ORIGINAL RESEARCH

Cost-effectiveness of modified-release prednisone in the treatment of moderate to severe rheumatoid arthritis with morning stiffness based on directly elicited public preference values

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Background: Assessing the cost-effectiveness of treatments in rheumatoid arthritis (RA) is of growing importance due to the chronic nature of the disease, rising treatment costs, and budget-constrained health care systems. This analysis assesses the cost-effectiveness of modified-release (MR) prednisone compared with immediate-release (IR) prednisone for the treatment of morning stiffness due to RA.

Methods: A health state transition model was used to categorize RA patients into four health states, defined by duration of morning stiffness. The model applied a 1-year time horizon and adopted a UK National Health Service (NHS) perspective. Health benefits were measured in quality-adjusted life years (QALYs) and the final output was the incremental cost-effectiveness ratio (ICER). Efficacy data were derived from the CAPRA-1 (Circadian Administration of Prednisone in Rheumatoid Arthritis) study, drug costs from the British National Formulary (BNF), and utility data from a direct elicitation time-trade-off (TTO) study in the general population. Sensitivity analyses were conducted.

Results: Mean treatment costs per patient were higher for MR-prednisone (£649.70) than for IR-prednisone (£46.54) for the duration of the model. However, the model generated an incremental QALY of 0.044 in favor of MR-prednisone which resulted in an ICER of £13,577. Deterministic sensitivity analyses did not lead to significant changes in the ICER. Probabilistic sensitivity analysis reported that MR-prednisone had an 84% probability of being cost-effective at a willingness-to-pay threshold of £30,000 per QALY. The model only considers drug costs and there was a lack of comparative long-term data for IR-prednisone. Furthermore, utility benefits were not captured in the clinical setting.

Conclusion: This analysis demonstrates that, based on the CAPRA-1 trial and directly elicited public preference values, MR-prednisone is a cost-effective treatment option when compared with IR-prednisone for RA patients with morning stiffness over one year, according to commonly applied UK thresholds (£20,000–£30,000 per QALY). Further research into the costs of morning stiffness in RA is required.

Keywords: modified-release prednisone, rheumatoid arthritis, morning stiffness, cost-effectiveness analysis, cost utility analysis, quality of life

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease with prevalence rates varying from 0.45% in southern Europe up to 0.66% in northern/middle Europe and the US, which increase to approximately 2% in those aged ≥60 years.[1] RA patients present with progressive damage to the synovial-lined joints, leading to symptoms

such as joint swelling, tenderness, stiffness, and severe impairment of movement.[2]

RA patients have reduced health-related quality of life (HRQoL), including impaired physical, psychologic, and social functioning.[3] Synovial symptoms of RA, such as joint stiffness and functional disability, are particularly severe in the morning.[2,4,5] This morning stiffness has been shown to contribute to the worsening of HRQoL. A survey in 11 European countries found that 82% of RA patients stated that their morning symptoms had a significant impact on their HRQoL.[6] This is noteworthy, considering that morning stiffness is prevalent in 41% and 79% of patients with controlled and uncontrolled RA, respectively.[7] Further, 73% of patients in paid employment reported that impairment in morning function affected their working life, including time off work and reduced career progression.[6]

The economic consequences of RA and morning stiffness, including loss of earnings and out-of-pocket costs, are substantial for the individual.[8] RA is also a considerable burden to the state in terms of health care spending, welfare payments, and decreased productivity.[8] RA is treated chronically by a number of therapies, including disease-modifying antirheumatic drugs, glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDS), and biologics,[3] which relieve symptoms and modify the disease process.[9] Whilst the introduction of biological therapies has provided a notable advance in the treatment of RA, it has also significantly increased the direct costs.[9] Given this and the prevalence of RA, the treatment and management of RA represents a significant economic burden to health care systems. In the UK in 2009, estimates suggest that National Health Service (NHS) health care costs attributable to RA amounted to approximately £560 million.[10]

Glucocorticoids such as prednisone inhibit the circadian release of proinflammatory cytokines and hence reduce the duration of morning stiffness symptoms.[11] Immediate-release (IR) prednisone is taken upon waking,[11] which is too late to impact upon morning symptoms. Preventing the timely rise of proinflammatory cytokines through appropriate timing of drug administration or use of modified-release (MR) preparations may result in an improvement in morning stiffness duration.[12] MR-prednisone (Lodotra®; Horizon Pharma AG, Reinach, Switzerland) is indicated for the "treatment of moderate to severe, active rheumatoid arthritis in adults, particularly when accompanied by morning stiffness". Lodotra tablets have an MR formulation which is designed to deliver prednisone at the most physiologically efficient time in order to relieve morning symptoms in RA.[13] No adverse impact of

MR-prednisone on the hypothalamic-pituitary-adrenal axis was detected.[14]

The Circadian Administration of Prednisone in Rheumatoid Arthritis Study (CAPRA-1) was a Phase III trial involving 288 patients with ≥45 minutes of morning stiffness due to active RA previously treated with disease-modifying antirheumatic drugs (DMARDS), nonsteroidal anti-inflammatory drugs, and glucocorticoids.[13] Patients were randomly assigned to either MR-prednisone (n = 144) or to IR-prednisone (n = 144). The primary endpoint was the relative change in duration of morning stiffness from baseline to the end of the 12-week double-blind phase (calculated from daily patient diaries).[13] At the end of the study period, patients in the MR group achieved a mean reduction of 43.9 minutes compared with 22.7 minutes in the IR group.[13] In addition to this, a 9-month, open-label extension of the CAPRA-1 trial investigated the long-term efficacy of MR-prednisone.[11] The reduction in morning stiffness duration established in the double-blind phase was sustained during follow-up. Further, recently published research from the CAPRA-2 trial reported a significantly greater median relative reduction in duration of morning stiffness at 12 weeks for MR-prednisone compared with placebo ($P < 0.004$). The response was also achieved rapidly, with a significant difference in response rates for MR-prednisone in comparison with placebo reported as early as week 2.[15]

