Appendix F Full health economic report

Introduction

The National Institute for Health and Clinical Excellence (NICE) has been asked to produce a guideline on decision making around the management of an acute painful sickle cell episode.

This is the health economic analysis developed to support the guideline development group (GDG) in making recommendations. The analysis was conducted according to NICE methods outlined in the Guide to the methods of technology appraisals, 2008 and the Guidelines Manual 2009. Therefore, it follows the NICE reference case (the framework NICE requests all cost-effectiveness analysis to follow) in its methods.

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Decision problem

Population

The population in this analysis is adults, children and young people with any genotype for sickle cell disease who have presented to hospital with an acute painful sickle cell episode. The guideline scope suggests that pregnant women should be considered a subgroup of interest; however, no separate analyses were possible, because there are insufficient data relating to this subgroup.

Interventions and comparators

1. Route of administration of opioid analgesia: patient-controlled analgesia (PCA) *versus* standard care (continuous intravenous infusion

or intermittent intramuscular, subcutaneous or intravenous bolus injections).

2. Adjunctive therapy: low molecular weight heparin (LMWH) *versus* standard care only.

3. Appropriate setting: dedicated sickle cell day centres in addition to hospital / accident and emergency department (A&E) admission *versus* hospital / A&E admission only.

Outcomes

To explore the economic consequences of PCA and LMWH, we performed cost–utility analyses, estimating expected costs and benefits (in terms of quality-adjusted life-years (QALYs) for each comparator. Given that the interventions are not entirely mutually exclusive, the clinical outcome measures we used in these analyses to estimate differences in treatment effect are similar.

We undertook additional cost minimisation analyses where data were insufficient to estimate the effectiveness of different treatment strategies, and it was reasonable to assume equivalence of the approaches being compared.

Systematic review of published literature

We performed a search for published health economic analyses addressing the questions of interest. We searched the following databases: MEDLINE, MEDLINE in-process, EMBASE, Cochrane Library Health Economic Evaluations Database and the NHS Economic Evaluation Database.. The searches yielded a total of 1189 unique citations. We reviewed the titles and abstracts of these studies to identify relevant economic evaluations comparing both the costs and health consequences of the alternative modes of management under consideration. However, we did not identify any studies that were eligible for further consideration. Therefore, we proceeded to undertake a *de novo* economic evaluation.

De novo model: Methods

Model structure

Figure 4 below presents a simplified model structure based on the natural history of an acute painful episode and inputs from the GDG. Patients start in the 'uncomplicated' state which is meant to capture their pain experience and duration of hospital stay. Pain is treated in this state as a continuous variable – rather than a dichotomous variable with a 'pain' state and 'pain-free' state – as the evidence suggests that even at steady state, patients still have some residual level of pain. Patients can remain in the 'uncomplicated' state during which their pain is expected to subside progressively until discharge or they can have a complication which results in a longer duration of hospital stay and/or ongoing morbidity from the complication. Simulated patients entering the 'complications' state are also subject to a risk of death. In the model's base case, there is no possibility of death from an uncomplicated episode, as it is assumed that the risk of mortality in acute painful sickle cell episodes arises as a result of acute complications (the impact of this assumption was examined in sensitivity analysis; see below).

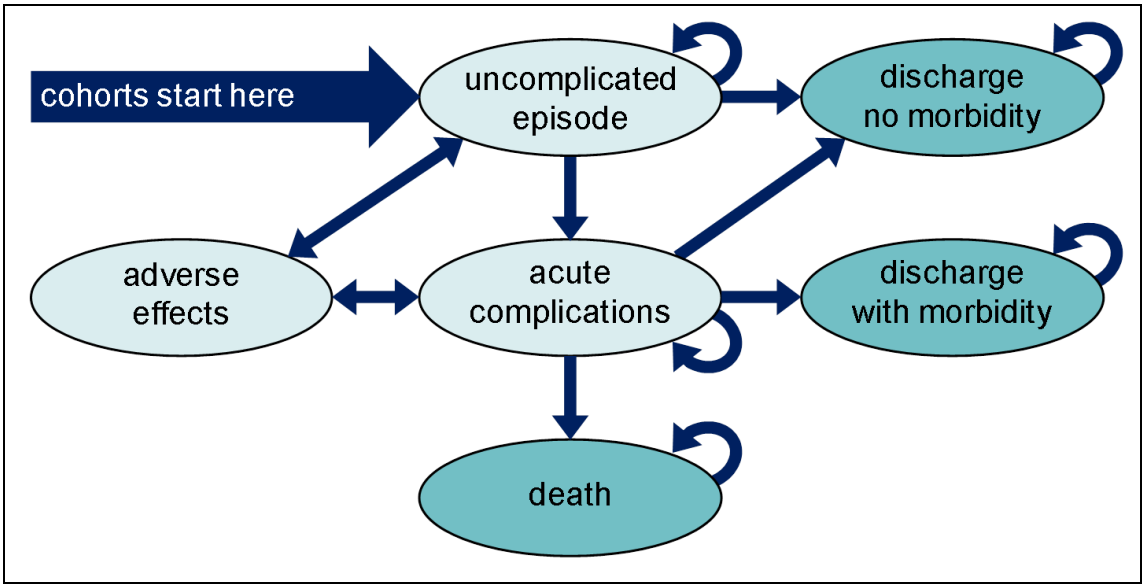

Figure 4: model structure

A proportion of patients are expected to experience adverse effects of treatment while in hospital. The death state and the 2 discharge states – 'with morbidity' and 'without morbidity' – are absorbing states.

We chose an hourly cycle length for this analysis. This appeared to be a reasonable interval during which changes in pain levels could be captured. Also, expert opinion suggests that patients on average are monitored hourly.

The model was constructed in Microsoft Excel 2007. Costs and benefits were discounted at 3.5% per annum each.

Time horizon

Ideally, a lifetime time horizon would be adopted to measure all the potential benefits of a treatment in line with NICE's methods guide. However, given that an uncomplicated acute painful sickle cell episode is self-limiting (Platt et al, 1991) and runs a relatively short clinical course (1–2 weeks), it would be inappropriate to perform detailed modelling over a lifetime horizon in this instance. We therefore selected a time horizon of 28 days, as GDG opinion suggested this should be adequate to capture complicated and uncomplicated cases. However, the model also calculates long-term consequences of the acute episode – such as morbidity and mortality impacts and their associated costs – for the full lifetime of patients. This is because we need to know the average life expectancy and HRQoL of people with sickle cell in order to capture the impact of death and health forgone from an acute episode.

Assumptions

When modelling the acute painful sickle episode, certain assumptions and simplifications were made to reduce complexity and account for lack of evidence. All the assumptions and simplifications were checked with clinical experts.

Box 1: Summary of key assumptions adopted in model

- Pain (VAS) determines
  - LOS (in some scenarios)
  - HRQoL
  - likelihood of complications
  - resource use.
- An acute sickle cell episode is self-limiting and death only arises due to complications.
- In simulating the acute complications of an acute painful sickle cell episode, it is reasonable to focus on the most commonly reported (ACS) and the one with most serious consequences (stroke).
- The average daily costs of inpatient admission for an acute painful sickle cell episode can be approximated using a weighted average of several heterogeneous values from the NHS Reference Costs.
- Severity of pain at baseline is driven by an underlying process of developing complications, for example ACS (scenarios 1A and 2A) **or**
- The likelihood of developing ACS is driven by pain (or pain control) (scenarios 1B and 2B).
- The likelihood of experiencing stroke during an acute painful sickle cell episode is directly proportional to the probability of experiencing ACS.

Modelling pain over time

Because pain (measured on a visual analogue scale [VAS]) is the one outcome that is reported with some consistency in effectiveness studies, we configured the model to simulate patient experience as a function of pain level. For this reason, the model assumes a relationship between pain (VAS) and

- health-related quality of life (utility)
- likelihood of complications
- requirement for analgesia
- length of hospital stay (in some scenarios; see below) and

- resource use.

We assume that irrespective of mode of management, people will end up with the same pain score at discharge – on average, discharge occurs when VAS comes down to 3 (Kofi et al. unpublished.). However, the rate at which the VAS score drops and consequently the time to discharge will vary depending on the mode of management, i.e. the VAS score determines the length of hospital stay (LOS). This assumption is based on expert opinion which suggests that an uncomplicated acute painful sickle cell episode is a self-limiting condition ((Platt et al, 1991; Sergeant et al, 1994), and patients' pain experience will differ depending on the mode of management.

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Generic parameters

Overriding principles

For all estimates, we attempted to find a source that had a large sample size, consisted of UK patients with a diagnosis of sickle cell disease (with an acute painful sickle cell episode) and was a recently published study. In instances where UK-based parameters were unavailable, we looked for sources from other countries with a similar disease profile. In cases where there was paucity of published literature, data were obtained from unpublished sources; further details are provided below. The parameters used in the model are summarised in

Parameter	**Estimate**	**Distribution**	**Parameters**	**Source**	**Notes**
Discount rate (costs)	0.035			NICE methods	
Discount rate (benefits)	0.035			NICE methods	
Cohort demographics at baseline					
Age	variable				Model input
Sex (% male)	0.526	Beta	$\alpha = 5587$; $\beta = 5038$	HES 2010/11	
Weight: z-score for children with SCD	-0.800	Normal	$\mu = -0.8$; $\sigma = 0.183$	Barden et al. 2002	36 US children aged 5–17 with SCD compared with population

Parameter	Estimate	Distribution	Parameters	Source	Notes
					norms
Average weight of an adult man with SCD (kg)	65.00	uniform	[60,70]	assumption	no primary data identified; values assumed following discussion with GDG
Average weight of an adult woman SCD (kg)	55.00	uniform	[50,60]		
LOS calculation					
Weibull alpha shape parameter (children)	2.705	Normal	μ = 2.705 ; σ = 0.235	Orringer et al. 2001	only study identified providing time-to-event data for duration of episode; treatment (poloxamer 188) and control arms averaged
Weibull alpha shape parameter (adults)	2.997	Normal	μ = 2.997 ; σ = 0.397		
When basing LOS on VAS distribution:					
Threshold for discharge VAS	3.012	Normal	μ = 3.012 ; σ = 0.151	Anie 2011 unpublished	average VAS at discharge
Threshold at which VAS begins to define discharge (d)	0.500			assumption	value assumed following discussion with GDG, on basis of their advice that, once a patient has been admitted and treatment started, 12hrs represents a minimum stay
VAS calculation					
VAS score at baseline	5.159	Beta	a = 0; b = 10; α = 602.0 ; β = 564.8	Anie 2011 unpublished	
Utilities					
Decrement for chronic SCD	0.198			Anie 2011 unpublished; McClish et al. 2005; Anie 2002; Woods 1997	weighted average of studies estimating utility of chronic SCD using SF-36, deducted from utility for general population of same average age and sex
Utility v VAS					
Constant	0.887	multivariate normal	dependent on variance–covariance matrix of regression model	Anie 2011 unpublished	new analysis of raw IPD; see text
VAS	-0.124				
VAS^2	0.014				
VAS^3	-0.001				
Residual decrement for post-stroke with dependence	0.565			Dorman et al. 2000	cost-effectiveness analysis of anti-platelet therapy in
Residual decrement for post-stroke	0.162				

Parameter	Estimate	Distribution	Parameters	Source	Notes
with independence					
Residual decrement for stroke	0.302				general population; decrement calculated by deducting utility for dependent (0.312) / independent (0.718) states from value for those who were judged to have 'recovered' from stroke (0.880)
Complication decrements					
Decrement for ACS	0.560	lognormal	μ = −2.207; σ = 0.147	Lloyd et al. 2007	no SCD-specific data identified; reported utility value for asthma exacerbation requiring hospitalisation (0.33) deducted from utility value for chronic asthma (0.89)
Decrement for stroke event	0.565			assumption	no SCD-specific data identified; assumed utility of experiencing any stroke is equal to long-term decrement of major stroke
Adverse event decrements					
constipation	0.088	uniform +/- 50%	[0.04416, 0.13248]		
nausea/vomiting (severe)	0.149	uniform +/- 50%	[0.07456, 0.224]	Smith et al. 2000	HRQoL of pregnant women experiencing nausea/vomiting
nausea/vomiting (mild)	0.050	uniform +/- 50%	[0.025, 0.075]	Beusterien et al. 2010	HRQoL of people undergoing chemotherapy experiencing nausea/vomiting
IV morphine requirement predicted from VAS:					
Intercept	-1.687	multivariate normal	dependent on variance–covariance matrix of regression model	analysis of data from Bartolucci et al. 2009	linear regression
Slope	15.362				
Probability of nausea predicted from morphine exposure:					
Intercept	-0.090	multivariate normal	dependent on variance–covariance matrix	Roberts et al. 2005	study of relationship between morphine exposure and nausea/vomiting in
Slope	0.407				
Probability of vomiting predicted					

