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Economic evaluation of early administration of prednisolone and/or aciclovir for the treatment of Bell's palsy

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ABSTRACT

Objectives

Bell's palsy (BP), which causes facial paralysis, affects 11-40 people per 100,000 per annum in the UK. Its cause is unknown but as many as 30% of patients have continuing facial disfigurement, psychological difficulties and occasionally facial pain. We present a RCT based economic evaluation of the early administration of steroids (prednisolone) and/or antivirals (acyclovir) compared to placebo, for treatment of BP.

Methods

The RCT was not powered to detect differences in the cost-effectiveness (CEA); therefore, we adopted a decision analytic model approach as a way of gaining precision in our CEA comparisons (e.g. prednisolone only (PO) vs. acyclovir only vs. prednisolone and acyclovir vs. placebo; prednisolone vs. no prednisolone (NP) and acyclovir vs. no acyclovir (NA)). We assumed that trial interventions affect the probability of being cured/not cured but their consequences are independent of the initial therapy. We used the percentage of individuals with a complete recovery (based on House-Brackmann grade=1) at 9 months and QALYs (e.g. derived on responses to the Health Utilities Index 3) as measures of effectiveness. Other parameter estimates were obtained from trial data.

Results

PO dominated -i.e. was less costly and more effective- all other therapy strategies in the four arms model (77% probability of CE). Moreover, Prednisolone dominated NP (77% probability of being cost effective (CE) at £30,000 threshold) while NA dominated aciclovir (85% chance of CE), in the two arms models, respectively.

Conclusions

Treatment of BP with prednisolone is likely to be considered cost-effective while treatment with aciclovir is highly unlikely to be considered cost-effective. Further data on costs and utilities would be useful to confirm findings.

KEYWORDS

Economic evaluation, Bell's Palsy, Prednisolone, Acyclovir, cost effectiveness analysis, cost utility analysis.

Conflicts of interest

None

Source of funding

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Introduction

Bell's palsy is an acute unilateral paralysis of the facial nerve.(1) Its cause is unknown but it affects 11-40 people per 100,000 in the population per annum, most commonly in the age group 30–45.(2) The condition is most common amongst pregnant women and people who have diabetes, influenza, a cold, or some other upper respiratory ailment. Although most recover, as many as 30% of people have a poor recovery with continuing facial disfigurement, psychological difficulties and sometimes facial pain.(2-4) In the absence of an established aetiology, treatment continues to be based upon the established pathophysiology: swelling and entrapment of the nerve.

Two Cochrane reviews have examined the effectiveness of oral prednisolone and aciclovir for the treatment of Bell's palsy (5, 6) and both report insuffient evidence on the effectiveness. In addition, high dose steroid therapy has numerous potential side effects including peptic ulceration, hypertension and confusional states.(7) Antiviral therapy is expensive and it has been argued should be reserved for circumstances where definite benefits are likely to be obtained.

Given this lack of evidence the UK NHS R&D Health Technology Assessment Programme commissioned a RCT to determine whether prednisolone or aciclovir, used separately or in combination and used early in the course of Bell's palsy, is an effective and efficient treatment. The aim of this paper is to report evidence on the relative efficiency of these therapies.

3 Methods

Details of the RCT have been reported elsewhere.(8) Briefly, this was a multi-centre, double-blind, placebo controlled, randomised, factorial trial involving patients with Bell's palsy who were recruited within 72 hours after onset of symptoms. Five hundred and fifty one patients were recruited from primary care settings and referred to 17 hospitals in Scotland between June 2004 and June 2006, where eligible patients were randomly assigned to receive 10 days of treatment of: 25mg twice daily with prednisolone (n=138), or 400mg five times daily with acyclovir (n=138), both agents (n=134), or placebo (n=141). Follow-up was 9 months. The primary outcome was complete recovery of facial function as rated on the House-Brackmann scale. Secondary outcomes included quality of life, appearance, pain, costs and relative efficiency. The study included adults of 16 years or older with unilateral facial weakness of no identifiable cause who presented to primary care or emergency department and could be referred to a collaborating otorhinolaryngologist within 72 hours of the onset of symptoms. Exclusion criteria were pregnancy, breast-feeding, diabetes, peptic ulcer disease, suppurative otitis media, herpes zoster, multiple sclerosis, systemic infection, sarcoidosis and other rare conditions, and an inability to provide informed consent. All participants gave written informed consent. The study was approved by the Multicentre Research Ethics Committee for Scotland.