The CAPRA-1 trial also collected HRQoL information using the Health Assessment Questionnaire (HAQ) and Short-Form 36 questionnaire (SF-36). The SF-36 data were converted into utility values using the Brazier equation,[16] which demonstrated that there was a 0.0132 utility improvement for patients treated with MR-prednisone compared with IR-prednisone;[17] this numeric improvement was not statistically significant. This may be due to several reasons. For example, it has been acknowledged that generic instruments can lack sensitivity in chronic diseases,[18–21] and in addition, these instruments were not used in the most effective manner in the CAPRA-1 study (HRQoL measures were only captured at week 0 and week 12, and instruments were administered as part of a general visit and not specifically in the morning). It is also important to note that morning stiffness in RA does not necessarily correlate with generic HRQoL scores; Khan et al found that morning stiffness showed only a moderate correlation with Health Assessment Questionnaire (HAQ) scores.[7] Due to these limitations, a separate study directly eliciting health state utilities associated with differing durations of morning stiffness in RA has been conducted.[22] This UK population-based direct elicitation study demonstrated

that a reduction in morning stiffness duration in RA is associated with improved HRQoL.

Economic evidence regarding the use of MR and IR-prednisone in RA patients with morning stiffness is limited. Given the chronic nature and increasing prevalence of RA, the rising costs of treatment, and health care budget constraints, assessing the cost-effectiveness of RA treatment is of growing importance.[23] This study aimed to build on the findings of the CAPRA-1 trial and the direct elicitation time-trade-off (TTO) study for health state utilities. We assessed the cost-effectiveness of MR-prednisone compared with IR-prednisone in the treatment of morning stiffness due to RA from a UK health care system perspective.

Materials and methods
Methods

A cost utility model was developed in which health was measured in quality-adjusted life years (QALYs) and costs in British Pounds Sterling (£). The final output of the model was the incremental cost-effectiveness ratio (ICER), which measured the incremental cost and health gain of MR-prednisone compared with IR-prednisone. The model categorized RA patients into a series of four discrete health states defined by duration of morning stiffness symptoms. The distributions of patients were elicited from the pivotal Phase III CAPRA-1 trial comparing MR-prednisone and IR-prednisone.[13]

Model structure

The model applied a 1-year time horizon, meaning that discounting was not necessary. The 1-year time horizon for the model was justified given the 3-month duration of the double-blind CAPRA-1 trial and the 9-month single-arm, open-label extension.[13,15] The evaluation adopted the perspective of the UK health care payer, the National Health Service (NHS). No attempt was made to capture costs or benefits which fall outside of the health service. The health state transition model was developed in Microsoft Excel 2007, and an overview of the model structure is provided in Figure 1.

The health states were developed with input from three key opinion leaders in the RA field, three RA patients with morning stiffness, and clinical trial data from CAPRA-1. Four health states were identified, each with a 1-hour difference in duration of morning stiffness.[22] The four health states applied in the model were based on a morning stiffness duration of less than 1 hour, 1–2 hours, 2–3 hours, and ≥3 hours (Figure 1). The health states were deemed to be a clinically meaningful change for patients and key opinion leaders (KOLs), and the duration was also expected to lead to a tangible change in health status.[22]
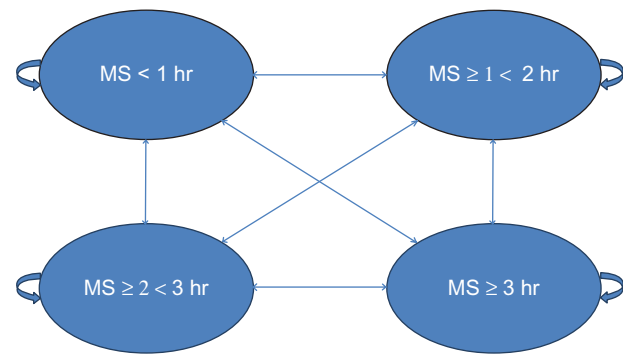

Figure 1 Overview of model structure.
Abbreviation: MS, morning stiffness.

The distributions of patients in such health states were determined from the pivotal Phase III CAPRA-1 trial for MR-prednisone, the primary objective of which was to assess whether MR-prednisone is superior to IR-prednisone in reducing the duration of morning stiffness following 3 months of treatment.[11] This randomized, multicenter, double-blind trial included 288 subjects with a documented history of RA, who met the American College of Rheumatology criteria for RA, including symptoms of morning stiffness (average daily duration of 45 minutes during the last 7 days of the screening process), joint pain, tender and swollen joints, and an inflammatory state with elevated erythrocyte sedimentation rate or C-reactive protein. Table 1 provides a full breakdown of patient demographics. The development of these health states is described further in a direct preference elicitation study designed to identify utility values attributable to each health state.[22]

Table 1 Patient demographics for CAPRA-1

Demographic, mean	MR-prednisone (n=144)	IR-prednisone (n=144)
Age	54.6	55.4
Women	125 (87%)	122 (85%)
Ethnic origin		
White	143 (99%)	144 (100%)
Asian	1 (1%)	0
Duration of morning stiffness of the joints (min)	164.1	182.5
Pain score (VAS [mm])	57.9	59.7
Health assessment questionnaire disability index	1.5	1.5
Total duration of RA (years)	9.6	9.6
<2 years	19 (13%)	18 (13%)
2–5 years	37 (26%)	37 (26%)
5–10 years	33 (23%)	31 (22%)
>10 years	55 (38%)	58 (40%)

Notes: Reprinted from *The Lancet*, 371(9608), Buttgereit F, Doering G, Schaeffler A, Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial, 204–214. Copyright © 2008, with permission from Elsevier.[13]
Abbreviations: CAPRA-1, Circadian Administration of Prednisone in Rheumatoid Arthritis study; RA, rheumatoid arthritis; VAS, visual analog pain score; MR, modified-release; IR, immediate-release.