Parameter	Estimate	Distribution	Parameters	Source	Notes
from morphine exposure:			of regression model		postoperative analgesia
Intercept	-0.055	multivariate normal			
Slope	0.199				
Complications					
Baseline odds of ACS in regression cohort	0.268			Buchanan et al. 2005	
OR per VAS unit	1.660	lognormal	μ = 1.660; σ = 0.152		
Mean baseline VAS in regression cohort	7.902	Beta	a = 0; b = 10; α = 572.4; β = 152		
Historical frequency of stroke relative to ACS	0.097	Beta	α = 203; β = 1893	Sebastiani et al. 2007	6% of people in CSSCD cohort experienced stroke; 62% experienced ACS
Reduction in frequency of stroke in 20th century	0.376	lognormal	μ = 0.376; σ = 0.370	Fullerton et al. 2004	applied to reflect lower incidence of stroke now than was experienced during period of CSSCD data collection
Probability stroke is major (results in dependency)	0.347	Beta	α = 758; β = 1427	Bruins Slot et al. 2008	proportion of people in Oxford and Lothian stroke cohorts with modified Rankin score of 3 or higher 6 months after event
Primary threshold for complications (days)	7.000	uniform +/- 50%	[3.5, 10.5]	assumption	assumption following discussion with GDG; reflects their view that most complications occur fairly soon after admission, but a small proportion develop later
Proportion of complications occurring by primary threshold	0.750	uniform	[0.5,1]		
Final threshold for complications (days)	14.000	uniform +/- 50%	[0,14]		
Death					
Probability of death from stroke	0.074	gamma	α = 3.31; β = 0.02	Fullerton et al. 2004; Ohene-Frempong et al. 1998; Strouse et al. 2009	random-effects meta-analysis of proportion of deaths reported in three papers
Mean length of stay for stroke	9.361			Fullerton et al. 2004; Strouse	weighted average of LOS reported in two papers

Parameter	Estimate	Distribution	Parameters	Source	Notes
				et al. 2009	
Probability of death from ACS	0.027	Beta	α = 18; β = 653	Vichinsky et al. 2000	18 of 671 episodes were fatal
Mean length of stay for ACS	10.500				
Probability of death during uncomplicated episode	0	Uniform	[0.000,0.001]	assumption	
Costs					
Daily cost of inpatient care					
Average daily cost of inpatient with SCD crisis	£455.63	Gamma	Weighted average of sampled values from individual gamma distributions for each cost code (see Table 90)	NHS reference costs 2010/11	weighted average of costs under various codes (see text)
Average daily cost of inpatient with SCD crisis (child)	£588.51	Gamma	Weighted average of sampled values from individual gamma distributions for each cost code (see Table 90)		
Drugs					
Morphine (mg)	£0.10			BNF	
Long-term costs					
'Minor' stroke (independent)				Chambers et al. 1999	Cost-effectiveness analysis of antiplatelet therapy; inflated from 1996 costs to 2011 value
Ambulatory rehab (single cost in first six months)	£66.87	Gamma	α = 25.0; β = 2.675		
Annual care	£1,450.06	Gamma	α = 25.0; β = 58.002		
'Major' stroke (dependent)					
Ambulatory rehab (single cost in first six months)	£1,263.52	Gamma	α = 25.0; β = 50.541		
Annual care	£18,709.96	Gamma	α = 25.0; β = 748.398		
Transfusions for people who have had strokes					
Standard red cells (per 500 ml bag)	£124.85	Gamma	α = 25.0; β = 4.994	NHS Blood and Transplant	
Yearly frequency	12.00	Normal	μ = 12.00 ; σ = 2.4		
Proportion of patients requiring iron chelation	100%			assumption	based on GDG advice

Parameter	Estimate	Distribution	Parameters	Source	Notes
Red cells for exchange transfusion (per 500 ml bag)	£184.13	Gamma	α = 25.0; β = 7.365	NHS Blood and Transplant	
Yearly frequency	8.00	Normal	μ = 8.00; σ = 1.6		
Proportion of patients requiring iron chelation	0%			assumption	based on GDG advice
Proportion of patients receiving exchange transfusion	20%	triangular	[0%,20%,40%]	assumption	based on GDG advice
Iron chelation					
Oral					
Deferasirox - unit cost (£ / 125mg)	£4.20			BNF	
Dose (mg/kg)	20	triangular	[10,20,30]		
Parenteral					
Desferrioxamine mesilate - unit cost (£ / 500mg vial)	£4.26			BNF	
Average daily dose (mg / kg)	40.00	triangular	[20,40,60]	SPC	
Proportion of patients receiving oral chelation	90%	triangular	[80%,90%,100%]	assumption	based on GDG advice
Total mean annual cost of transfusion, etc., for adult	£13,152.73			calculation	calculated using above values and assumptions
Total mean annual cost of transfusion, etc., for child	£7,385.14				

, below.

Clinical parameters and variables

Length of hospital stay

In scenarios in which the model predicted LOS independently of VAS, we used a Weibull distribution to model the likelihood of discharge over time, using the standard cumulative distribution function:

$$1 - e^{-\left(x/\beta\right)^{\alpha}} \quad , \qquad (1)$$

where x is a measure of time, α is the 'shape' parameter of the distribution and β is the 'scale' parameter of the distribution.

We estimated the parameters of the distribution directly; where LOS data were available in the relevant clinical effectiveness publication(s) (see question-specific parameters, below). Where the publication(s) provided

insufficient data from which to estimate the parameters of the distribution, we assumed a fixed shape (α) parameter, and calculated the scale (β) parameter that would be associated with the reported mean LOS. This is achieved by rearranging the formula providing the mean of the distribution as follows:

$$\beta = \frac{m}{\Gamma\left(1 + \frac{1}{\alpha}\right)} \quad , \qquad (2)$$

where m is the reported mean LOS and Γ is the gamma function.

In these instances where direct evidence on the shape of the distribution was not available, the shape (α) parameter we used was drawn from the only study we identified in which detailed time-to-event data were reported (Orringer et al 2001). This study provided time-to-crisis-resolution data in the form of a series of Kaplan–Meier curves (although this is not quite the same as time-to-discharge, we took the view that the shape function of the distribution was likely to be very similar, as the possibility discharge is overwhelmingly dictated by resolution of symptoms). Because we were, for present purposes, uninterested in the comparison reported in this trial (standard care + poloxamer 188 *versus* standard care + placebo), we extracted data from both arms, and calculated a weighted average of experience between them. Orringer et al. report data for children (aged 15 or younger) separately; we used these data to inform the shape parameter whenever the model was to simulate a cohort with mean age lower than 16. Data for adults are not reported separately; however, we approximated these by extracting data from the curve representing the entire trial population and subtracting from these the results for children. The shape (α) parameter derived for children was 2.705; for adults, it was 2.997. In a Weibull distribution, shape (α) parameters greater than 1 indicate that the event rate increases over time; in this instance, this means that the rate of discharge rises as time goes on (so, on any given day, the proportion of the remaining cohort that will be discharged from hospital is greater than the proportion of yesterday's cohort that was discharged, and so on). We drew reassurance

from the fact that estimates for adults and children were closely comparable, suggesting that, though differences may exist between populations in the scale of the distribution, the shape function is more likely to be generalisable.

Pain (VAS) over time

In scenarios in which the model predicted LOS as a function of VAS, it was necessary to adopt an assumption about the distribution of VAS scores matching a given mean and SD. Because VAS scores are limited at both ends, we used a beta distribution constrained between −0.5 and 10.5. It was necessary to expand the range of numbers considered by 0.5 at either end to approximate a continuous distribution from an 11-point (0–10) ordinal scale (that is, each point on the scale was considered to represent a continuous pain score of $x \pm 0.5$). The model estimates the parameters of the distribution (α, β) for a given mean ($\bar{x}$) and SD (σ), using the following formulae (consecutive minuses retained to clarify parameterisation):

$$\hat{\alpha} = \frac{\bar{x} - -0.5}{10.5 - -0.5} \cdot \left(\frac{\frac{\bar{x} - -0.5}{10.5 - -0.5} \cdot \left(1 - \frac{\bar{x} - -0.5}{10.5 - -0.5}\right)}{\frac{\sigma^2}{(10.5 - -0.5)^2}} - 1 \right) \quad \text{and} \qquad (3)$$

$$\hat{\beta} = \left(1 - \frac{\bar{x} - -0.5}{10.5 - -0.5}\right) \cdot \left(\frac{\frac{\bar{x} - -0.5}{10.5 - -0.5} \cdot \left(1 - \frac{\bar{x} - -0.5}{10.5 - -0.5}\right)}{\frac{\sigma^2}{(10.5 - -0.5)^2}} - 1 \right). \qquad (4)$$

Complication rates – acute chest syndrome

The model assumes a relationship between pain (VAS) and the likelihood of acute complications (stroke and acute chest syndrome [ACS]).

We derived a complication function from the relationship between VAS at baseline and ACS from the study by Buchanan et al. (2005). This study reports an odds ratio – from logistic regression modelling – for the likelihood of ACS as predicted by a unit increase in pain (VAS) at baseline. By

calculating the odds of ACS in Buchanan et al.'s cohort, relating this to average VAS at baseline, and applying the odds ratio to estimate odds of ACS in people with higher and lower VAS scores, we were able to estimate the functional relationship between VAS at baseline and odds of ACS. Odds were then converted to probabilities using the standard formula: $prob = odds / (1 + odds)$. See Figure 5, below.

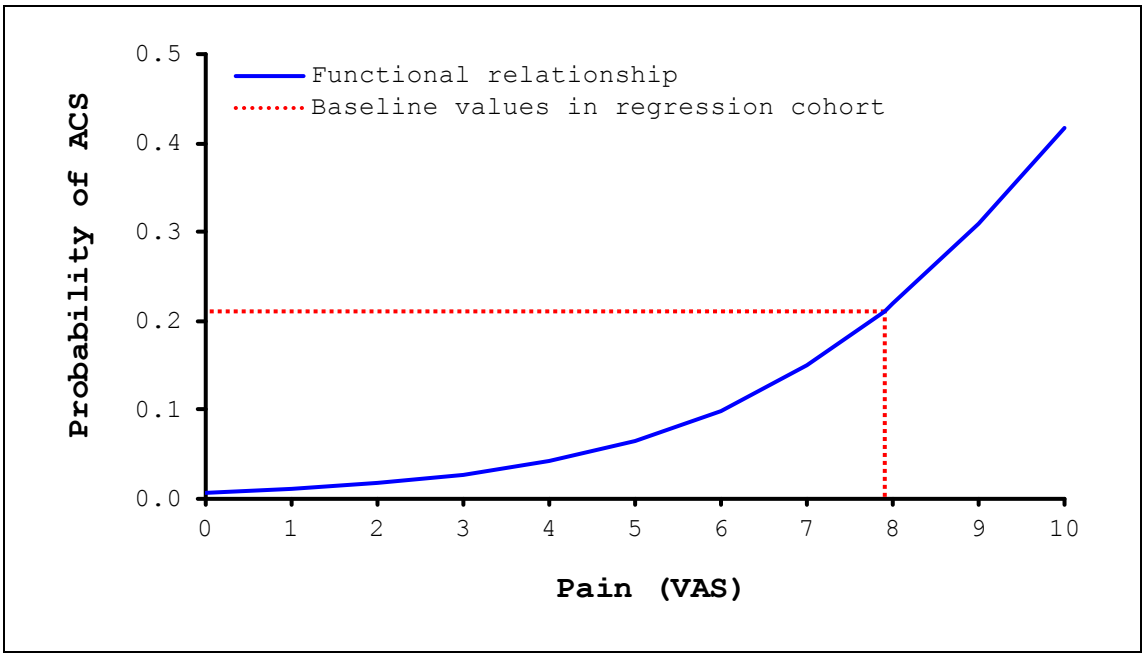

Figure 5: Relationship between pain and probability of developing ACS

However, the temporal and causal relationship between pain and ACS is unclear. For example severe pain could be a predisposing factor for ACS (perhaps mediated via shallow breathing). Conversely, incipient ACS could be a cause of severe pain (chest pain). To address this uncertainty, we modelled the pain and ACS function in two ways:

- **Scenario A:** Baseline pain score defines a probability of ACS which remains fixed irrespective of subsequent changes in VAS. This assumes that the severity of pain at baseline is driven by an underlying process of ACS. In this scenario, the frequency of ACS will not differ between simulated treatment arms.

- **Scenario B:** The probability of ACS is dynamically linked to pain and will alter as time progresses (that is, the quicker you control people's pain, the

less likely they are to develop ACS). This assumes that severity of pain at baseline is driven by an underlying process of ACS As a result, frequency of ACS may differ between simulated treatment arms.

Complication rates – stroke

We did not identify any data on the likelihood of stroke occurring during the acute episode. For this reason, the likelihood of stroke was calculated as a simple relative ratio of the frequency of ACS. In the CSSCD study, the incidence of stroke at any time was approximately one-tenth the incidence of ACS (6% *versus* 62%; Sebastiani et al. 2007). However, there is good evidence that, in the period since these data were collected (the CSSCD study recruited in the 1970s and 1980s), incidence of stroke has greatly reduced in people with sickle cell disease, largely due to increased monitoring and prophylactic blood transfusion (Fullerton et al. 2004). Therefore, we assumed that a reduced frequency of stroke (37.6% of the historical value; Fullerton et al. 2004) would apply. From these data, we derived an assumed relative frequency of stroke compared with ACS of 3.6% (that is, we expect one stroke for every 27 incidents of ACS). We applied this ratio to the VAS-dependent calculation of ACS likelihood to estimate the probability of stroke relative to VAS.

Relationship between pain and morphine consumption

In the model, pain predicts morphine consumption. We obtained data on the relationship between pain (VAS) and morphine consumption from the trial reported by Bartolucci et al. (2009). This was a randomised, placebo-controlled trial of Ketoprofen (IV) in adult patients admitted with an acute painful sickle cell episode of ≥ 24 hrs. The study reported separate paired observations of pain over time and morphine dose over time. These data were extracted (from both trial arms) and analysed using simple linear regression. The results showed a strong linear correlation between pain and morphine dose (coefficient of correlation = 0.979). See Figure 6, below, for details.