The economic evaluation conducted as part of this trial adopted a modelling approach as a means of gaining precision in cost-effectiveness estimates. Decision analytic models were constructed to compare the relative efficiency of the four randomised arms and also for the 2 randomised comparisons from the 2x2

factorial design: prednisolone against no prednisolone and aciclovir against no aciclovir. As the time horizon of the economic analyses mirrors that of the original study, we believe this type of model gives a well representation of the decision problem. An example of the model structure is shown in Figure 1a. Within these models it is assumed that the different trial interventions affect the probability of being cured or not cured and the consequences are assumed to be independent of the assigned therapy.

3.1 Parameter estimates used in the model

Parameter estimates for probabilities, costs and effectiveness required to populate the model were developed from trial data. These data related to risk of being cured or not cured at different time points, health services resource use and costs and health state utilities.

3.1.1 Probability of cure and not cure

Table 1 shows the proportion of subjects cured and not cured at three and nine months, used as probabilities within the model. Normal probability distributions were attached to the difference in proportions between groups to allow for parameter uncertainty.

3.1.2 Health care resource use and costs

The costs estimates used in the model were based on the cost of the initial treatments and follow-up costs. Follow-up costs included the use of resources in primary and secondary care, and the subsequent use of other medications. These resources were costed using readily available unit costs.

Treatment costs

The doses and length of treatment for trial medications were defined by the trial protocol. The unit costs were obtained from British National Formulary (BNF)(9), (Table 2a).

Follow-up costs

Primary and secondary care resource use

Health Care resources used were collected from primary care case notes in a convenience sample of 74 study subjects on any contacts made with health services or resources used by trial participants. This sub-sample appears representative of the whole study sample (see website Suplementary Data for details of baseline characteristics). The number of contacts are described in Table 2b split by whether the data referred to cured or not cured patients (see website Supplementary Data for further details on Resource Use). Hospital based services (inpatient days, day cases, and outpatient visits) were costed using data from the Information Services Department (ISD) for Scotland(10) after deducting overheads allocated to the particular cost category (see website Supplementary Data). Unit cost for primary care based services were obtained from Curtis & Netten 2006 (11) and from the BNF for medications.(9)

Total Costs

Using all the data described above estimates of the total mean costs for those cured and not cured were estimated (Table 2b). A simple ordinary least squared (OLS) regression was fitted to the data obtained from those people for whom data were able to be collected (n=74). The total mean values used within the

model were £210 (s.e. 58) for cured with not cured being £105 (s.e. 112) more costly at three months. Normal distributions were added to the total cost of being cured and not cured with the total cost of not cured bounded at zero within the probabilistic sensitivity analysis.

3.1.3 Estimation of utilities

The RCT (8) collected data on Health Utilities Index mark III (HUI III) (12) at baseline, three months and, if trial participants were not cured at three months, also at nine months. Two analyses of covariance adjusting for baseline HUI III scores were used to obtain utility weights for participants who were cured and not cured at three and nine months (Table 3). In order to reflect the statistical imprecision surrounding these estimates when used in the model, normal distributions were attached to the mean difference in values based upon the results of a regression analysis.

Base case analysis

Base case analysis was conducted for all four randomised arms (e.g. four arms model). Secondary analyses comparing prednisolone vs. no prednisolone and aciclovir vs. no aciclovir were also conducted. For all analyses cumulative mean costs were estimated for the nine months follow-up period of the trial. All costs were expressed in 2006/07 pounds Sterling. The perspective of the analyses was that of the British National Health Service. Effectiveness was measured in terms of number of cases cured (e.g. House-Brackmann score = 1), and mean QALYs for the nine month time horizon. As the time horizon for the analyses was less

than a year, neither cost nor effectiveness outcomes were discounted. Incremental cost effectiveness ratios (ICER) were calculated.

