, 2014. **32**(12): p. 1157-1170.
 27. Hamburg, M.A. and F.S. Collins, *The path to personalized medicine.* N Engl J Med, 2010. **363**(4): p. 301-4.
 28. Rosen, C.F., et al., *Patients with psoriatic arthritis have worse quality of life than those with psoriasis alone.* Rheumatology, 2012. **51**(3): p. 571-6.