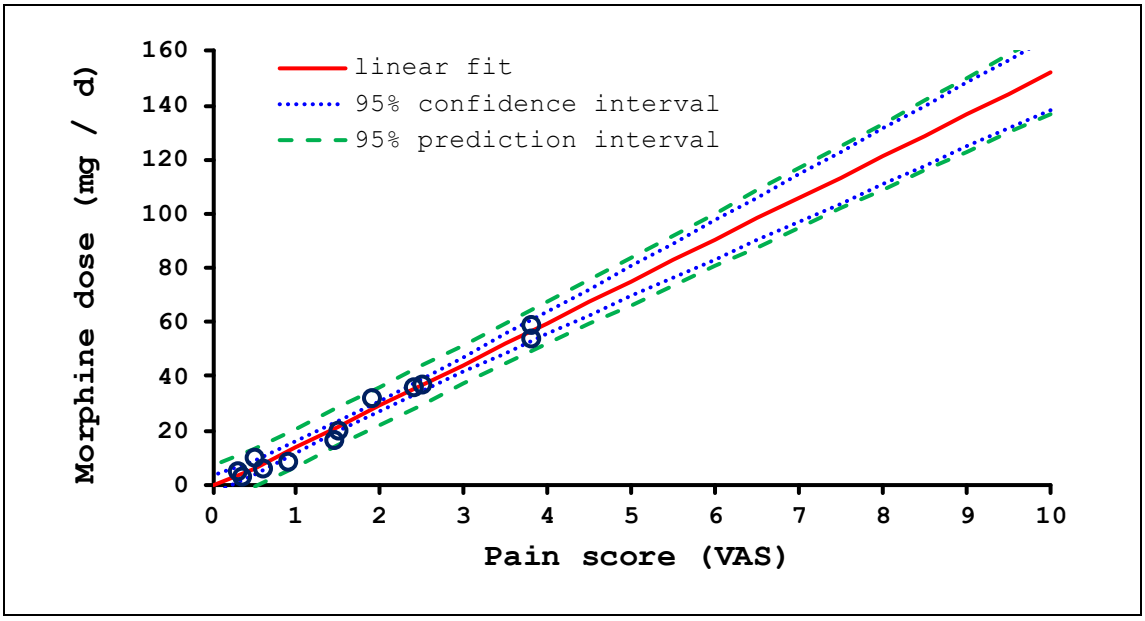

Figure 6: Relationship between pain and expected morphine dosage

The mean weights of the participants were obtained from the authors and these were used to estimate the average dose / kg / h of morphine required for each pain score (Table 87).

Table 87: Predicted morphine dose per VAS score

Pain (VAS)	Predicted morphine dose	
	(mg/day)	(mg/kg/h)
0	0.0	0.000
1	13.7	0.011
2	29.0	0.023
3	44.4	0.035
4	59.8	0.047
5	75.1	0.059
6	90.5	0.071
7	105.8	0.083
9	136.6	0.107
10	151.9	0.119

Adverse effects

Nausea and vomiting

The likelihood of nausea and vomiting was derived as function of morphine dose (mg/day for adults >18yrs and mg/kg/day <18yrs) which, in turn, is a

function of pain as described above. We based this relationship on data reported by Roberts et al. (2005), which showed a strong linear relationship between log (base 10) of morphine dose and nausea (coefficient of determination = 0.981) and between log (base 10) of morphine dose and vomiting (coefficient of determination = 0.975) in postoperative patients. See Figure 7, below. The approach adopted by Roberts et al. – performing linear regression on dosage quartiles with probability of nausea/vomiting as a continuous dependent variable – is technically flawed, because it exaggerates uncertainty (reducing a dataset of 193 people to four data points) and leads to the possibility of obtaining probabilities greater than 1 (as can be seen in the confidence interval for nausea in Figure 7). A superior approach would have been to perform a logistic regression on the dichotomous outcome of nausea/vomiting, using data from all study participants. However, in the absence of a data source using this approach, we used Roberts et al.'s suboptimal estimate, constraining all probabilities to ≤1 in probabilistic analysis.

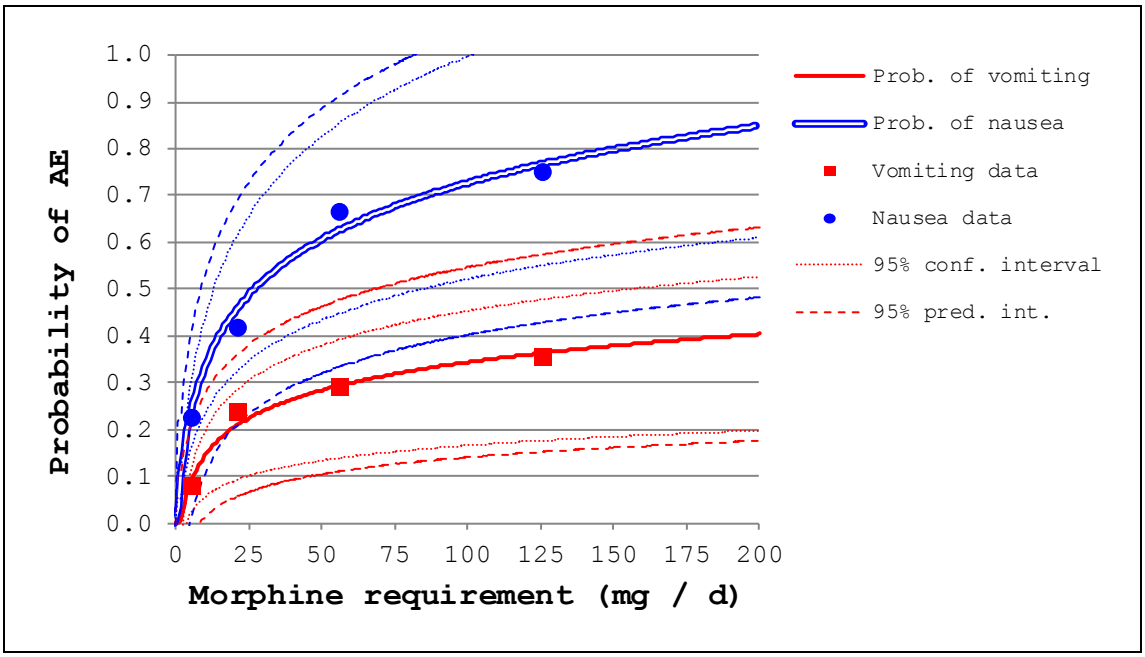

Figure 7: Relationship between morphine requirement and probability of experiencing nausea and vomiting

Constipation

As constipation is a known complication of opioid consumption, we searched for data that would enable us to assume a functional relationship between extent of opioid exposure and likelihood of complication. However, we were not able to identify any such evidence. Therefore, where the clinical effectiveness data on which the models are based did not directly report frequency of constipation, we assumed a fixed likelihood of constipation (37.5%; van Beers et al. 2007) for all treatments throughout the duration of inpatient treatment.

Mortality

Background mortality associated with sickle cell disease

To assess the impact of mortality as a result of an acute painful sickle cell episode, it is necessary to estimate the years of life expectancy that have been lost. We were unable to find any data on the current life expectancy of people with sickle cell disease in the UK. Therefore, we applied hazard ratios reflecting the excess risk of death associated with sickle cell anaemia in the US to general UK population mortality data (Figure 8). We calculated the hazard ratios from CSSCD data reported by Platt et al. (1994). In this study, a cohort 3,764 people – from birth to 66 years of age – with sickle cell disease in America were followed up to determine their life expectancy and risk factors for early death. Kaplan–Meier survival curves for people with sickle cell disease were compared with that of the general population in the US (matched for age and sex). We calculated a hazard ratio of 8.23 for men and 7.56 for women. This means that, at any given time, people with sickle cell disease are around eight times more likely to die than an average person of the same age in the general population.

Though the **absolute** survival of the historical American sickle cell population is expected to differ from that of the current UK sickle cell population, the hazard ratios – which reflect the **relative** excess mortality attributable to sickle cell disease – are more likely to be generalisable across populations and eras. When these hazard ratios were applied to the UK general population life

tables, the model predicted that a cohort of people with sickle cell disease starting at age zero today would achieve a median survival of 64.5 years for men; 70.5 years for women (Figure 8). These estimates may appear relatively high in comparison with published survival data from sickle cell population; however it should be remembered that this calculation projects the expected survival of people who are assumed to be born today.

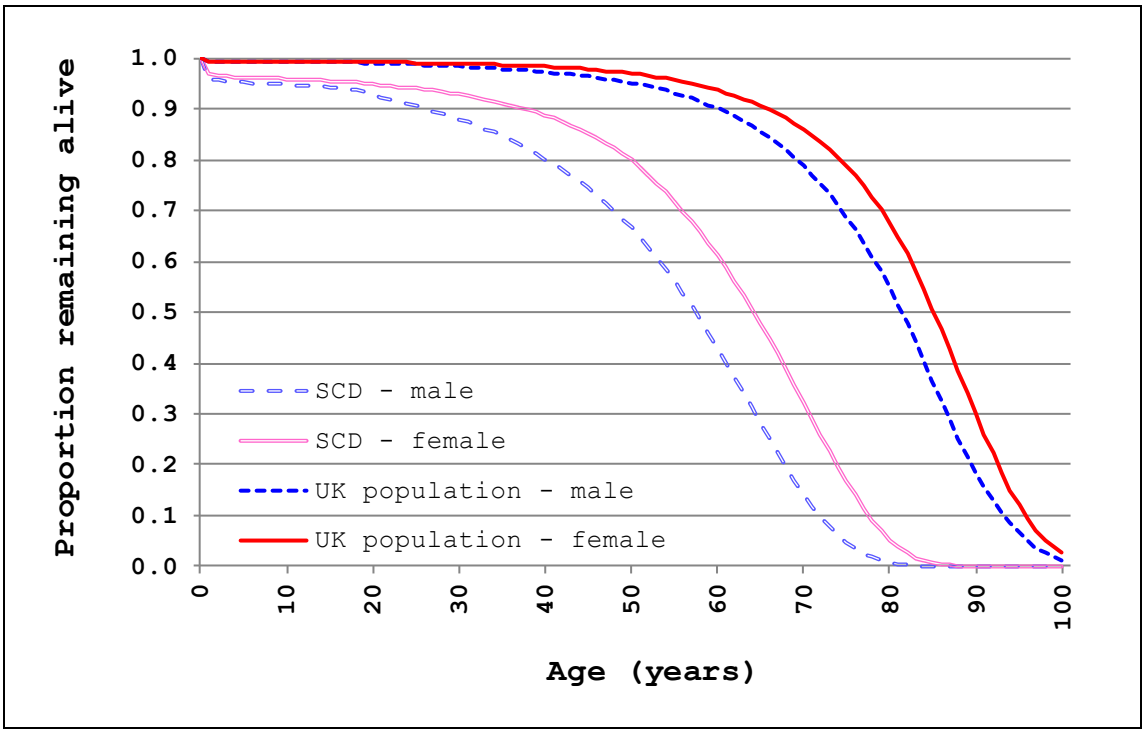

Figure 8: Predicted survival curves for people with sickle cell disease in the UK compared with general population

Risk of death associated with ACS

We obtained the probability of death from ACS during an acute sickle episode (0.027) from the study by Vichinsky et al. (2000) where 18 deaths occurred in 671 episodes of ACS.

Risk of death associated with acute stroke

We identified three studies reporting mortality rates from acute stroke in sickle cell disease. As we had no reason to prefer any of these data sources, we pooled all three using random-effects meta-analysis to derive an average

estimate of the probability of death from stroke during an acute sickle episode (0.074). Details are provided in Table 88.

Table 88: Risk of death associated with acute stroke – meta-analysis

Study	Deaths/ episodes	% (95%CI)	Weight
Ohene-Frempong et al. 1998 (CSSCD)	11/133	8.3% (4.2, 14.3%)	32.1%
Fullerton et al. 2004	1/93	1.1% (0.0, 5.8%)	35.2%
Strouse et al. 2009	34/255	13.3% (9.4, 18.1%)	32.8%
Pooled estimate (random effects)		7.4% (0.0, 15.4%)	

Health-related quality of life

Relationship between utility and pain

We undertook a search to identify studies that report health-related quality of life (HRQoL) during an acute painful sickle cell episode, but we were unable to identify any published evidence. However, a member of the GDG was able to provide individual patient data from an unpublished source (Anie et al. 2011 unpublished), comprising 510 UK patients (mean age 29; 62% female) with sickle cell disease who presented with an acute painful episode. Patients were administered a self assessment questionnaire and were asked to record their pain (VAS) and EQ-5D scores at 3 intervals (T1 – admission, T2 – discharge and T3 – 7 days after discharge). In this dataset, the mean pain score (VAS) was 5.159 on admission and 3.012 at discharge.

Utility weights were calculated for each set of raw EQ-5D measurements, using UK population tariffs (Kind et al. 1999).

Paired VAS and EQ-5D scores were available for a total of 718 measurements (275 at T1, 248 at T2 and 195 at T3). Preliminary analysis of the dataset showed that, as would be expected, there was a relationship between both time-point and VAS and time-point and EQ-5D, with pain decreasing and HRQoL improving as time progressed. However, there was no significant interaction between time-point and VAS in predicting EQ-5D (in

other words, the relationship between VAS and EQ-5D did not change over time). Therefore, we used data from all time-points to estimate the relationship between VAS and EQ-5D. This approach meant that there were multiple individuals who had more than one pair of measurements in the dataset, so it was necessary to account for within-person correlation in characterising the relationship between pain and utility. For this reason, we used a random-effects time-series regression model with patient ID as a panel variable (`xtreg` command in Stata 8.0).