Sensitivity analysis

Deterministic and probabilistic sensitivity analyses were conducted. The latter involved attaching probability distributions to the model parameters and conducting Monte Carlo simulations (MCS). One thousand iterations were obtained for each MCS conducted. These MCS were used to produce cost-effectiveness acceptability curves (CEACs) –Figure 2a- from which the likelihood of an intervention being considered cost-effective for society's willingness to pay at threshold values of £10,000, £20,000, £30,000 and £50,000 were calculated (Table 4) and cost-effectiveness scatterplots (Figure 2b & 2c). CEACs for the two arms models are reported as website Supplementary Data.

Further sensitivity analyses related to changes in key parameters used in the model e.g. unit cost values or to changes in model assumptions relating to the derivation of cost and the definition of cure. Cost data are typically skewed to the right as there are usually a few trial participants for which costs are extremely high. A sensitivity analysis was conducted taking these potential outliers out of the analysis.

Potential drivers in these models are the probability of being cured or not cured at three months; therefore, threshold analysis was also used to explore the effect of the probability of being cured or not cured on the model results. In addition, subgroup analyses by age and sex were also performed. Finally, structural

uncertainty was explored by assuming an exponential regression and gamma regression (together with gamma distributions for Monte Carlo simulations) analyses for total costs instead of the original ordinary least squared regression.

4 Results

4.1 Comparison of all four randomised groups

On average, prednisolone only is the least costly and most effective of the four alternative interventions (Table 4). Furthermore, it has approximately an 80% chance of being considered cost-effective compared with the other treatments (Figure 2a & Table 4).

4.2 Prednisolone vs. no prednisolone model

When the proportion of cases cured (Cost-effectiveness analysis) or QALYs (Cost-utility analysis) are used as the measure of effectiveness prednisolone has a lower mean cost and is more effective than the no prednisolone alternative (Table 4). Thus, prednisolone dominates the 'no prednisolone intervention. Table 4 also shows that prednisolone is likely to be considered a cost-effective treatment at all values for society's willingness to pay for a QALY. Figure 2b shows the cost-effectiveness scatterplot. The majority of the Monte Carlo simulation cost effectiveness result dots lay within the sout east quadrant and for these prednisolone treatment is more effective and less costly than no prednisolone treatment.

4.3 Aciclovir vs. no aciclovir model

Table 4 shows the incremental cost per case cured and per QALY for the comparison of aciclovir with no aciclovir. The no aciclovir alternative has on average lower costs and a higher proportion of individuals recovered. Therefore, on average no aciclovir dominates aciclovir treatment. The probabilistic analysis reinforces this finding (Table 4 and Figure 2c).

4.4 Sensitivity analysis

A wide range of sensitivity analyses were conducted. Results were not sensitive to the exclusion of the higher cost participants from the analysis, to halving or doubling the unit costs, or when an exponential regression was used to estimate total cost for cured or not cured participants to allow the right skew for the cost data. Prednisolone only appeared less likely to be considered cost-effective when gamma regression and gamma distributions were used.

One-way sensitivity analyses were conducted on the difference in the probability of being cured at three months. The 95%CI upper and lower limits for the difference in cure rates were used for this (Table 1). Cost-effectiveness or cost-utility analyses results were not sensitive to these changes for prednisolone vs. no prednisone model.

However, results were sensitive to the probability of being cured at three months within the aciclovir vs. no aciclovir model. When the difference in the probability of being cured at three months between the aciclovir arm and no aciclovir arm was 3.3% (the upper limit of the 95%CI), the ICER was £9,576. Further threshold analyses were conducted and ICERs of about £20,000 and £30,000 were obtained

for 2% and 1.5% differences in the absolute probability of cure, respectively. Therefore, the confidence interval surrounding the difference in cure rates between aciclovir arm and no aciclovir arm is sufficiently wide to contain clinically and economically important differences.

Age group and gender

Regression analyses for total cost and for utility weights show age group variables as well as gender were statistically non-significant. Given these data no estimates of incremental cost per QALY were estimated for different age groups or by gender.