Costs

For costs, j represents treatment, where $j = 1$ refers to MR-prednisone and $j = 2$ refers to IR-prednisone; C_j is the total cost of drug for treatment j; Y is the expected duration for each treatment (months); and D_j is the monthly average cost per treatment arm (see Table 4). Hence,

$$C_j = Y * D_j.$$

Therefore, the incremental cost between the treatment arms is:

$$C_1 - C_2.$$

Quality-adjusted life years

Q_j is the total QALY for treatment; K represents health states 1–4; t is time; P_{jtk} is the distribution for treatment j across health state k, at time t (see Table 2), and U_k is the health state utility values (see Table 3). For a particular treatment, the total QALY is:

$$Q_j = \sum_{t=0}^{t11} (P_{jt1} * U_1 + P_{jt2} * U_2 + P_{jt3} * U_3 + P_{jt4} * U_4).$$

Therefore, the ICER is:

$$\frac{C_1 - C_2}{Q_1 - Q_2}.$$

Efficacy inputs

Treatment efficacy data were derived from the CAPRA-1 trial. Analyses were conducted using the original trial data to obtain patient distributions for the different health states.[24] Monthly distributions of patients across the health states were obtained

from this analysis at baseline, and at 4, 8, and 12 weeks (see Table 2). These outcomes were used to populate the model at baseline, month 1, month 2, and month 3, respectively.

An average distribution of patients across both treatment arms was used at baseline to ensure that any differences in treatment efficacy were not attributable to the baseline patient distributions. For example, patient distribution for those with less than 1 hour morning stiffness ($K = 1$) at baseline for MR-prednisone was 0.104 compared with 0.085 in the IR-prednisone arm; this was adjusted to a mean distribution of 0.095 for both arms. This adjustment was made by calculating the difference in distribution at baseline and applying these differences to the distributions for each arm at each time point of the model. This analysis did not capture age-related mortality of patients; it was deemed reasonable to assume that mortality is equivalent between the treatment arms.

The model applied a 1-year time horizon; after month 3, patients were assumed to remain in the same health state for the remainder of the analysis to reflect the availability of double-blind clinical data. However, longitudinal open-label data suggest that the efficacy of MR-prednisone continues to increase over time.[11] Therefore, it may be reasonable to assume that the modeling method chosen in the base case is conservative with regard to the results for MR-prednisone.

Utility input data

Utility input data were derived from a previously published direct elicitation study.[22] Four health states were developed based on evidence derived from peer reviewed literature,[7,25,26] clinical trial data,[13] and patient diaries.[27] Each health state was developed with the Euro-QoL 5D[28] as the contextual framework. The health states were refined through input from

Table 2 Patient distribution across health states for baseline and months 1–3 (unadjusted baseline values and adjusted baseline to month 3 as used in analysis)

Time point (hours)	MR-prednisone (mean)				IR-prednisone (mean)			
	MS <1 K = 1	MS 1–2 hours K = 2	MS 2–3 hours K = 3	MS ≥3 hours K = 4	MS <1 K = 1	MS 1–2 hours K = 2	MS 2–3 hours K = 3	MS ≥3 hours K = 4
CAPRA-1 distribution at baseline	0.104	0.288	0.240	0.368	0.085	0.264	0.240	0.411
Baseline t = 0	0.095	0.276	0.240	0.389	0.095	0.276	0.240	0.389
Month 1 t = 1	0.341	0.261	0.120	0.278	0.213	0.207	0.179	0.401
Month 2 t = 2	0.391	0.273	0.114	0.221	0.268	0.210	0.181	0.341
Month 3 t = 3	0.432	0.223	0.108	0.237	0.262	0.264	0.126	0.348

Abbreviations: CAPRA-1, Circadian Administration of Prednisone in Rheumatoid Arthritis study; MS, morning stiffness; K, health state; t, time; IR, immediate-release; MR, modified-release.

Table 3 Utility values for health states based on different durations of morning stiffness in RA

Health state (k)	Mean TTO Utility score U_k (SD) [SE]	Lower confidence interval*	Upper confidence interval*
MS < 1 hr (U_1)	0.78 (±0.20) [0.19]	0.74	0.82
MS ≥ 1 and <2 hr (U_2)	0.61 (±0.25) [0.24]	0.57	0.66
MS ≥ 2 and <3 hr (U_3)	0.50 (±0.28) [0.27]	0.45	0.55
MS ≥ 3 hr (U_4)	0.45 (±0.29) [0.28]	0.40	0.51

Notes: *95% confidence intervals were used to determine the lower and upper bounds of confidence. Reproduced with permission of Informa Healthcare, Iqbal I, Dasgupta B, Taylor P, Heron L, Pilling C, Elicitation of health state utilities associated with differing durations of morning stiffness in rheumatoid arthritis, *J Med Econ*, 2012;15(6):1192–2000, Copyright © 2012, Informa Healthcare.[22]
Abbreviations: MS, morning stiffness; RA, rheumatoid arthritis; SD, standard deviation; SE, standard error; TTO, time-trade-off; U_k, health state utility values.

two expert rheumatologists, a consultant rheumatology nurse, and three RA patients with morning stiffness. The four health states were then tested using a TTO approach which was conducted with 109 members of the general public sampled from seven regions in the UK in 2011.[22] These published utility scores, based on the four health states represented in this model, are presented in Table 3.