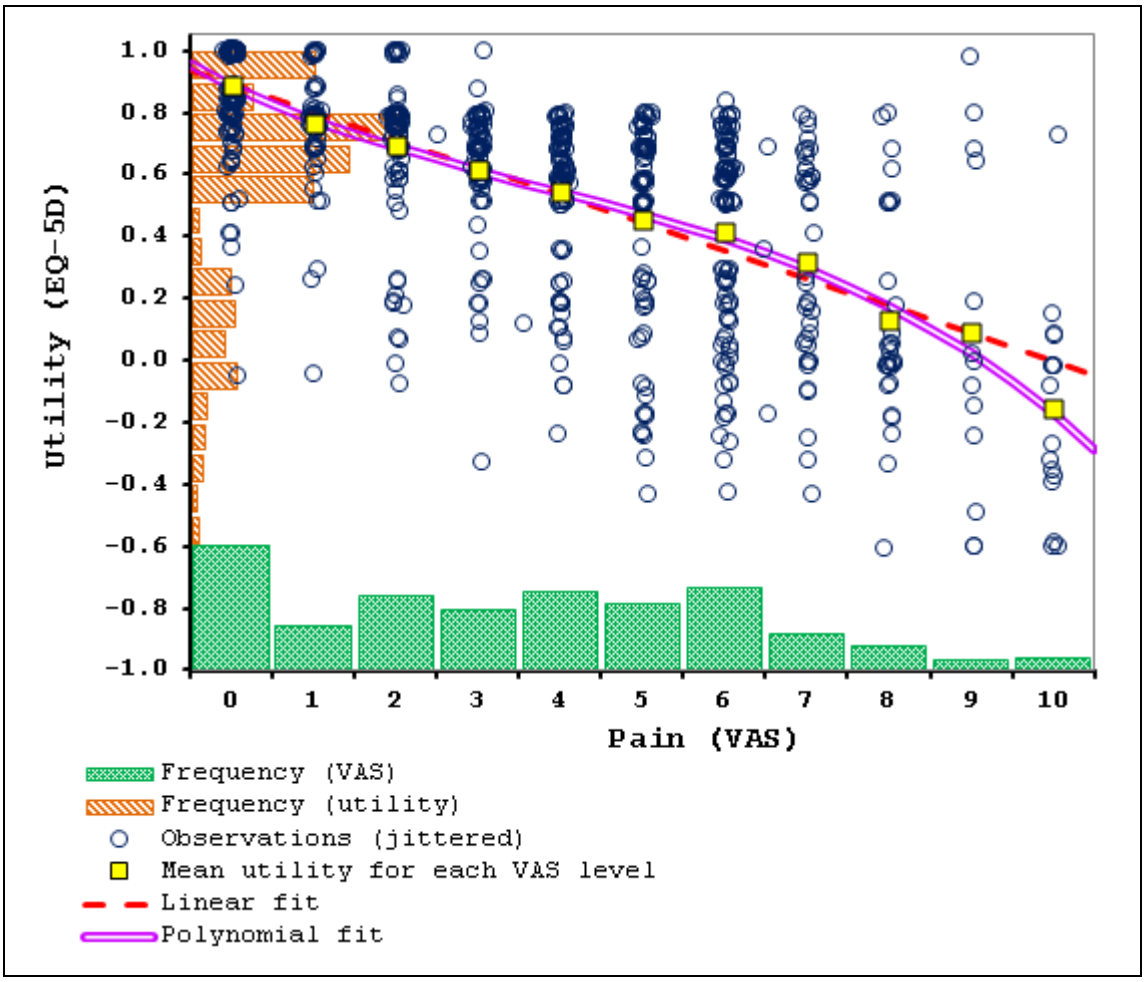

Figure 9: Relationship between pain and utility, with frequency distributions and fitted linear and polynomial models

The model estimated a simple linear relationship as:

$$\text{Utility} = 0.890 + (-0.089 \times \text{VAS}).$$

The coefficient of determination (R^2) for this model was 0.437

We obtained a slightly better fit to the data by incorporating square and cube functions of VAS into the model (polynomial function). The polynomial model is expressed as:

$$\text{Utility} = 0.887 - (0.124 \times \text{VAS}) + (0.014 \times \text{VAS}^2) - (0.001 \times \text{VAS}^3)$$

$$R^2 = 0.445$$

We chose to rely on the polynomial model because it gives a slightly better fit to the data. Moreover, we considered it appropriate that the polynomial model was sensitive to very high VAS scores, producing lower estimated utility values. It is known that EQ-5D measurements are subject to ‘floor’ effects, and it is credible that the most excruciating pain imaginable (a VAS score of 10) would be considered worse than death (utility of < 0) by most people.

When we included them in the model, age and sex were not significant predictors of utility (either as individual variables or in interaction with VAS), so we did not pursue these covariates.

The polynomial model was used to estimate the baseline utility of people in all states throughout the 28-day acute phase of the model.

QALY estimation

In addition to life expectancy, utility (HRQoL) is needed to calculate QALYs of the simulated cohort going into the future. This was estimated by applying utility decrements:

- general population age-specific utility
- minus utility decrement for SCD
- minus utility decrement from ongoing morbidity from stroke for a proportion of cohort (see below)

We identified four sources of data reporting the utility of people in steady-state SCD, with good agreement between them (see Table 89). In our base case, we used an average of all these values (weighted according to the number of participants measured).

Table 89: Health-related quality of life associated with ongoing sickle cell disease

Study		Location	N	estimate	instrument
Anie et al. raw data (T3)		UK	195	0.788	EQ-5D
McClish et al. 2005	male	USA	122	0.717	SF-36
	female	USA	186	0.700	SF-36
Anie et al. 2002		UK	96	0.721	SF-36
Woods et al. 1997		USA	143	0.720	SF-36
Weighted average				**0.732**	

Comparing this value with general population utility for people of the average age and gender-mix of the cohorts represented here (0.93 as reported by Kind et al. 1999), we were able to estimate a utility decrement of 0.198 for people with sickle cell disease. This decrement was applied to age- and gender-specific population utilities (from the same source) in the model, reflecting the assumed age and gender-mix of the cohort under simulation in each instance.

We identified an additional, large, recent US study by Dampier et al. (2011); however, because this study reports HRQoL using the SF-36v2, it was not possible to translate the data to utility weights and amalgamate it with the other identified values.

Utility and acute complications

For the proportion of the simulated cohorts that develop complications, a decrement is subtracted from baseline VAS-dependent utility, to reflect a worsening of condition. We were unable to find any evidence on the HRQoL of people with sickle cell disease experiencing ACS or stroke, so we extrapolated from data reflecting people experiencing analogous events.

- For **ACS**, we used a value reported for people with an acute asthma exacerbation requiring hospitalisation (chronic asthma = 0.89; exacerbation = 0.33; decrement = 0.67; Lloyd et al. 2007). No long-term morbidity from ACS was assumed: although acquired pulmonary dysfunction (so-called ‘chronic sickle lung’) is a significant problem in sickle cell disease, all evidence we were able to identify suggested that its

incidence is not directly associated with frequency of ACS (Machado R.F. et al. 2005)

- For sickle-cell–related **stroke**, we relied on utilities reported following stroke in the general population. (It should be noted that such values reflect the HRQoL of people who tend to be rather older than the average sickle cell patient.) Two levels of stroke were considered: ‘major’ stroke (a stroke resulting in morbidity and dependency) and ‘minor’ stroke (where the person remains able to live independently despite ongoing health challenges). We assumed that 35% of strokes are ‘major’ (3–5 on modified Rankin scale; Bruins Slot et al. 2008).

  – To capture the effect of stroke events on the future HRQoL of the simulated cohorts, we applied a decrement to the utility by which projected life expectancy is weighted for the proportion of people who experience a stroke. We calculated this residual utility decrement using reported utility following ‘major’ (0.315) and ‘minor’ (0.718) stroke, subtracted from that of people who are judged to have recovered completely from a stroke (0.880; Dorman et al. 2000). A weighted average of these decrements – relative to the assumed frequency of ‘major’ and ‘minor’ strokes – was used. This resulted in a residual decrement for stroke of 0.302.

  – In the absence of data regarding the immediate HRQoL of people experiencing a stroke, we assumed that the utility decrement associated with **having** a stroke of any severity during the acute episode was equal to that of **having had** a major stroke (0.565).

Utility and adverse effects

The model also applies utility decrements for the proportion of people who are simulated to experience adverse effects of treatment.

- We did not identify any sickle-cell–specific data on the utility associated with **nausea and vomiting**. We identified a variety of studies reporting

HRQoL associated with nausea and vomiting in pregnant women and patients receiving chemotherapy. As the applicability of these values was uncertain, we adopted the highest identified utility decrement to reflect vomiting (0.149, Smith et al. 2000), the lowest identified utility decrement to reflect nausea (0.05, Beusterien et al. 2010; 0.07), and explored the impact of using different values in sensitivity analyses.

- For **constipation**, we used values calculated from a systematic review of controlled, raw SF-36 data reported by Belsey et al. (2010), converted into utility weights using the mapping algorithm of Ara et al. (2008). This resulted in a decrement of 0.088.

Application of multiple decrements

It should be clear, from the above, that a proportion of each modelled cohort is subject to multiple utility decrements (for example, VAS-dependent baseline utility adjusted by a decrement for ACS and a decrement for nausea). A recent review by the NICE Technology Appraisal Programme's Decision Support Unit (DSU) noted that there is currently no consensus on the best method for combining multiple utility decrements and provided an interim recommendation that a multiplicative method may be preferred (Ara and Wailoo, 2011). However, this approach is only mathematically tractable where utilities are constrained to be positive. In our model, negative utility values are possible, and it is not clear how a multiplicative method could be applied. For this reason, and also because we believed it was important to capture very substantial fluctuations in short-term HRQoL for people who may be in excruciating pain, we used an additive method to combine decrements.

According to this approach, an individual with a pain score (VAS) of 10, who was also experiencing ACS, vomiting and constipation would have a utility of −0.970. Although a utility score as low as this is unusual in health economic models, we considered this to be an appropriate reflection of the HRQoL impact of such a combination of acute health problems. We tested the impact of this approach in sensitivity analysis.

Costs

Cost of hospital admission

We derived the daily cost of hospital admission for acute painful sickle cell episode from the NHS reference cost guide (2011). We used weighted averages of costs recorded in four ‘department’ categories:

- ‘Non-Elective Inpatient (Long Stay)’
- ‘Non-Elective Inpatient (Long Stay) Excess Bed Day’
- ‘Non-Elective Inpatient (Short Stay)’
- ‘Day Cases’

All elective codes were excluded from consideration. We included costs recorded under three ‘currency’ codes:

- For children, we used PA47Z ('Sickle-cell Anaemia with Crisis')
- For adults, we used an activity-weighted average of
  - SA10E ('Sickle Cell Anaemia with crisis or with complication or co-morbidity’) and
  - SA10F ('Sickle Cell Anaemia without complication or co-morbidity’)

The resulting estimates were £589 per day for children and £456 per day for adults. Details are provided in Table 90.

531 **Table 90: Costs of inpatient admissions for acute sickle cell episodes in NHS Reference Costs, 2010/11**

Currency Code	Currency Description	Activity	Unit cost			Bed-days	Average LOS (d)	Total cost	Mean cost / d
			Mean	LoQ	HiQ				
TPCTNEI_L	**Non-Elective Inpatient (Long Stay)**								
PA47Z	Sickle cell anaemia with crisis	1440	£2411	£1645	£2903	5712	3.97	£3,471,808	£608
SA10E	Sickle cell anaemia with crisis or with CC	3763	£2311	£1273	£2711	17,809	4.73	£8,694,536	£488
SA10F	Sickle cell anaemia without CC	103	£2015	£795	£2302	273	2.65	£207,519	£760
TPCTNEI_L_XS	**Non-Elective Inpatient (Long Stay) Excess Bed Days**								
PA47Z	Sickle cell anaemia with crisis	373	£361	£238	£426	373		£134,485	£361
SA10E	Sickle cell anaemia with crisis or with CC	3216	£297	£203	£414	3216		£956,109	£297
SA10F	Sickle cell anaemia without CC	294	£343	£248	£456	294		£100,833	£343
TPCTNEI_S	**Non-Elective Inpatient (Short Stay)**								
PA47Z	Sickle cell anaemia with crisis	967	£581	£351	£688	967	1.00	£562,297	£581
SA10E	Sickle cell anaemia with crisis or with CC	3637	£437	£246	£584	3637	1.00	£1,589,525	£437
SA10F	Sickle cell anaemia without CC	317	£363	£214	£389	317	1.00	£115,126	£363
TPCTDC	**Day Cases**								
PA47Z	Sickle cell anaemia with crisis	82	£364	£210	£406	82	1.00	£29,871	£364
SA10E	Sickle cell anaemia with crisis or with CC	314	£403	£212	£477	314	1.00	£126,583	£403
SA10F	Sickle cell anaemia without CC	486	£440	£364	£555	486	1.00	£213,857	£440
	All long-stay cases (long stay plus excess bed days)								
PA47Z	Sickle cell anaemia with crisis	1440	£2504	£1706	£3013	6085	4.23	£3,606,293	£593
SA10E+SA10F	Sickle cell anaemia with crisis or with CC / without CC	3866	£2576			21,592	5.59	£9,958,996	£461
	All short-stay cases (short stay plus day cases)								
PA47Z	Sickle cell anaemia with crisis	1049	£565	£340	£666	1,049	1.00	£592,168	£565
SA10E+SA10F	Sickle cell anaemia with crisis or with CC / without CC	4754	£430			4754	1.00	£2,045,092	£430
	All								
PA47Z	Sickle cell anaemia with crisis	2489	£1687	£1131	£2024	7134	2.87	£4,198,461	£589
SA10E+SA10F	Sickle cell anaemia with crisis or with CC / without CC	8620	£1,393			26,346	3.06	£12,004,088	£456

Long-term costs

We did not account for the cost of ongoing care for sickle cell disease following recovery from an acute painful episode, as the clinical course of the disease is chronic and not directly influenced by management of an acute episode.