4 Discussion

The results of the economic evaluation suggest that the use of prednisolone is likely to be considered cost-effective. Aciclovir, in contrast, appears to be on average no more effective but more costly than no treatment or treatment with prednisolone. Thus, it is unlikely to be considered cost-effective. The time horizon of the model was only nine months. Therefore, an implicit assumption is that there are no further benefits and cost savings from the use of prednisolone after the end of the time horizon. Given the difference in cure rates that existed at nine months it is possible that should the time horizon be extended treatment of Bell's palsy with prednisolone would be associated with further gains in quality of life. Furthermore, it is likely that those who did not receive prednisolone would make more use of health services; thus, increasing their cost relative to those who received prednisolone.

The economic analysis used a modelling framework to estimate relative efficiency. This approach has the advantage of making the best use of the limited data available but it made the assumption that the main determinant of relative efficiency is whether or not the Bell's palsy was cured or not. If a standard trial based cost-effectiveness analysis had been conducted it is likely that, on average, similar but less precised results would have been obtained. Furthermore, the lack of data on costs and the decision not to follow-up those deemed cured at three months would have necessitated similar assumptions being made in order to handle the missing cost and utilities data(13).

The data on costs used within the model came from a sample of only 74 of the trial participants. This led to a reduction in the precision of the estimates. Efforts were made to obtain data from more trial participants but these efforts were hampered by the fact that some general practices refused permission to view notes even though the participant had granted permission for their records to be reviewed. This appeared to be caused by uncertainty over whether the prior consent to view notes would still apply several months after initial recruitment of the participant and also the inconvenience of allowing investigators access to the practice Despite this limitation these data appear representative of the whole sample and the reasons for non-response were unconnected to the therapy the participant received or their outcomes (see additional web tables 1a & 1b). With respect to the estimation of QALYs measurements of health state utilities were censored for those trial participants who were judged to be cured at the three month follow-up. Therefore an assumption was made within the modelling exercise that was tantamount to

imputing utility data using the 'last value carried forward' method. Ordinarily this approach while simple is normally considered to be a limited method of imputation.(14, 15) However, in this situation it may not be wholly unrealistic as these trial participants were judged to be cured at the time of censoring. Nevertheless, it assumes that there is no possible further improvement in health status for these people nor is there any possibility of relapse. This latter situation is clinically implausible unless there is an unrelated new episode of Bell's palsy. The results of the economic evaluation would have been strengthened by further data on both costs and health state utilities.

Within the model the results are driven by the probability of being cured at three months and to a lesser extent, the probability of being cured at nine months. Both probabilistic and deterministic sensitivity analyses were conducted. The probabilistic sensitivity analysis focused on the statistical imprecision surrounding the model parameters using parameter distributions that were plausible and based upon the available data. Further deterministic sensitivity analysis was conducted to address uncertainty in the model structure or uncertainty surrounding model parameters that were obtained from outwit the RCT. The results of these sensitivity analyses indicate that conclusions are only sensitive to assumptions on the probability of being cured for the aciclovir vs. no aciclovir model.

Conclusions

Overall, based on the data available it appears that treatment of Bell's palsy with prednisolone is likely to be considered cost-effective while treatment with

aciclovir is highly unlikely to be considered cost-effective. Given the limited data available on costs and utilities further data would be useful to confirm findings. Similarly even though it is unlikely to change conclusion further data on costs and outcomes in the longer term (i.e. for a follow-up greater than nine months) would also serve to confirm the findings of the study.