Cost inputs

The economic evaluation considered the drug costs of MR-prednisone and IR-prednisone. Table 4 presents the estimates of the daily costs of treatment from the British National Formulary 63.[29] Prednisone does not appear in the British National Formulary (BNF) 63, so drug costs for prednisolone were used because prednisone is the prodrug of prednisolone. The costs of both interventions were based on a daily dose of 7 mg as per the mean dose in the trial (6.38 mg/day in CAPRA-1; 6.8 mg/day during the open-label extension). The average dose is therefore a conservative estimate and also accounts for wastage (because the smallest available tablet is 1 mg). MR-prednisone and IR-prednisone are self-administered, so there are no additional resource implications for the NHS that directly relate to drug administration.

Costs associated with adverse events were not included in the cost calculations. Data from the CAPRA-1 trial show that the most frequently reported drug-related adverse events were similar in both treatment groups.[30] No single drug-related treatment-emergent adverse event (TEAE) occurred in more than 6% of patients, and there was never more than a 3% difference in drug-related TEAE between treatment arms.[30] Therefore, it is reasonable to assume that patients treated with either drug will display similar treatment costs and resource use due to adverse events. Other health care resources incurred by treating RA patients, such as hospital outpatient visits, were not included in this analysis. It is reasonable to assume that RA patients with longer durations of morning stiffness may require additional health care professional attention. However, these potential health care resources are excluded due to an absence of robust evidence.

Sensitivity analysis
Deterministic sensitivity analyses
Deterministic one-way sensitivity analyses were carried out on the utility values. One-way sensitivity analyses for the utility data assessed the impact on the ICER by varying model inputs using the lower and upper bounds of each of the health states of the reported confidence intervals (Table 3). The impact of applying a longer time horizon (discount factor of 3.5% used, as per UK National Institute of Health and Clinical Excellence [NICE] guidance),[21] to reflect the chronic nature of RA, and a shorter time horizon to reflect the availability of clinical evidence, were also analyzed. After month 3, a conservative assumption of "no further improvement" is applied, as per the base case analysis.

Scenario analyses
Three alternative scenarios related to the efficacy input data were tested as part of the sensitivity analyses:
- Scenario 1: extension of effect to 6 months. Distributions of patients from the CAPRA-1 trial were applied for the

Table 4 Drug cost and quantities per day/month (UK 2012)[29]

	Unit quantity	Unit cost	Price per tablet	Number of tablets per day	Daily cost	Monthly cost
MR-prednisone						
2 mg	30	£26.70	£0.89	1	£0.89	
5 mg	30	£26.70	£0.89	1	£0.89	
Total MR-prednisone (D_1)					£1.78	**£54.14**
IR-prednisone						
1 mg	28	£1.18	£0.04	2	£0.08	
5 mg	28	£1.21	£0.04	1	£0.04	
Total IR-prednisone (D_2)					£0.12	**£3.88**

Note: Monthly cost = daily cost of both tablets x 365/12
Abbreviations: D, average monthly cost of drug per treatment arm; IR, immediate-release; MR, modified-release.

first 3 months of treatment; following this, the mean change from 0 to 3 months was applied between months 3 and 6. Patients then remained in the same health state for the remainder of the model (up to month 12).

- Scenario 2: use of open-label study data. Distributions of patients from the CAPRA-1 trial were applied for the first 3 months for treatment with MR-prednisone. A 9-month, single-arm, open-label extension of the CAPRA-1 trial investigated the long-term efficacy of MR-prednisone (n = 249, all patients from CAPRA-1).[11] Data at 12 months from the open-label study (distributions of patients, adjusted for baseline differences: k = 1, 0.416; k = 2, 0.177; k = 3, 0.142; k = 4, 0.266) were applied for this scenario. Monthly distributions of patients across health states were not available between week 12 and week 52; therefore, the model assumed a constant linear monthly change in patient distributions. This distribution was calculated by examining the difference in distributions across health states at week 52 and week 12 and dividing this by 9 to obtain a monthly change in distribution, assuming a linear change. The proportion of patients treated with IR-prednisone was based on the baseline to 3 month CAPRA-1 trial data and no further response was assumed after 3 months.

- Scenario 3: patient distributions using CAPRA-1 trial data. To test whether the adjustment for differences in patients' baseline distribution had any impact on results, a scenario was undertaken where no adjustment was made. Actual monthly distributions of patients across the health states were applied from the CAPRA-1 trial (see baseline distribution in Table 2) from baseline to month 3. After month 3, a conservative assumption of "no further improvement" is applied, as per the base case.

Probabilistic sensitivity analysis

The robustness of the ICER and uncertainty in the two key input parameters of patient distributions across health states and utility values was also investigated by probabilistic sensitivity analysis. The Dirichlet distribution was applied to patient distributions across the four different health states at baseline, month 1, month 2, month 3, and month 12 for both MR-prednisone and IR-prednisone. Probabilities for the Dirichlet distribution were determined by random draw in Excel (a random number from 0 to 1), and alpha distributions were determined by the number of patients in each health state in the base case.

For the utility data, standard errors and mean utility values were used to calculate the alpha and beta values for the utility scores associated with each health state. The

formulas used for calculating alpha and beta distributions are presented below:

$$\alpha = \mu * [\mu * (1 - \mu)/(SE^2) - 1]$$

$$\beta = \mu * (1 - \mu)/(SE^2) - 1 -$$

SE = standard error; μ = expected value.