The only long-term costs included in the model are those relating to care following stroke events. We obtained these from a cost–utility model of anti-platelet therapies to prevent recurrent stroke (Chambers et al. 1999). The values are subdivided by ‘minor’ and ‘major’ strokes (defined, respectively, as those after which the person can continue to live independently and those after which the person becomes dependent on others). They comprise a one-off cost to reflect immediate rehabilitation and an annual cost to reflect ongoing care and support. We inflated these costs to 2011/12 values (using Hospital and Community Health Services pay and price inflation indices), resulting in the following estimates:

- ‘Minor’ stroke:
  - Rehabilitation: £66.87
  - Annual care: £1450.06
- ‘Major’ stroke:
  - Rehabilitation: £1263.52
  - Annual care: £18,709.96

In addition, we estimated the cost of maintenance transfusion that is routinely performed in people with sickle cell disease who have had a stroke. Where people receive standard transfusions, it is also necessary for them to receive chelation therapy, to counteract iron overload resulting from frequent blood transfusions, so we included the costs of chelation for a proportion of people. We arrived at an average annual cost of £13,152.73 per adult and £7385.14 per child. Details are provided in Table 91.

Table 91: Annual costs of transfusion and iron chelation for people with sickle cell disease who have had a stroke

Item	Value
Standard red cells	
Unit cost	£124.85
Yearly frequency	12
Annual cost	£1498.20
Proportion of patients requiring iron chelation	100%
Red cells for exchange transfusion	
Unit cost	£184.13
Yearly frequency	8
Annual cost	£1473.04
Proportion of patients receiving exchange transfusion	0.20
Proportion of patients requiring iron chelation	0%
Iron chelation	
Oral	
Deferasirox - unit cost (£ / 125mg)	£4.20
Dose (mg/kg)	20.00
No. of 125mg doses required daily for adult	10
Annual cost for adult	£15,330.00
No. of 125mg doses required daily for child	5
Annual cost for child	£7665.00
Parenteral	
Desferrioxamine mesilate - unit cost (£ / 500mg vial)	£4.26
Average daily dose (mg / kg)	40.00
No. of 500mg vials required daily for adult	5
Annual cost for adult	£7774.50
No. of 125mg doses required daily for child	3
Annual cost for child	£4664.70
Proportion of patients receiving oral therapy	0.90
Annual cost for adult	£14,574.45
Annual cost for child	£7364.97
Total	
Annual cost for adult	£13,152.73
Annual cost for child	£7385.14

All drug costs were obtained from the BNF. A bottom-up costing approach was used for the cost analysis of PCA.

Cost of adverse effects

We assumed that the costs of nausea, vomiting and constipation were included in the cost of hospital admission, and would be relatively small. Moreover, because patients are often offered pre-emptive anti-emetics, we assumed that costs associated with nausea and vomiting will not be entirely dependent on the frequency of these events.

571 **Table 92 Parameters common to PCA and LWMH models**

Parameter	Estimate	Distribution	Parameters	Source	Notes
Discount rate (costs)	0.035			NICE methods	
Discount rate (benefits)	0.035			NICE methods	
Cohort demographics at baseline					
Age	variable				Model input
Sex (% male)	0.526	Beta	α = 5587; β =5038	HES 2010/11	
Weight: z-score for children with SCD	-0.800	Normal	μ = −0.8; σ = 0.183	Barden et al. 2002	36 US children aged 5–17 with SCD compared with population norms
Average weight of an adult man with SCD (kg)	65.00	uniform	[60,70]	assumption	no primary data identified; values assumed following discussion with GDG
Average weight of an adult woman SCD (kg)	55.00	uniform	[50,60]		
LOS calculation					
Weibull alpha shape parameter (children)	2.705	Normal	μ = 2.705; σ = 0.235	Orringer et al. 2001	only study identified providing time-to-event data for duration of episode; treatment (poloxamer 188) and control arms averaged
Weibull alpha shape parameter (adults)	2.997	Normal	μ = 2.997; σ = 0.397		
When basing LOS on VAS distribution:					
Threshold for discharge VAS	3.012	Normal	μ = 3.012; σ = 0.151	Anie 2011 unpublished	average VAS at discharge
Threshold at which VAS begins to define discharge (d)	0.500			assumption	value assumed following discussion with GDG, on basis of their advice that, once a patient has been admitted and treatment started, 12hrs represents a minimum stay
VAS calculation					
VAS score at baseline	5.159	Beta	a = 0; b = 10; α = 602.0; β = 564.8	Anie 2011 unpublished	
Utilities					
Decrement for chronic SCD	0.198			Anie 2011	weighted average of studies

Parameter	Estimate	Distribution	Parameters	Source	Notes
				unpublished; McClish et al. 2005; Anie 2002; Woods 1997	estimating utility of chronic SCD using SF-36, deducted from utility for general population of same average age and sex
Utility v VAS					
Constant	0.887	multivariate normal	dependent on variance–covariance matrix of regression model	Anie 2011 unpublished	new analysis of raw IPD; see text
VAS	-0.124				
VAS^2	0.014				
VAS^3	-0.001				
Residual decrement for post-stroke with dependence	0.565			Dorman et al. 2000	cost-effectiveness analysis of anti-platelet therapy in general population; decrement calculated by deducting utility for dependent (0.312) / independent (0.718) states from value for those who were judged to have 'recovered' from stroke (0.880)
Residual decrement for post-stroke with independence	0.162				
Residual decrement for stroke	0.302				
Complication decrements					
Decrement for ACS	0.560	lognormal	μ = −2.207; σ = 0.147	Lloyd et al. 2007	no SCD-specific data identified; reported utility value for asthma exacerbation requiring hospitalisation (0.33) deducted from utility value for chronic asthma (0.89)
Decrement for stroke event	0.565			assumption	no SCD-specific data identified; assumed utility of experiencing any stroke is equal to long-term decrement of major stroke
Adverse event decrements					
constipation	0.088	uniform +/- 50%	[0.04416,0.13248]		
nausea/vomiting (severe)	0.149	uniform +/- 50%	[0.07456, 0.224]	Smith et al. 2000	HRQoL of pregnant women experiencing nausea/vomiting
nausea/vomiting (mild)	0.050	uniform +/- 50%	[0.025, 0.075]	Beusterien et al.	HRQoL of people undergoing

Parameter	Estimate	Distribution	Parameters	Source	Notes
				2010	chemotherapy experiencing nausea/vomiting
IV morphine requirement predicted from VAS:					
Intercept	-1.687	multivariate normal	dependent on variance–covariance matrix of regression model	analysis of data from Bartolucci et al. 2009	linear regression
Slope	15.362				
Probability of nausea predicted from morphine exposure:					
Intercept	-0.090	multivariate normal	dependent on variance–covariance matrix of regression model	Roberts et al. 2005	study of relationship between morphine exposure and nausea/vomiting in postoperative analgesia
Slope	0.407				
Probability of vomiting predicted from morphine exposure:					
Intercept	-0.055	multivariate normal			
Slope	0.199				
Complications					
Baseline odds of ACS in regression cohort	0.268			Buchanan et al. 2005	
OR per VAS unit	1.660	lognormal	μ = 1.660; σ = 0.152		
Mean baseline VAS in regression cohort	7.902	Beta	a = 0; b = 10; α = 572.4; β = 152		
Historical frequency of stroke relative to ACS	0.097	Beta	α = 203; β = 1893	Sebastiani et al. 2007	6% of people in CSSCD cohort experienced stroke; 62% experienced ACS
Reduction in frequency of stroke in 20th century	0.376	lognormal	μ = 0.376; σ = 0.370	Fullerton et al. 2004	applied to reflect lower incidence of stroke now than was experienced during period of CSSCD data collection
Probability stroke is major (results in dependency)	0.347	Beta	α = 758; β = 1427	Bruins Slot et al. 2008	proportion of people in Oxford and Lothian stroke cohorts with modified Rankin score of 3 or higher 6 months after event
Primary threshold for complications (days)	7.000	uniform +/- 50%	[3.5, 10.5]	assumption	assumption following discussion with GDG; reflects their view
Proportion of complications occurring by primary threshold	0.750	uniform	[0.5,1]		

Parameter	Estimate	Distribution	Parameters	Source	Notes
Final threshold for complications (days)	14.000	uniform +/- 50%	[0,14]		that most complications occur fairly soon after admission, but a small proportion develop later
Death					
Probability of death from stroke	0.074	gamma	α = 3.31; β = 0.02	Fullerton et al. 2004; Ohene-Frempong et al. 1998; Strouse et al. 2009	random-effects meta-analysis of proportion of deaths reported in three papers
Mean length of stay for stroke	9.361			Fullerton et al. 2004; Strouse et al. 2009	weighted average of LOS reported in two papers
Probability of death from ACS	0.027	Beta	α = 18; β = 653	Vichinsky et al. 2000	18 of 671 episodes were fatal
Mean length of stay for ACS	10.500				
Probability of death during uncomplicated episode	0	Uniform	[0.000,0.001]	assumption	
Costs					
Daily cost of inpatient care					
Average daily cost of inpatient with SCD crisis	£455.63	Gamma	Weighted average of sampled values from individual gamma distributions for each cost code (see Table 90)	NHS reference costs 2010/11	weighted average of costs under various codes (see text)
Average daily cost of inpatient with SCD crisis (child)	£588.51	Gamma	Weighted average of sampled values from individual gamma distributions for each cost code (see Table 90)		
Drugs					
Morphine (mg)	£0.10			BNF	

Parameter	Estimate	Distribution	Parameters	Source	Notes
Long-term costs					
'Minor' stroke (independent)				Chambers et al. 1999	Cost-effectiveness analysis of antiplatelet therapy; inflated from 1996 costs to 2011 value
Ambulatory rehab (single cost in first six months)	£66.87	Gamma	α = 25.0; β = 2.675		
Annual care	£1,450.06	Gamma	α = 25.0; β = 58.002		
'Major' stroke (dependent)					
Ambulatory rehab (single cost in first six months)	£1,263.52	Gamma	α = 25.0; β = 50.541		
Annual care	£18,709.96	Gamma	α = 25.0; β = 748.398		
Transfusions for people who have had strokes					
Standard red cells (per 500 ml bag)	£124.85	Gamma	α = 25.0; β = 4.994	NHS Blood and Transplant	
Yearly frequency	12.00	Normal	μ = 12.00; σ = 2.4		
Proportion of patients requiring iron chelation	100%			assumption	based on GDG advice
Red cells for exchange transfusion (per 500 ml bag)	£184.13	Gamma	α = 25.0; β = 7.365	NHS Blood and Transplant	
Yearly frequency	8.00	Normal	μ = 8.00; σ = 1.6		
Proportion of patients requiring iron chelation	0%			assumption	based on GDG advice
Proportion of patients receiving exchange transfusion	20%	triangular	[0%,20%,40%]	assumption	based on GDG advice
Iron chelation					
Oral					
Deferasirox - unit cost (£ / 125mg)	£4.20			BNF	
Dose (mg/kg)	20	triangular	[10,20,30]		
Parenteral					
Desferrioxamine mesilate - unit cost (£ / 500mg vial)	£4.26			BNF	
Average daily dose (mg / kg)	40.00	triangular	[20,40,60]	SPC	
Proportion of patients receiving oral chelation	90%	triangular	[80%,90%,100%]	assumption	based on GDG advice
Total mean annual cost of transfusion, etc., for adult	£13,152.73			calculation	calculated using above values and assumptions

Parameter	Estimate	Distribution	Parameters	Source	Notes
Total mean annual cost of transfusion, etc., for child	£7,385.14				

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Sensitivity analysis

Sensitivity analysis was conducted to explore the various areas of uncertainty and their impact on the model. "*Uncertainty, ultimately with regard to the precision of the ICER, is inherent in any economic evaluation* (Fox-Rushby and Cairns 2005).

One-way deterministic sensitivity analysis

One-way sensitivity analyses were conducted to explore the impact on the results of changing the value of one parameter while keeping the value of all other parameters unchanged. It also highlights areas where further exploration of uncertainty may be useful.

Threshold analysis

Following one-way sensitivity analyses, parameters which the model results were most sensitive to (those which appear to change the cost–utility conclusions) were further subjected to threshold analyses. In this instance, the size of each of those parameters is varied over a range to determine the level above or below which the cost-utility conclusions change, and hence the 'threshold' point at which neither of the options are preferred over the other.

Probabilistic sensitivity analysis (PSA)

PSA is the preferred method of exploring uncertainty which arises as a result of random sampling variation around mean estimates of parameters used in the model. It considers uncertainty around all parameters simultaneously and demonstrates how the decision at hand changes given different WTP. PSA involves using a Monte Carlo simulation where parameters are expressed as distributions (reflecting plausible values) rather than point estimates (means). Different values are randomly drawn from the distributions and on each occasion a different ICER point is generated. This is repeated numerous times (10,000 iterations per scenario in this instance). The resulting ICER pairs can be plotted as a joint distribution on the cost–utility plane. In addition, the values from all simulated scenarios can be aggregated to give the mean

expected ICER (which may be different from the result from the deterministic analysis).

Parameters particular to PCA model

We based the clinical effectiveness parameters for the PCA model on the RCT reported by van Beers et al (2007), in which 25 episodes of acute painful sickle cell crisis were randomly assigned to morphine administration via PCA or via continuous intravenous infusion (C-IV).

Clinical parameters and variables

Pain (VAS) over time

Because van Beers et al. only report a single data-point for reduction in VAS following two days of treatment; we were unable to deduce the shape of the function of VAS over time in their trial. For this reason, we assumed a simple exponential decline.

To enable the exploration of different starting values for VAS, we assumed that the reported relative reduction in pain for each trial arm could be applied. Accordingly, we assumed that, over two days, the VAS of people treated with PCA would reduce by 59.3%, and the VAS of people treated with C-IV would reduce by 47.2%. We tested the impact of using an absolute reduction, instead – that is, the VAS of people treated with PCA reducing by 3.8, and the VAS of people treated with C-IV reducing by 2.4 – in sensitivity analysis.