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Table 1 Probability parameters

	Probability being cured at 3 months	Probability being cured at 9 months given not cured at 3 months
Four arms model		
Prednisolone alone	0.84	0.71
(s.e.)	(0.03)	(0.11)
Aciclovir alone	0.60	0.44
(s.e.)	(0.04)	(0.07)
Aciclovir & prednisolone	0.78	0.68
(s.e.)	(0.04)	(0.09)
Placebo alone	0.65	0.57
(s.e.)	(0.04)	(0.08)
Prednisolone vs. no prednisolone		
Prednisolone	0.83	0.49
No prednisolone	0.64	0.61
Difference (95% CIs)	0.19 (0.12 , 0.27)	
PD* Assumed for difference	Normal	
Aciclovir vs. no aciclovir model		
Aciclovir	0.71	0.49
No acyclovir	0.76	0.61
Difference (95% CIs)	-0.05 (-0.12 , 0.03)	
PD Assumed for difference	Normal	

* PD = probability distribution

Table 2a Resource use and costs: drug treatment

Drug	Dose	Cost	Note	BNF WebPage *
Prednisolone	50mg/day x 10d	4.32	Prednisolone Tablets, 25 mg, 56-tab pack = £12.09	http://www.bnf.org/bnf/bnf/53/4259.htm
Aciclovir	2000mg/day x 10d.	6.57	Aciclovir Tablets, 400 mg, 56-tab pack = £7.31; 800 mg, 35-tab pack = £9.22	http://www.bnf.org/bnf/bnf/53/37356.htm

* Accessed: 21st May 2007

Table 2b Resource use and costs: Health care resource use by main cost categories. Cured or not cured patients

	Cured at three months			Cured at nine months			Not cured		
Concept	Primary Care (contacts)	Hospital (inpatient days & day cases)	Hospital Outpatient (visits)	Primary Care (contacts)	Hospital (inpatient days & day cases)	Hospital Outpatient (visits)	Primary Care (contacts)	Hospital (inpatient days & day cases)	Hospital Outpatient (visits)
N	52	53	51	11	11	10	9	9	9
Mean (s.d.)	2.15 (3.9)	0.11 (0.38)	0.49 (1.17)	3.82 (3.68)	0.09 (0.3)	1.8 (2.62)	3.22 (2.73)	0 (0)	1.22 (1.56)
Median [IQR]	1 [0 - 2]	0 [0 - 0]	0 [0 - 1]	3 [1 - 5]	0 [0 - 0]	0.5 [0 - 3]	3 [2 - 3]	0 [0 - 0]	1 [0 - 1]

Table 3 HUI III regression analysis for three and nine months cured and not cured utility weights

Dependent variable: HUI III at three months				
Number of obs	= 487			
	Coefficient	Std. Err.	[95% Conf.	Interval]
Constant	0.6146	0.0235	0.5684	0.6609
hb3cured	0.0574	0.0132	0.0314	0.0834

Dependent variable: HUI III at nine months				
Number of obs	= 137			
	Coefficient	Std. Err.	[95% Conf.	Interval]
Constant	0.5265	0.0495	0.4287	0.6243
Cured	-0.0019	0.0293	-0.0599	0.0561

Utility weights (mean values)		
Cured at 3 months	Cured at 9 months	Not cured
0.9947	0.9900	0.9919

Baseline characteristics. HUI III data All participants			
Mean:	0.786	sd	0.216

Table 4 Cost-effectiveness results

Treatment	Cost (£)	Cured cases* at 9 months (%)	ICER**	QALYs	ICER***	Probability that intervention is cost-effective for different threshold values for society's willingness to pay for a QALY (%)			
						£10,000	£20,000	£30,000	£50,000
Four arms model									
Prednisolone only	182.34	85.6%		0.719		79.1%	77.4%	76.9%	75.9%
Aciclovir + Prednisolone	198.09	78.0%	Dominated	0.718	Dominated	0.0%	0.0%	0.0%	0.1%
No treatment	205.14	78.0%	Dominated	0.717	Dominated	12.5%	9.5%	7.2%	5.2%
Aciclovir only	219.62	78.0%	Dominated	0.716	Dominated	8.4%	13.1%	15.9%	18.8%
Prednisolone vs. No prednisolone model									
Prednisolone	231.98	94.4%		0.718		79.3%	77.5%	77.0%	76.0%
No Prednisolone	248.05	81.6%	dominated	0.717	Dominated	20.7%	22.5%	23.0%	24.0%
Aciclovir vs. No aciclovir model									
No Aciclovir	235.33	90.8%		0.718		91.1%	85.1%	82.2%	79.0%
Aciclovir	246.63	85.4%	dominated	0.717	Dominated	8.9%	14.9%	17.8%	21.0%