Monte Carlo simulations employing 1,000 iterations were performed.

Results
Base case results

Over a 12-month period, the mean per patient treatment costs were higher in the MR-prednisone arm compared with the IR-prednisone arm (Table 5). However, MR-prednisone generated an increase in QALYs of 0.044 over 12 months, thereby resulting in an ICER of £13,577.

Deterministic sensitivity analyses

Table 6 shows the impact of changes made to the key parameters in the model. Across all of the sensitivity analyses performed, the ICER remained below a cost-effectiveness threshold of £20,000 per QALY.

Scenario analyses

Table 7 shows the impact of different assumptions related to the efficacy inputs (distribution of patients across health states). The results of the scenario analyses demonstrate that the ICER is relatively insensitive to changes in these assumptions, because the ICER remained below a cost-effectiveness threshold of £20,000 per QALY.

Probabilistic sensitivity analysis

Compared with the base case results, the probabilistic sensitivity analysis resulted in an identical incremental cost of £603.16 (as drug costs were not included in the probabilistic sensitivity analysis), an incremental QALY of 0.044 (95% confidence interval 0.014–0.074) and a similar ICER of £13,617 (95% confidence interval £8,080–£41,326). The

Table 5 Incremental cost-effectiveness results: baseline deterministic findings

	MR-prednisone	IR-prednisone	Incremental
Total cost per patient	£649.70	£46.54	£603.16
QALYs per patient	0.623	0.579	0.044
ICER			£13,577

Abbreviation: ICER, Incremental cost-effectiveness ratio; IR, immediate-release; MR, modified-release; QALYs, quality-adjusted life years.

Table 6 One-way sensitivity analysis results

Description	Incremental QALYs*	Incremental costs (£)**	ICER (£ per QALY)
Baseline results	0.044	603.16	13,577
Utility (MS < 1 hour) set to low CI	0.038	603.16	15,674
Utility (MS < 1 hour) set to high CI	0.050	603.16	11,975
Utility (MS 1–2 hours) set to low CI	0.045	603.16	13,322
Utility (MS 1–2 hours) set to high CI	0.043	603.16	13,911
Utility (MS 2–3 hours) set to low CI	0.046	603.16	13,221
Utility (MS 2–3 hours) set to high CI	0.043	603.16	13,953
Utility (MS ≥ 3 hours) set to low CI	0.050	603.16	12,162
Utility (MS ≥ 3 hours) set to high CI	0.038	603.16	15,780
All utility values set to low CI	0.046	603.16	13,199
All utility values set to high CI	0.042	603.16	14,393
Time horizon, 4 months	0.012	201.00	16,760
Time horizon, 5 years	0.223	2,818.63	12,634

Notes: *Figures rounded to three decimal places; **figures rounded to two decimal places.
Abbreviations: CI, confidence interval; ICER, incremental cost-effectiveness ratio; MS, morning stiffness; QALYs, quality-adjusted life years.

cost-effectiveness scatter plot demonstrates the high confidence in the input values of the model, which have resulted in a limited spread of results (Figure 2).

The cost-effectiveness acceptability curve based on the Monte Carlo simulations performed is presented in Figure 3. The curve shows that, at a willingness-to-pay threshold of £20,000 per QALY gained, the estimated probability that

Table 7 Scenario analysis results

Description	Incremental QALYs*	Incremental costs (£)**	ICER (£ per QALY)
Base case results	0.044	603.16	13,577
Scenario 1, extension of effect to 6 months	0.045	603.16	13,247
Scenario 2, use of open-label study data	0.041	603.16	14,797
Scenario 3, patient distribution using CAPRA-1 trial data	0.054	603.16	11,067

Notes: *Figures rounded to three decimal places; **figures rounded to two decimal places.
Abbreviations: CAPRA-1, Circadian Administration of Prednisone in Rheumatoid Arthritis study; CI, confidence interval; ICER, incremental cost-effectiveness ratio; MS, morning stiffness; QALYs, quality-adjusted life years.

MR-prednisone is cost-effective was 84% and approached 95% at a willingness-to-pay of £30,000 per QALY gained.

Discussion

To the author's knowledge, this is the first study to investigate the cost-effectiveness of a treatment targeted to RA patients with morning stiffness. For a time horizon of 12 months, the mean treatment costs per patient were higher in the MR-prednisone arm compared with the IR-prednisone arm. However, the model generated an increase in QALYs of 0.044 in favor of MR-prednisone. The ICER was estimated to be £13,577. The cost-effectiveness threshold applied by NICE for decision-making in the UK is normally £20,000–£30,000 per QALY and technologies below this level are deemed cost-effective.[21] Our analysis therefore suggests that MR-prednisone represents a cost-effective use of NHS resources.

Deterministic one-way sensitivity analyses demonstrated that the ICER was relatively insensitive across changes in all of the model parameters. The probabilistic sensitivity analysis also reported that MR-prednisone has an 84% probability of being cost-effective at a willingness-to-pay threshold of £20,000 per QALY, which approaches 95% at a willingness-to-pay of £30,000 per QALY gained. Each of the scenario analyses, including increasing duration of treatment, and changes to efficacy and utility values, results in an ICER which is below £20,000 per QALY. Given the increase in health-related costs and the progressively stretched health care budgets, demonstrating cost-effectiveness is highly important in chronic diseases such as RA.[23] The results of this economic model, which demonstrate that MR-prednisone is cost-effective against IR-prednisone, are therefore significant and relevant.