In a similar way, the model scales the reported SD of changes by the baseline score reported in the publication. However, in order to estimate the SD of the distribution at follow-up (which is not provided in the publication), it is necessary to impute a value using known information. In the – much more common – case where SD at baseline (σ_b) and SD at follow-up (σ_f) are reported, but there is no information on the SD of changes between baseline and follow-up (σ_c), the missing value can be estimated according to the formula

$$\sigma_c = \sqrt{\sigma_b^2 + \sigma_f^2 - 2C\sigma_b\sigma_f}, \tag{5}$$

where C is the correlation coefficient between baseline and follow-up measurements (see http://www.mrc-bsu.cam.ac.uk/cochrane/handbook/chapter_16/16_1_3_2_imputing_standard_deviations_for_changes_from_baseline.htm).

To solve this equation in order to find SD at follow-up when the SD of changes is known, it can be rearranged into quadratic form ($ax^2 + bx + c = 0$):

$$1\sigma_f^2 + -2C\sigma_b\sigma_f + \left(\sigma_b^2 - \sigma_c^2\right) = 0\ . \tag{6}$$

This can then be solved with the standard formula:

$$x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}\ . \tag{7}$$

Therefore, follow-up SD may be estimated by

$$x = \frac{2C\sigma_b \pm \sqrt{\left(-2C\sigma_b\right)^2 - 4\left(\sigma_b^2 - \sigma_c^2\right)}}{2}. \tag{8}$$

For the combinations of parameters that are encountered in this setting, it is always the upper root that provides the plausible estimate of SD; therefore, the ± symbol in expression (8) may be read as + only.

For the correlation coefficient C, we were able to calculate the relationship between baseline and follow-up measurements directly in the raw data provided by a GDG member (Anie et al. 2011 unpublished), so we relied on this estimate (0.319) in the model.

Length of hospital stay

For LOS, van Beers et al. report a median and inter-quartile range for each arm. Weibull functions were fitted to these three data points and used in model scenarios 1A and 1B.

649 **Table 93 Parameters particular to PCA model**

Parameter	Estimate	Distribution	Parameters	Source	Notes
Effectiveness data					
VAS calculation					
Treatment 1 (C-IV)					
Base score at baseline	5.159	Beta	a = 0; b = 10; α = 602.0; β = 564.8	Anie 2011 unpublished	
Absolute reduction in VAS score	2.400	Normal	μ = 2.400; σ = 0.946	Van Beers et. al. (2007)	
Treatment 2 (PCA)					
Absolute reduction in VAS score	3.800	Normal	μ = 3.800; σ = 3.800	Van Beers et. al. (2007)	
LOS calculation					
Median	9.000	Normal	μ = 9.000; σ = 1.234	Van Beers et. al. (2007)	
Mean	9.345				calculated
Alpha	2.310				
Beta	10.548				calculated
Treatment 2 (PCA)					
Median	6.000	Normal	μ = 6.00; σ = 1.070	Van Beers et. al. (2007)	
Mean	6.498				calculated
Alpha	1.849				
Beta	7.315				calculated
Utilities					
Probability of constipation					
Treatment 1 (C-IV)					
daily	0.450	Beta	α = 49.357; β = 60.325	Van Beers et. al. (2007)	
Treatment 2 (PCA)					
daily	0.300	Beta	α = 14.986; β = 34.967	Van Beers et. al. (2007)	

Parameter	Estimate	Distribution	Parameters	Source	Notes
Resource-use and costs					
Acute phase					
PCA consumables	£11.81			NHS catalogue	
Lifespan of PCA consumables (days)	3			GDG	
PCA pump (large volume)	£2500			http://www.mhra.gov.uk	Type of pump in current practise was provided by the GDG

Adverse effects

Constipation

Constipation was an outcome for which data were collected in van Beers et al.'s trial. These data are reported as area-under-the-curve of a 10-point scale. Because a score of 10 indicated constipation and 0 indicated no problems, we interpreted these data as being approximately equivalent to ten times the daily probability of experiencing constipation. Therefore, we applied a daily probability of 0.45 for constipation in the C-IV arm and a daily probability of 0.30 in the PCA arm.

Parameters particular to LMWH model

We based the clinical effectiveness parameters for the LMWH model on the RCT reported by Qari et al (2007). Investigators randomly assigned 253 participants with acute painful sickle cell crisis to a therapeutic dose of LMWH (Tinzaparin at 175 units / kg / day) or placebo, in addition to standard care that included intravenous morphine (1 mg per hour) for all participants.

Clinical parameters and variables

Pain (VAS) over time

Qari et al. provide longitudinal data on the pain (VAS) scores of their cohorts over a seven-day period in a graph. We extracted these data for the two treatment arms and fitted parametric curves to extrapolate beyond the seven days' follow-up. We found that Weibull distributions (scaled from their [0,1] range to the [0,10] range of VAS data) provided an excellent fit to the observed data (R^2 for placebo = 0.99; R^2 for LWMH = 0.86).

Although there was a clear, statistically significant difference in VAS in favour of LMWH in the first three days' follow-up, the curves converged and then crossed as follow-up extended, with a small, non-statistically–significant benefit for the placebo arm on days 6 and 7. Because the model curves were fitted to extracted aggregate data rather than the underlying individual patient

data, there was a danger of placing undue emphasis on this feature in the model, and this would be exaggerated as follow-up was extrapolated beyond the observed seven days (as illustrated in Figure 10). For this reason, a separate curve was fitted to the average experience of the LMWH and placebo cohorts, and both arms were assumed to follow this course from halfway through day 5 onwards (see Figure 11). The impact of varying this assumption was tested in sensitivity analysis.

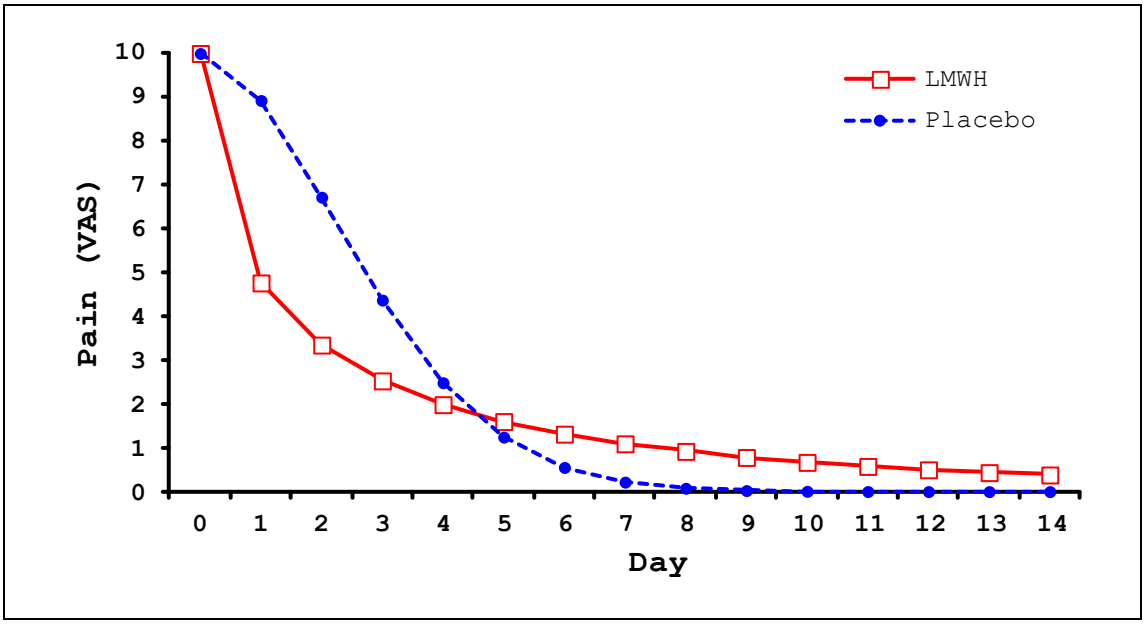


Figure 10: Pain over time for people taking LMWH or placebo – separate profiles throughout

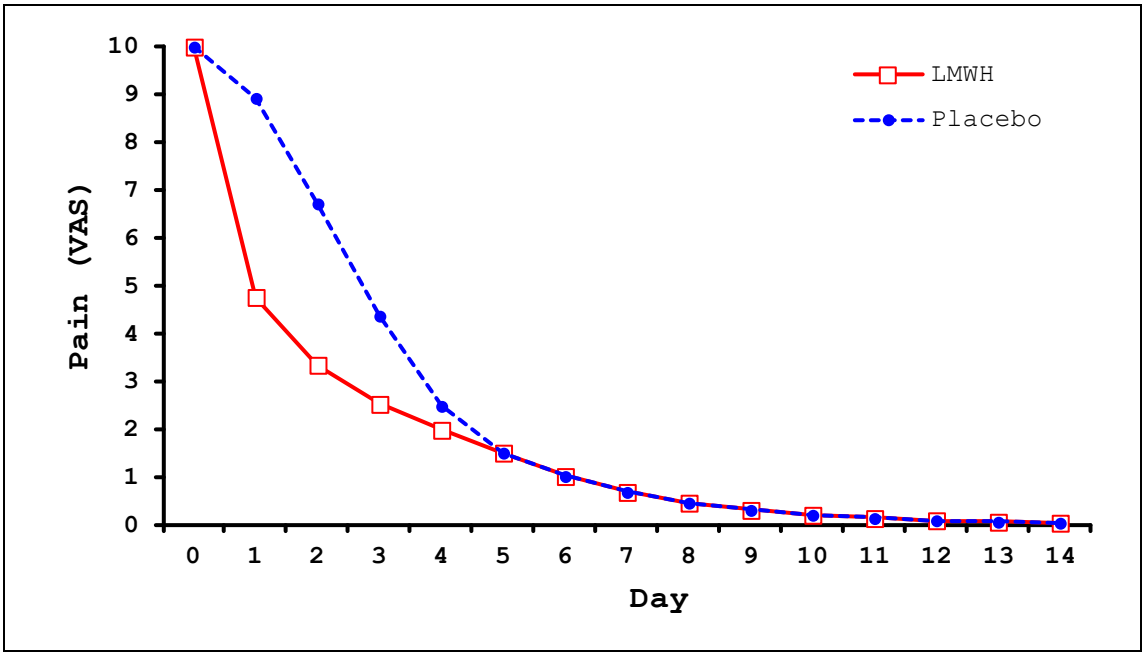


Figure 11: Pain over time for people taking LMWH or placebo – shared profile for day 5 onwards (used in base-case model)

689

690 **Table 94 Parameters particular to the LMWH model**

Parameter	Estimate	Distribution	Parameters	Source	Notes
Effectiveness data					
VAS calculation					
Treatment 1(LMWH)					

Base score at baseline	5.159	Beta	a = 0;
			b = 10;
			α = 602.0;
			β = 564.8
				Anie 2011 unpublished	

Alpha	1.808	Multivariate normal	dependent on variance–covariance matrix of regression model		
Ln(lambda)	-2.176			Qari et.al. (2007)	
Beta	3.331				calculated
Treatment 2 (placebo)				Qari et.al. (2007)	
Base score	5.159				calculated
Alpha	0.562	Multivariate normal	dependent on variance–covariance matrix of regression model		
Ln(lambda)	-0.299			Qari et.al. (2007)	
Beta	1.701				calculated
Treatments 1 & 2 averaged					
Alpha	1.035	Multivariate normal	dependent on variance–covariance matrix of regression model		
Ln(lambda)	-1.028			Qari et.al. (2007)	
Beta	2.699				calculated
Threshold at which shared parameters adopted (days)	4.500	Triangular	[0; 4.5; 9]	Qari et.al. (2007)	

Parameter	Estimate	Distribution	Parameters	Source	Notes
LOS calculation					
Treatment 1(LMWH)					
Median	11.951				calculated
Mean	12.060	Normal	μ = 12.060; σ = 0.196		
Alpha	2.997	Normal	μ = 2.997; σ = 0.397		
Beta	13.506				calculated
Treatment 2 (placebo)					
Median	7.016				calculated
Mean	7.080	Normal	μ = 7.080; σ = 0.160		
Alpha	2.997				calculated
Beta	7.929				calculated
Utilities					
Probability of constipation					
Treatment 1(LMWH)					
daily	0.375	Beta	α = 57.106; β = 95.176		
Treatment 2 (placebo)					
daily	0.375	Beta	α = 57.106; β = 95.176		
Resource-use and costs					
LMWH					
Dose (units / kg / d)	175			BNF	
Units per daily dose	10,545				calculated
Cost per patient per day	£8.71				calculated

Results: patient-controlled analgesia -v- continuous IV

Model output

The model simulated four different scenarios:

- **1A** Independent LOS with a fixed complication rate at baseline (Figure 14)
- **1B** Independent LOS with a dynamic complication rate (Figure 15)
- **2A** Pain predicts LOS with a fixed complication rate at baseline (Figure 16)
- **2B** Pain predicts LOS with a dynamic complication rate (Figure 17)

The model predicts that on average the rate of pain control is influenced by the method of delivery of analgesia (figure 9). Though patients in both arms end up with the same pain score at discharge, their pain experience is different – those in the PCA group experiencing a more rapid pain relief than those in the C-IV group. The effect of PCA becomes evident from the second day in hospital (figure 10) and persists until the second week on admission. This applies to all four scenarios.