* Cured cases defined as HB score = 1; ** Incremental cost effectiveness ratio using % cured cases; ***Incremental cost effectiveness ratio using QALYs

Figure 1a **Decision tree model for early treatment for Bells palsy: Prednisolone alone vs. aciclovir alone vs. prednisolone + aciclovir vs. no treatment (placebo)**

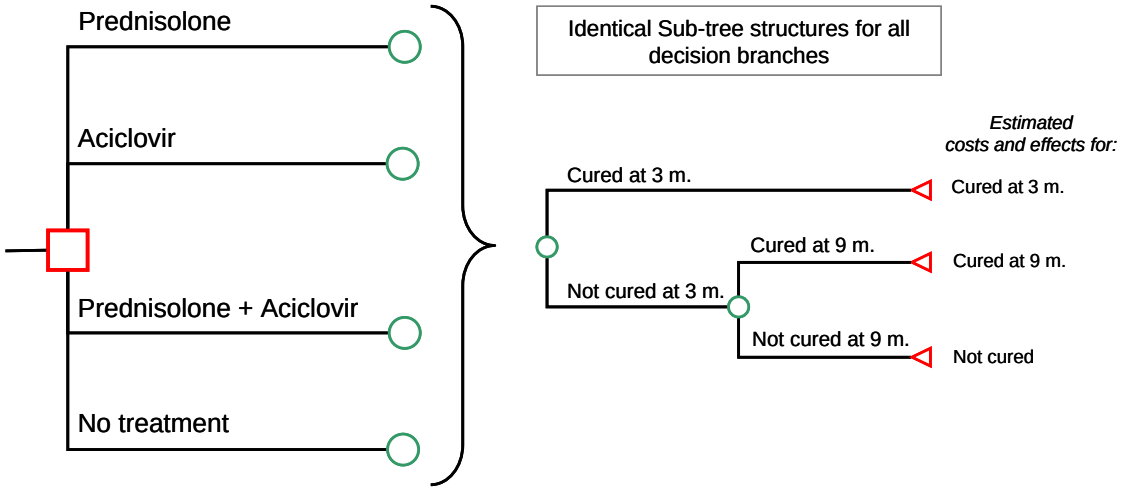


Figure 1a. The four decision branches reflect the four groups provided by the 2 x 2 factorial trial design. It has been assumed that the costs consequences of being cured or not cured are independent of the initial treatment a person was allocated to.