This research emphasizes the need for further research into the costs of morning stiffness because this model only considers drug costs and omits other potential costs to the payer and society. These costs have been omitted due to a lack of robust data relating specifically to the health states applied in this evaluation. However, a European study found that drug costs represent only 14% of the costs associated with RA, with other medical costs accounting for 21%, work productivity losses accounting for 32%, informal care for 19%, and nonmedical costs for 14%.[1] An observational study, which observed 1,185 RA patients treated with MR-prednisone over a 9-month period, found significant reductions in the number and proportion of patients receiving other therapies for RA, such as disease-modifying antirheumatic drugs. Similar reductions were seen with use of analgesics, nonsteroidal anti-inflammatory drugs, and gastroprotective treatments.[31] Additional data from Fautrel
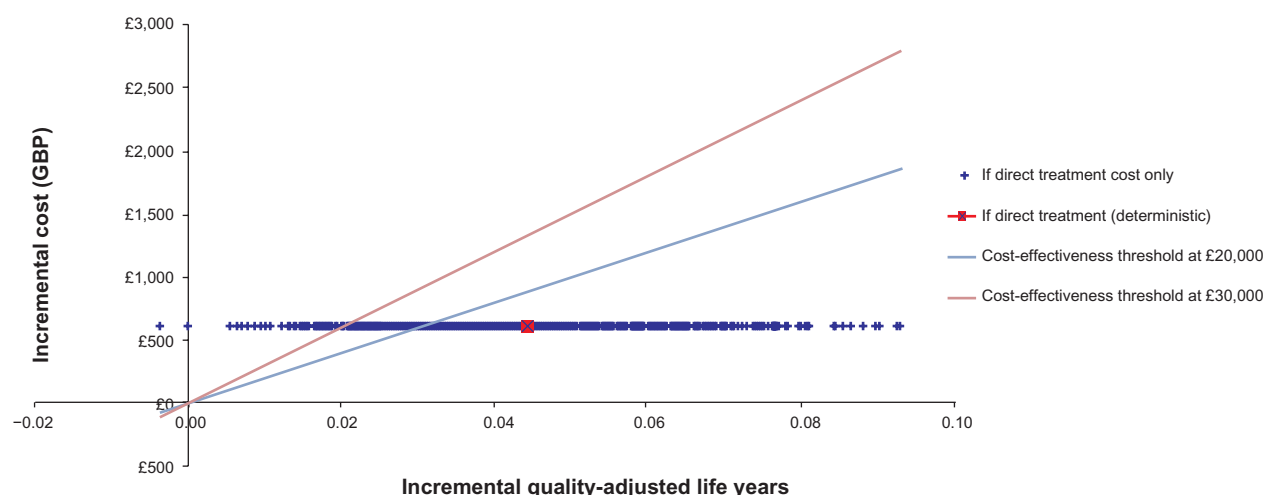
Figure 2 Cost-effectiveness scatter plot for modified-release prednisone.
Abbreviation: GBP, Great British Pound.

suggest that early treatment with glucocorticoids, including MR-prednisone, delays the need for costly biologics,[32] and in addition, a recent publication has highlighted the cost savings associated with delaying biologic treatment by use of MR-prednisone.[33] These data suggest that use of MR-prednisone may be associated with a reduction in health care costs, which would further reduce the ICER. This is particularly significant given the relatively low incremental drug costs of MR-prednisone. For example, a community nurse visit costs £768 over a 12-month period (assumes 1 hour per month),[34] which is more than the incremental cost of MR-prednisone (£603.16).

Another aspect to consider is that the model uses clinical effectiveness data drawn directly from the CAPRA-1 trial which was based in the German and Polish health care settings; however, the economic model is based on the UK NHS perspective. This assumes that the baseline distribution of patients and the treatment effect are similar between

Germany, Poland, and the UK. This is a universal limitation of using multinational trial data in country-specific models, and hence this limitation is not exclusive to this model. There is also considerable uncertainty about the long-term efficacy of MR-prednisone due to the limitations of open-label studies, and there is a lack of comparative data for the IR formulation. Despite these limitations, the initial long-term data relating to the efficacy of MR-prednisone are positive, with more than 29% of patients reporting less than 1 hour of morning stiffness after 12 months of treatment with MR-prednisone in the single-arm, open-label study.

The CAPRA-1 trial incorporated health-related quality of life variables, including the SF-36 and HAQ. However, these instruments were not able to capture HRQoL benefits despite clear improvements in the primary endpoint of morning stiffness duration.[13] This may be due to several reasons, as noted in the introduction, HRQoL measures were only captured at week 0 and week 12 and instruments were administered during a general visit and not specifically in the morning (ie, outside of the "morning stiffness period").[13] In addition, generic instruments may lack sensitivity in chronic diseases.[18–20] This may be due to extended intervals between data collection. For example in CAPRA-1, SF-36 data were collated to cover a recall period of 4 weeks. However, instruments which quantify HRQoL over the previous 24-hour period are much more responsive and the respondent does not need to consider long recall periods.[35] Furthermore, the SF-6D, which provides a means of using the SF-36 in economic evaluation, is also known to have a high floor which may limit its use in patients with more severe manifestations of RA.[36] Uncertainty over the sensitivity of generic quality of life measures has also been raised in the oncology setting,[37] with research suggesting that, at times, the QALY
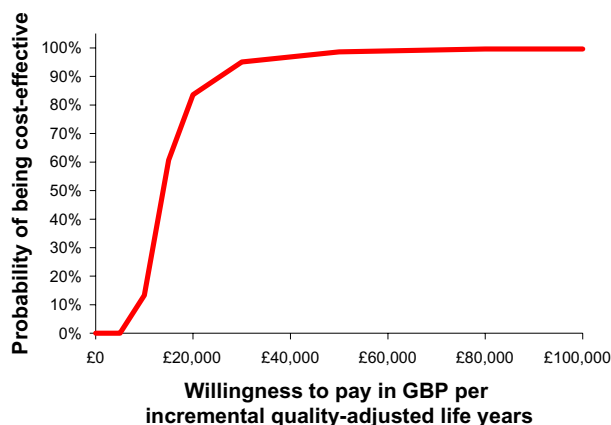

Figure 3 Cost-effectiveness acceptability curve for modified-release prednisone.
Abbreviation: GBP, Great British Pound.

construction methodology can be inadequate because it fails to capture important quality of life issues.