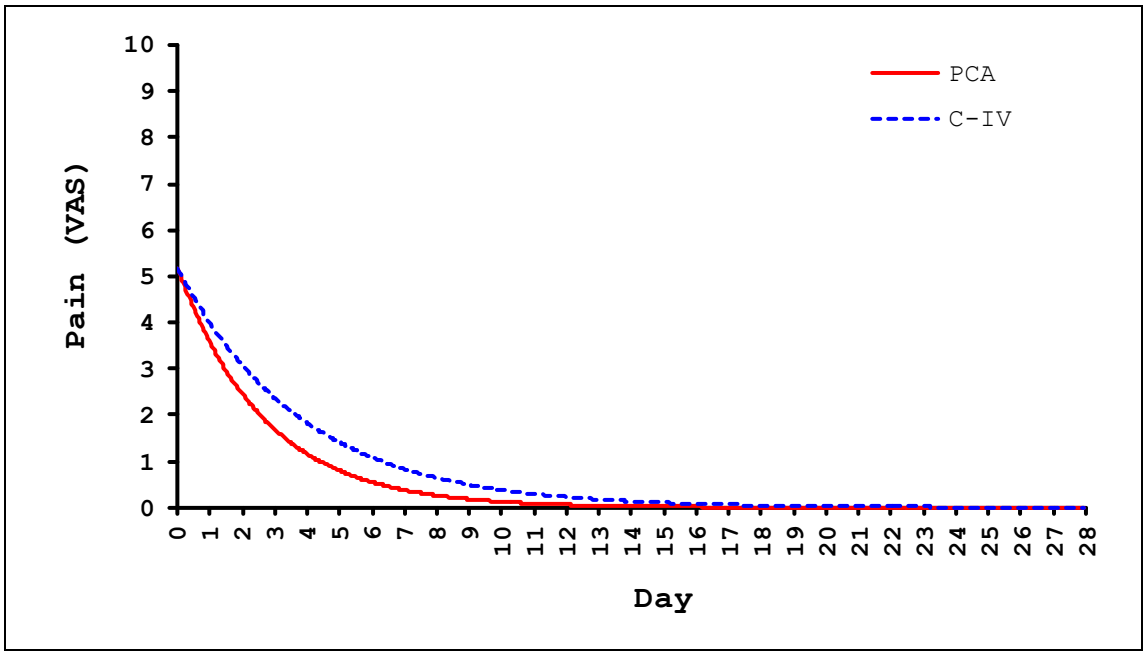


Figure 12: Modelled average pain score over time for people receiving morphine via PCA or C-IV (applies to all scenarios)

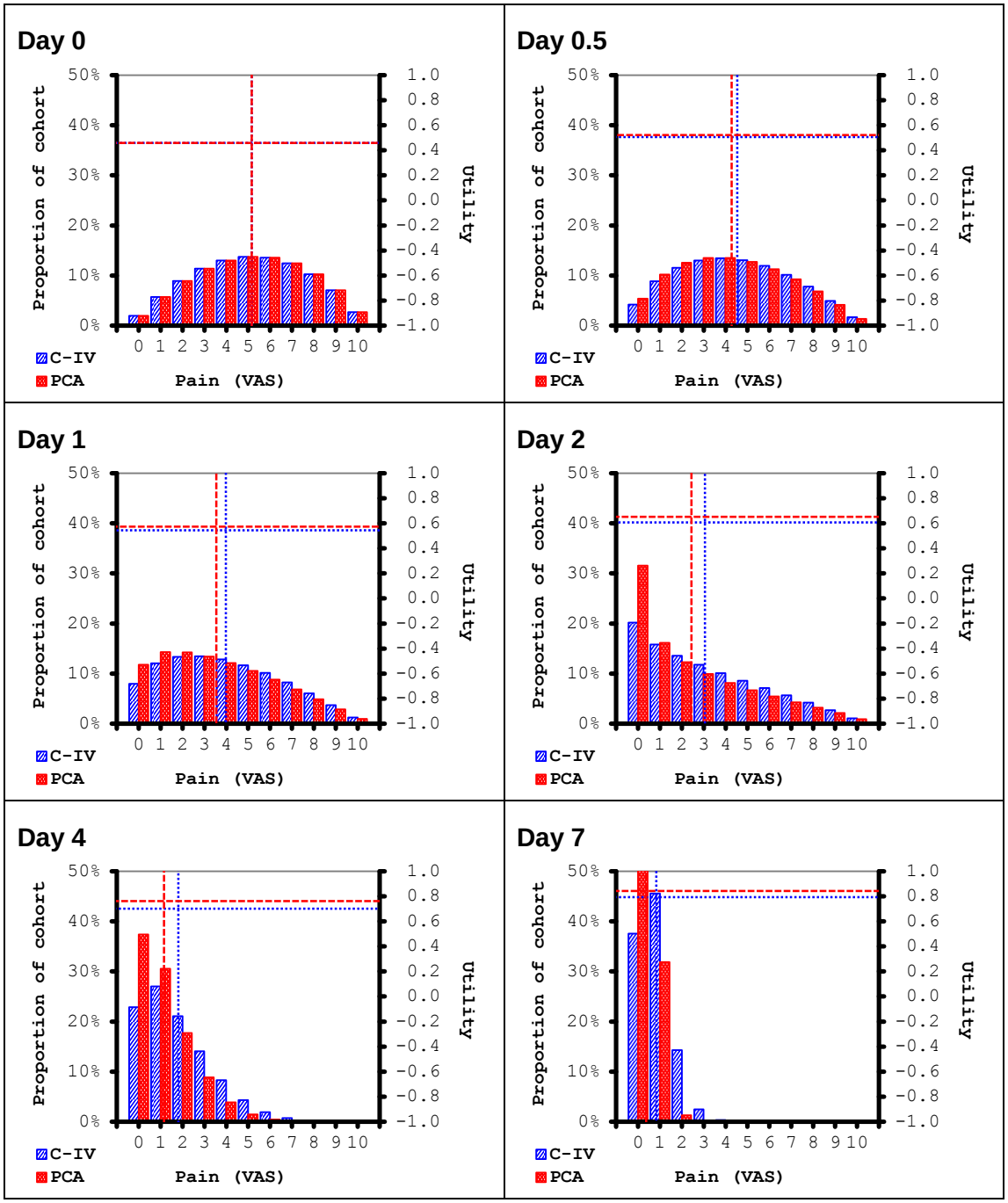


Figure 13: Modelled distribution of pain scores over time for people receiving morphine via PCA or C-IV (applies to all scenarios)

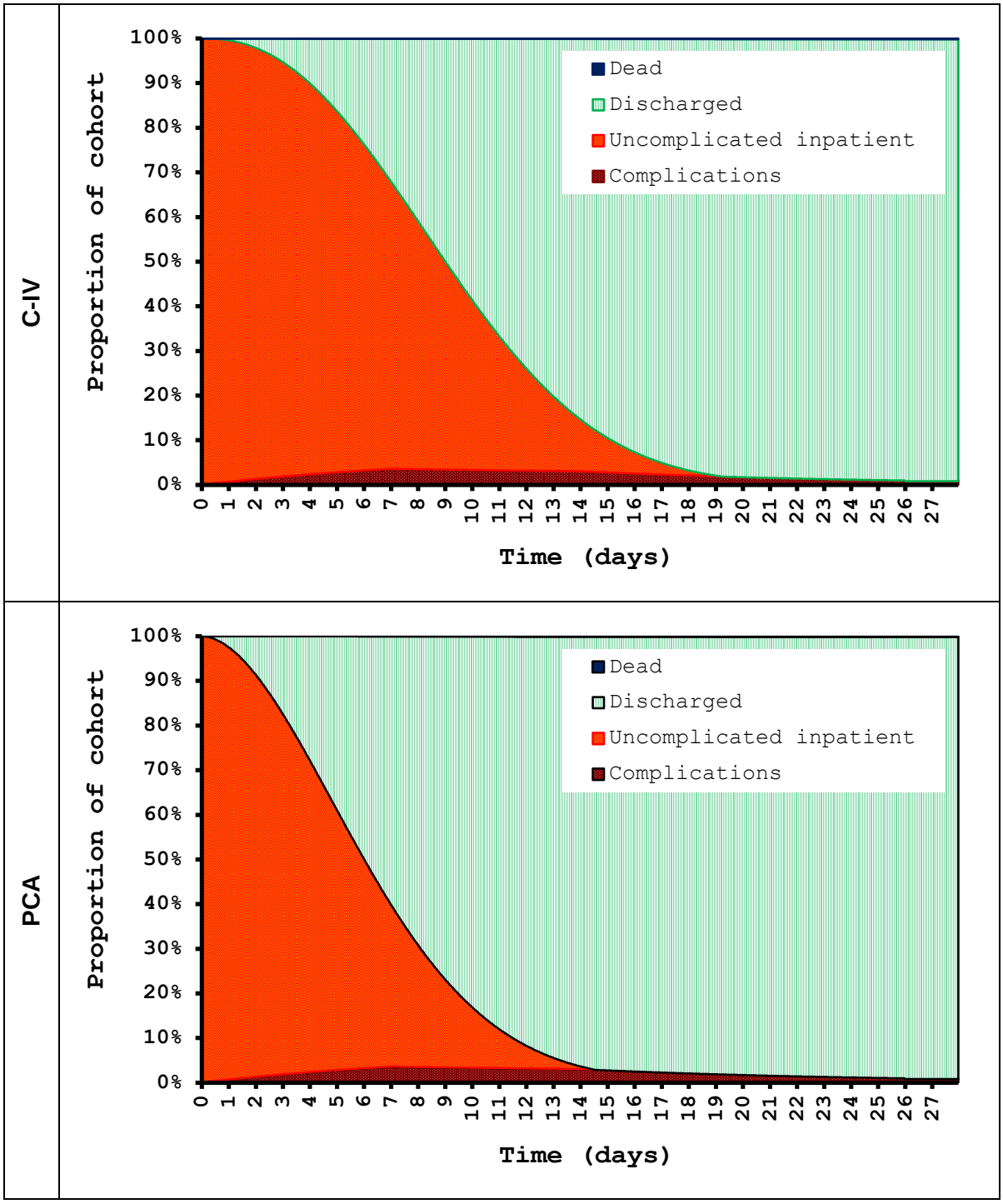
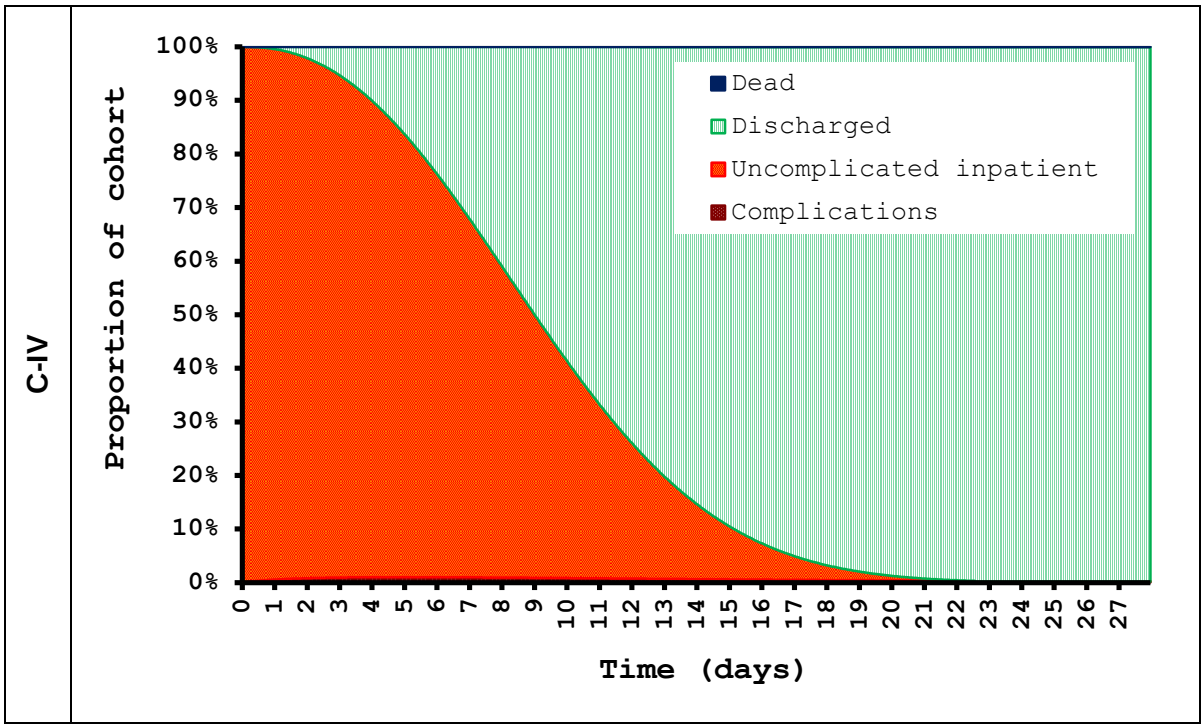