Figure 1b **Bell's palsy decision tree model: Prednisolone vs. no prednisolone**

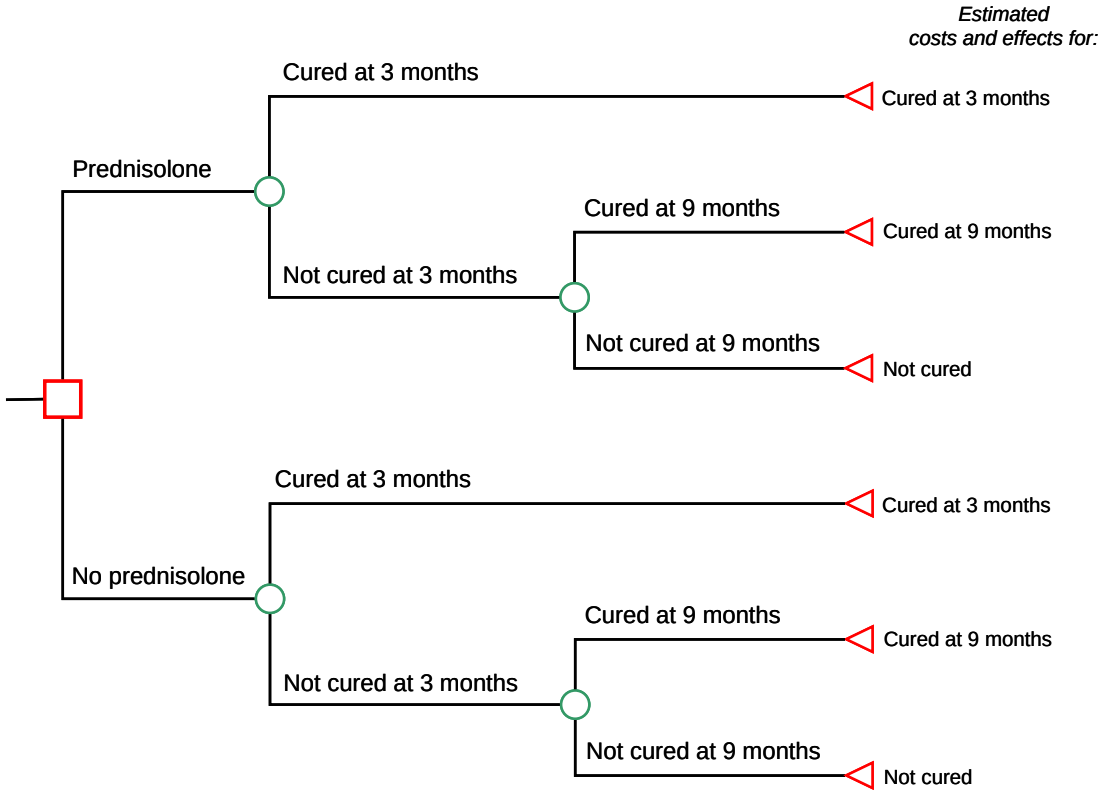
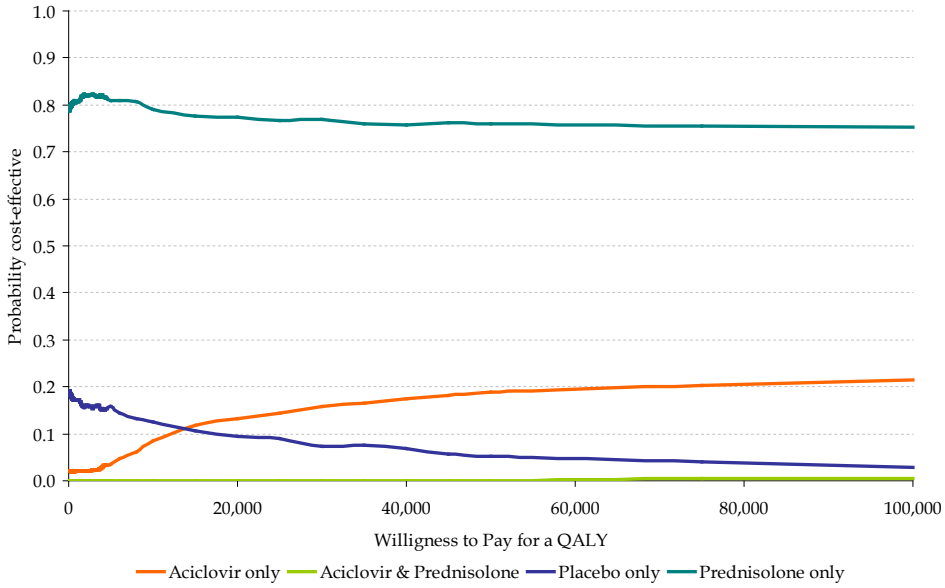


Figure 2a Cost-effectiveness acceptability curves. Four arms model.



These CEACs indicate that collectively the other interventions have only a 20% chance of being considered cost-effective.

Figure 2b Incremental cost effectiveness scatterplot. Prednisolone vs. No prednisolone model.