In instances where generic HRQoL instruments do not measure the desired aspects of a disease and there is uncertainty regarding their sensitivity, it is common to use utility values from published sources or to use direct elicitation measures.[38] Since there were no previously published utility values relating explicitly to duration of morning stiffness symptoms, a robust utility elicitation exercise was performed.[22] NICE recommends use of the TTO method in a representative sample of the UK population, as was the case in this model.[21] The published TTO study demonstrated that reduction in morning stiffness duration is associated with improvement in HRQoL for patients with RA.[22] Therefore, because MR-prednisone is associated with a reduction in morning stiffness duration, it is reasonable to assume that it improves HRQoL in comparison with IR-prednisone. The utility values cited in this model (from Iqbal et al)[22] are consistent with the findings of previous utility studies in RA. Recent research reported that the mean visual analog pain score (VAS) for late-stage RA was 33.52 ± 24.79,[39] which is comparable with the score obtained for the anchor state in the Iqbal et al study of 0.34 ± 0.16.[22] Further, a study conducted in 345 Irish patients with RA treated with biological therapy found that mean utility values were 0.54 ± 0.09 using the SF-6D and 0.43 ± 0.322 using the EQ-5D.[3] These scores are comparable with those elicited by Iqbal et al for the anchor health state (0.45) and health state 1 (0.50).[22]

The model applied a 1-year time horizon because this reflects the length of the CAPRA-1 trial (3 months) plus the 9-month open-label extension.[13,15] However, it is recognized that because RA is a life-long condition, examination of a lifetime time horizon may also be appropriate. Initial results from the long-term observational data show that the efficacy of MR-prednisone continues to increase over time.[11] Therefore, it may be reasonable to assume that the ICER presented in this study is a conservative short-term estimate. Furthermore, results from the 5-year sensitivity analysis suggest that MR-prednisone is deemed to be cost-effective over a longer time period.

The model currently only considers the "quality" aspect of the QALY outcome measure because survival is not captured within this economic evaluation. One other potential limitation is the exclusion of age-related mortality, that may overestimate the incremental QALY gain associated with MR-prednisone; however the impact of this is limited because it would affect both treatment groups.

Overall, this study suggests that, using a direct elicitation approach to generation of utility data, MR-prednisone in comparison with IR-prednisone is a cost-effective use of NHS resources in the treatment of RA patients with morning stiffness over a 12-month time horizon. Further, given that morning stiffness is known to be an important factor in reduced productivity and early retirement, the inclusion of drug costs only provides a potentially conservative analysis. Sensitivity analyses demonstrate that changes to key parameters do not lead to significant changes in the ICER, given that, in all sensitivity analyses conducted, ICERs remain below the acceptable cost-effective threshold applied by NICE.

Acknowledgments

Author contributions

The model was developed and validated by LH, WD, II, IK, and MO.

Disclosure

References

1. Lundkvist J, Kastang F, Kobelt G. The burden of rhematoid arthritis and access to treatments: health burden and costs. *Eur J Health Econ*. 2008;8(2):49–60.
2. Grassi W, De AR, Lamanna G, Cervini C. The clinical features of rheumatoid arthritis. *Eur J Radiol*. 1998;27(1):18–24.
3. Adams R, Walsh C, Veale D, Bresnihan B, FitzGerald O, Barry M. Understanding the relationship between the EQ-5D, SF-6D, HAQ and disease activity in inflammatory arthritis. *Pharmacoeconomics*. 2010;28(6):477–487.
4. Cutolo M. How should morning function in rheumatoid arthritis be assessed? Bibliographic study of current assessment. *Scand J Rheumatol Suppl*. 2011;125:17–22.

5. Sierakowski S, Cutolo M. Morning symptoms in rheumatoid arthritis: a defining characteristic and marker of active disease. *Scand J Rheumatol Suppl*. 2011;125:1–5.

6. da Silva JA, Phillips S, Buttgereit F. Impact of impaired morning function on the lives and well-being of patients with rheumatoid arthritis. *Scand J Rheumatol Suppl*. 2011;125:6–11.

7. Khan NA, Yazici Y, Calvo-Alen J, et al. Reevaluation of the role of duration of morning stiffness in the assessment of rheumatoid arthritis activity. *J Rheumatol*. 2009;36(11):2435–2442.

8. American Autoimmune Related Disease Association. The cost burden of autoimmune disease: the lastest front in the war on spending. National Institute of Health Progress in Autoimmune Disease Research Report, 2011. Available from: http://www.aarda.org/pdf/cbad.pdf. Accessed July 27, 2013.

9. National Institute for and Clinical Excellence. Rheumatoid arthritis: The management of rheumatoid arthritis in adults. NICE Clinical Guidelines, 2009. Available from: http://publications.nice.org.uk/rheumatoid-arthritis-cg79. Accessed July 27, 2013.

10. National Audit Office. Services for people with rhematoid arthritis. Report by the comptroller and auditor general 823, Session HC823. 2009. Available from: http://www.nao.org.uk/wp-content/uploads/2009/07/0809823.pdf. Accessed July 27, 2013.