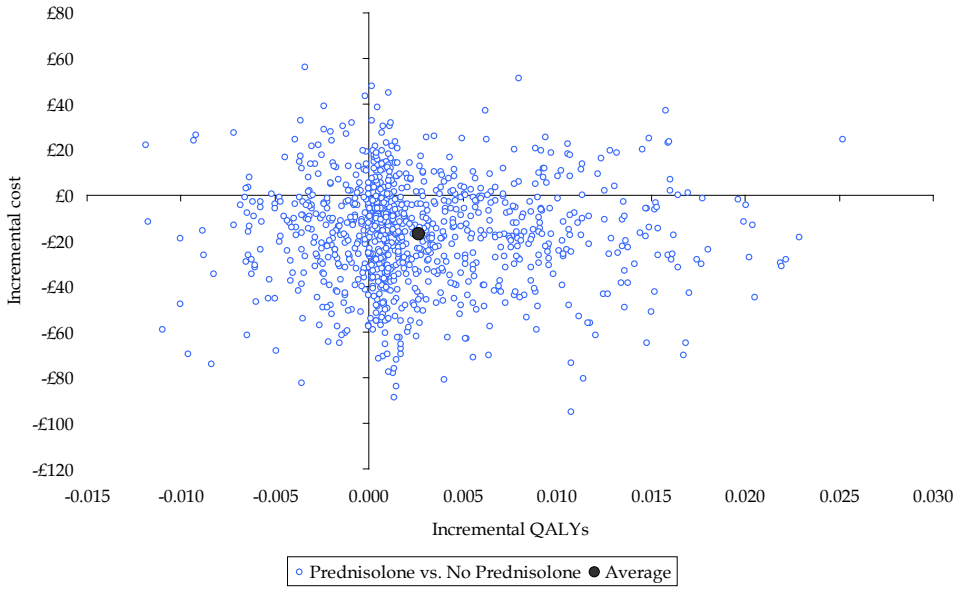


Figure 2b. Scatterplot of the difference in cost and QALY pairs for the comparison of prednisolone compared with no prednisolone from the Monte Carlo simulation. A high proportion of the dots are allocated within the SE quadrant. Therefore, for those cases,

prednisolone produced more QALYs and was less costly than no prednisolone and prednisolone is cost-effective for these iterations. The opposite argument applies to those cases that fall within the NW quadrant (e.g. no prednisolone option is cost-effective). Finally, for those iterations that fall within the NE and SW quadrants the decision for or against prednisolone will depend on threshold value of WTP for an extra QALY.

Figure 2c Incremental cost effectiveness scatterplot. Aciclovir vs. No aciclovir model.

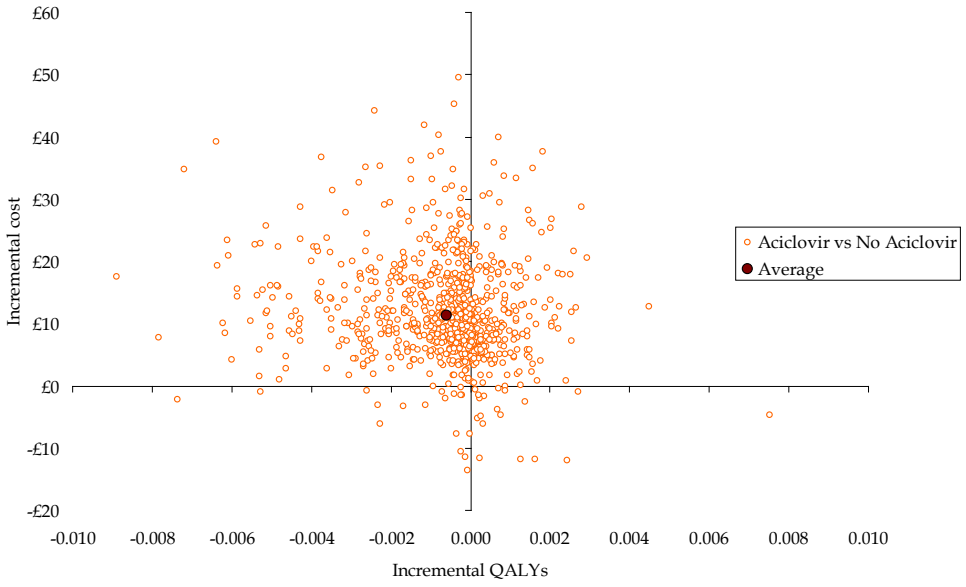


Figure 2c. Scatterplot of the incremental cost and QALY pairs from the Monte Carlo simulation shows that the majority of the iterations lie within the NW quadrant (e.g. aciclovir more costly and less effective that no aciclovir).