11. Buttgereit F, Doering G, Schaeffler A, et al. Targeting pathophysi-ological rhythms: prednisone chronotherapy shows sustained efficacy in rheumatoid arthritis. *Ann Rheum Dis*. 2010;69(7):1275–1280.

12. Arvidson NG, Gudbjornsson B, Larsson A, Hallgren R. The timing of glucocorticoid administration in rheumatoid arthritis. *Ann Rheum Dis*. 1997;56(1):27–31.

13. Buttgereit F, Doering G, Schaeffler A, et al. Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. *Lancet*. 2008;371(9608):205–214.

14. Alten R. Chronotherapy with modified-release prednisone in patients with rheumatoid arthritis. *Expert Rev Clin Immunol*. 2012;8(2):123–133.

15. Buttgereit F, Mehta D, Kirwan J, et al. Low-dose prednisone chrono-therapy for rheumatoid arthritis: a randomised clinical trial (CAPRA-2). *Ann Rheum Dis*. 2013;72(2):204–210.

16. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ*. 2002;21(2):271–292.

17. Mundipharma International. Data on file: IMS SF-6D results. 2011.

18. Aletaha D, Strand V, Smolen JS, Ward MM. Treatment-related improve-ment in physical function varies with duration of rheumatoid arthritis: a pooled analysis of clinical trial results. *Ann Rheum Dis*. 2008;67(2):238–243.

19. Papaioannou D, Brazier J, Parry G. How valid and responsive are generic health status measures, such as EQ-5D and SF-36, in schizophrenia? A systematic review. *Value Health*. 2011;14(6):907–920.

20. Espallargues M, Czoski-Murray CJ, Bansback NJ, et al. The impact of age-related macular degeneration on health status utility values. *Invest Ophthalmol Vis Sci*. 2005;46(11):4016–4023.

21. National Insititute for Health and Clinical Excellence. Guide to the methods of technology appraisal 2013. Available from: http://www.nice.org.uk/media/D45/1E/GuideToMethodsTechnologyAppraisal2013.pdf. Accessed July 27, 2013.

22. Iqbal I, Dasgupta B, Taylor P, Heron L, Pilling C. Elicitation of health state utilities associated with differing durations of morning stiffness in rheumatoid arthritis. *J Med Econ*. 2012;15(6):1192–2000.

23. Benucci M, Saviola G, Manfredi M, Sarzi-Puttini P, Atzeni F. Cost effectiveness analysis of disease-modifying antirheumatic drugs in rheumatoid arthritis. A systematic review literature. *Int J Rheumatol*. 2011;2011:845496.

24. Mundipharma International. Data on file: transition probabilities for CAPRA-1. 2011.

25. Murphy K, Spence S, McIntosh C, Connor-Gorber S. Health state descriptions for canadians: musculoskeletal diseases. *Statistics Canada*. 2006;82:1–38.

26. Yazici Y, Pincus T, Kautiainen H, Sokka T. Morning stiffness in patients with early rheumatoid arthritis is associated more strongly with func-tional disability than with joint swelling and erythrocyte sedimentation rate. *J Rheumatol*. 2004;31(9):1723–1726.

27. National Rheumatoid Arthritis Society. Living with RA: case studies. Available from: http://www.nras.org.uk/about_rheumatoid_arthritis/living_with_rheumatoid_arthritis/default.aspx. Accessed July 27, 2013.

28. EuroQol Group http://www.euroqol.org/about-eq-5d/eq-5d-nomencla-ture.html. Accessed 15, August 2013.

29. British National Formulary No 63. BNF Prednisone. 2012. Available from: http://www.medicinescomplete.com/mc/bnf/current/213856.htm. Accessed July 27, 2013.

30. Mundipharma International. Data on file: Drug related TEAE. 2006.

31. Pfeiffer B, Krenzer S, Dockhorn R, et al. Impact of modified-release prednisone on functional ability in patients with RA. *Rheumatol Int*. 2013;33(6):1447–1454.

32. Fautrel B. Economic benefits of optimizing anchor therapy for rheu-matoid arthritis. *Rheumatology (Oxford)*. 2012;51(4):21–26.

33. Boers M, Buttgereit F. A simple model that suggests possible cost sav-ings when modified-release prednisone 5 mg/day is added to current treatment in patients with active rheumatoid arthritis. *Rheumatology (Oxford)*. 2013;52(8):1435–1437.

34. Curtis L. Personal and Social Services Research Unit. Unit costs of health and social care. Available from: http://www.pssru.ac.uk/. Accessed July 27, 2012.

35. Ware JE. SF-36 Health Survey Update 2012. Available from: http://www.sf-36.org/tools/sf36.shtml. Accessed July 27, 2013.

36. Harrison MJ, Davies LM, Bansback NJ, Ingram M, Anis AH, Symmons DP. The validity and responsiveness of generic utility measures in rheumatoid arthritis: a review. *J Rheumatol*. 2008;35(4):592–602.

37. Garau M, Shah KK, Mason AR, Wang Q, Towse A, Drummond MF. Using QALYs in cancer: a review of the methodological limitations. *Pharmacoeconomics*. 2011;29(8):673–685.

38. Tosh JC, Longworth LJ, George E. Utility values in National Institute for Health and Clinical Excellence (NICE) Technology Appraisals. *Value Health*. 2011;14(1):102–109.

39. Mittendorf T, Dietz B, Sterz R, Cifaldi MA, Kupper H, von der Schulenburg JM. Personal and economic burden of late-stage rheuma-toid arthritis among patients treated with adalimumab: an evaluation from a patient's perspective. *Rheumatology (Oxford)*. 2008;47(2):188–193.