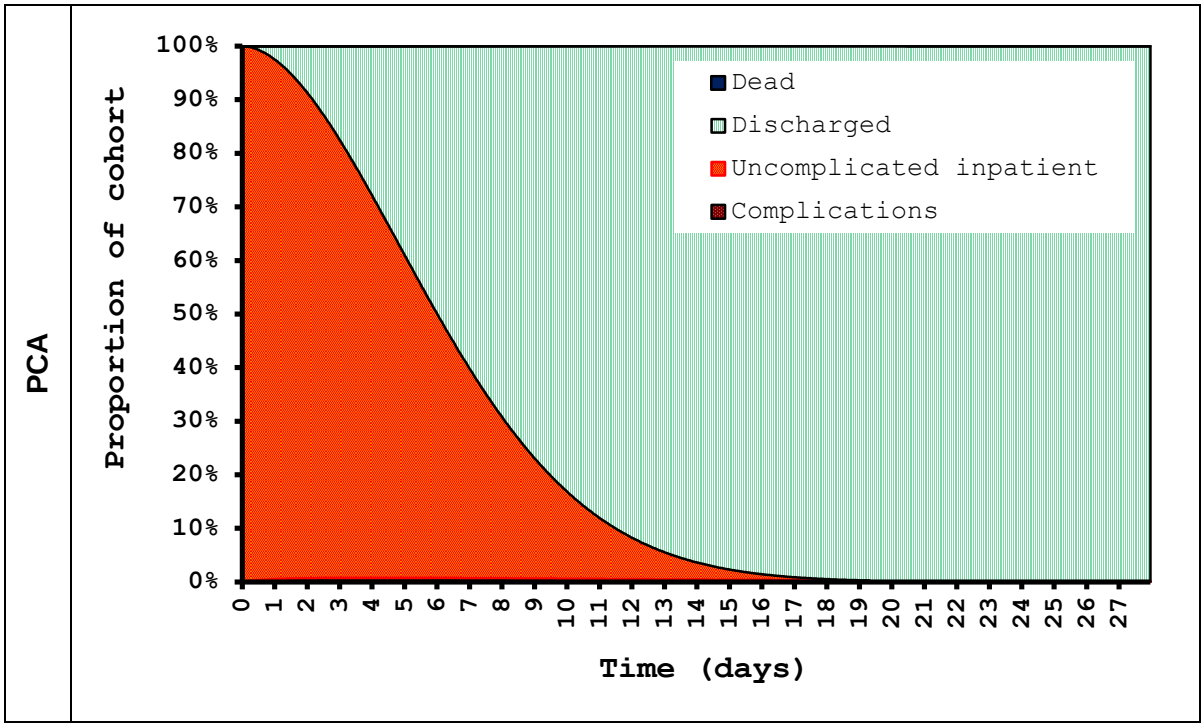
Figure 14: Modelled cohort composition – scenario 1A

In scenario 1A (figure 11), where LOS is independent of pain score and the likelihood of complication is derived as a function of baseline VAS, the model predicts that people with an uncomplicated acute episode remain on admission for as long as 3 weeks in the C-IV group compared to 2 weeks in the PCA group. Complication rates in both arms remain the same but the

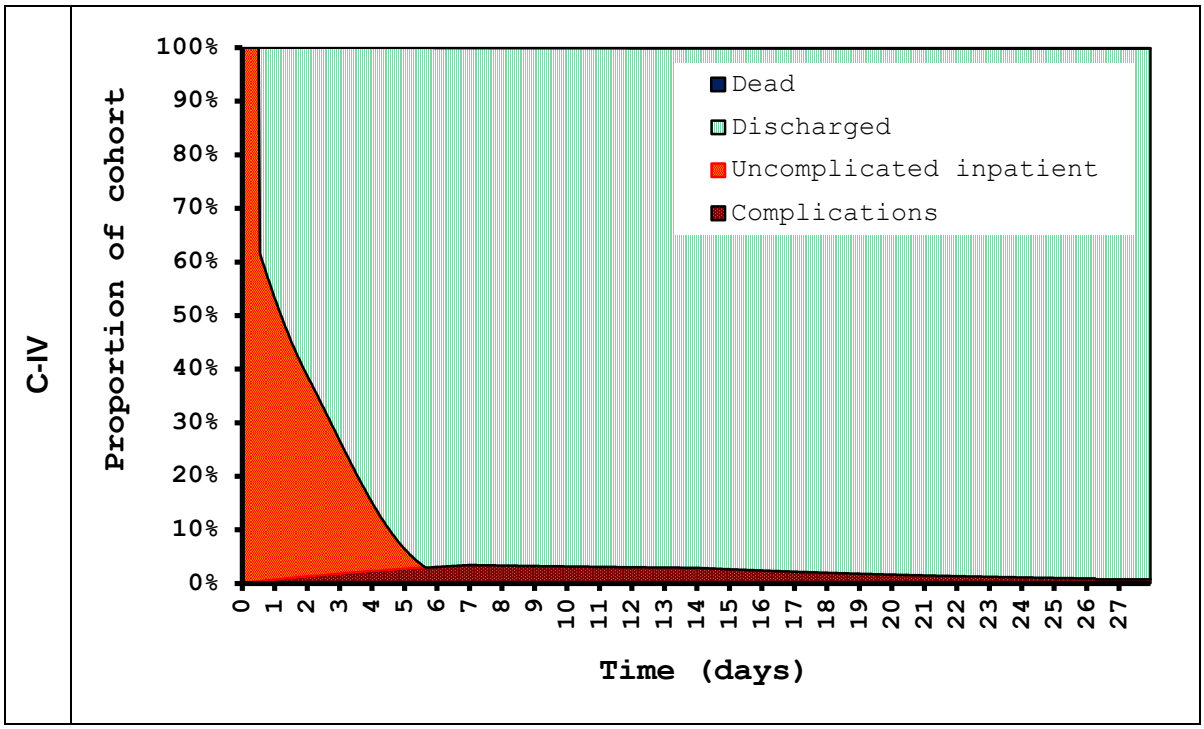
point beyond which all remaining inpatients are those who have incurred a complication is about 5 days shorter in the PCA arm than in the C-IV arm. This is reflective of the shorter length of hospital stay associated with the use of PCA in this scenario of the model.

A similar trend is observed in scenario 1B (figure 12), in which the likelihood of complications was assumed to be a dynamic function of pain. In this instance, the overall complication rates are lower than those observed in scenario 1A and, in relative terms, there are fewer complications in the PCA arm. This is because pain-scores on admission are relatively low (VAS of 5) and decrease over time. Thus the longer people stay in hospital, the lower their pain score becomes and the lower the likelihood of complications (which are a dynamic function of pain in this scenario).





729 **Figure 15: Modelled cohort composition – scenario 1B**



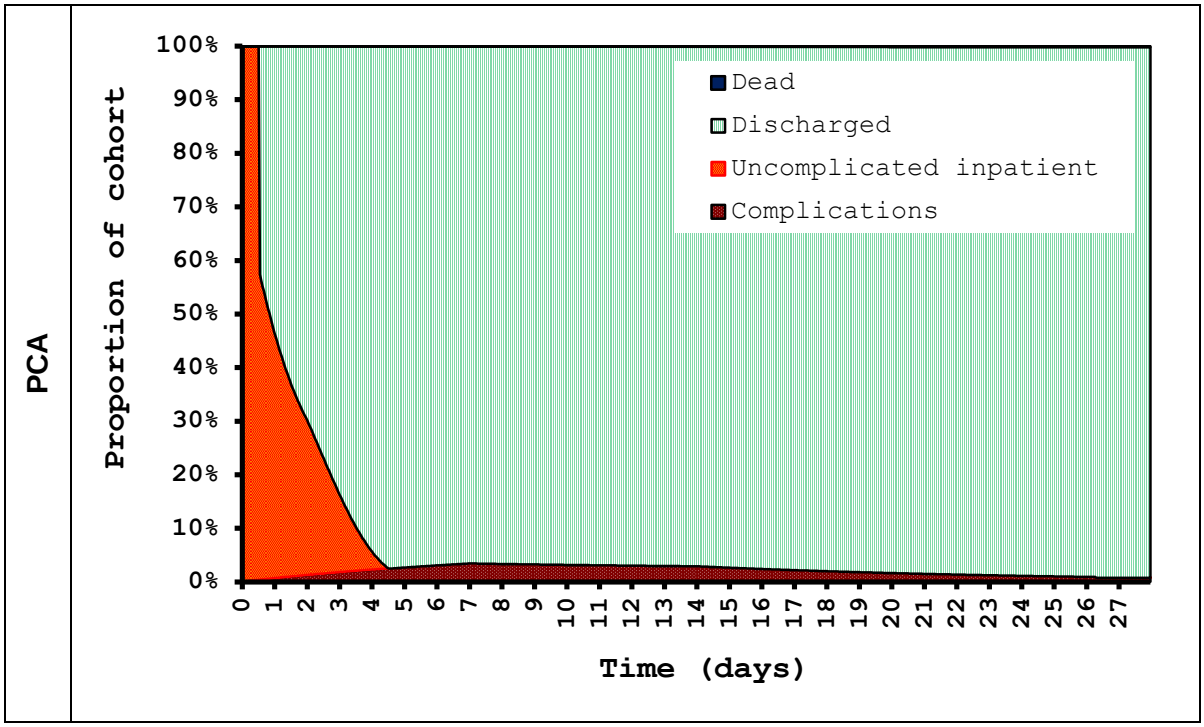


Figure 16: Modelled cohort composition – scenario 2A

In both scenarios 2A and 2B (figures 12 and 13) – where LOS is driven by pain – the model also shows that PCA provides quicker pain relief and on average LOS is reduced by about 1 day compared to C-IV. The complication rates in scenario 2A are the same in both PCA and C-IV arms, and are noticeably higher than those in scenario 2B for the same reasons as in 1A and 1B above.

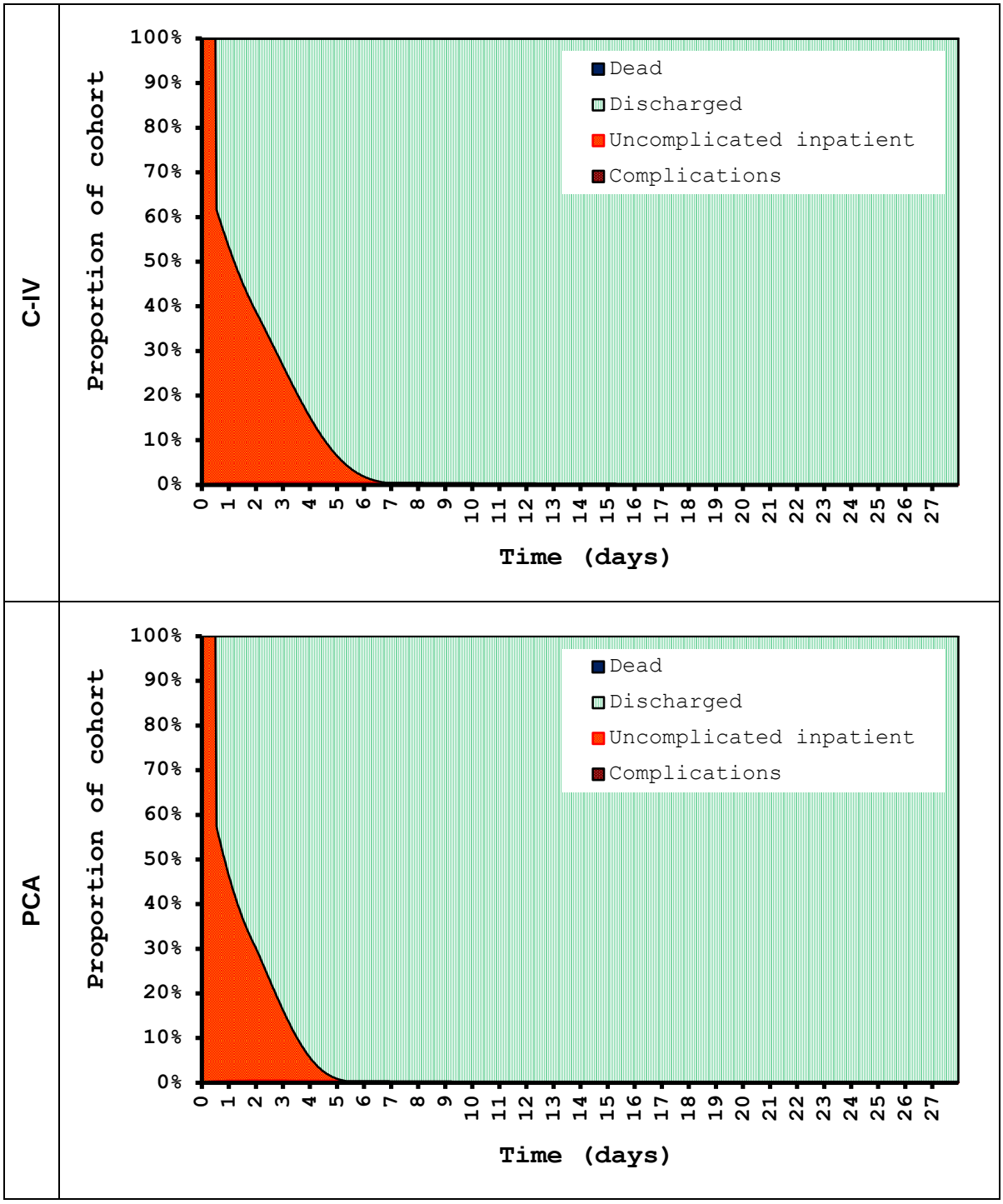


Figure 17: Modelled cohort composition – scenario 2B

Cost–utility results: deterministic base case

In its base case, the economic model suggests that PCA is likely to be preferred to C-IV for managing pain during an acute painful sickle cell episode.

The results show that providing PCA is associated with very small health gains of between 0.002 to 0.003 QALYs (depending on the assumption adopted) per person but with average cost savings of £170 to £1329 per person when compared with C-IV. These cost savings are primarily as a result of reduction in length of hospital stay in all 4 scenarios and also a reduction in complication rates in scenarios 1B and 2B.

Therefore C-IV is dominated by (that is, is more expensive and less effective than) PCA in all 4 scenarios and so would not be a viable option in an incremental analysis. This means that PCA would reflect excellent value for money irrespective of what the threshold for a QALY gain is set at.

The results also show that, compared with C-IV, PCA has a positive incremental net monetary benefit (INMB) at conventional thresholds per QALY in all four scenarios, likewise implying that PCA represents an effective use of NHS resources.

The deterministic base-case results (Table 95) are very similar the probabilistic results (Table 97Table 96), indicating that the expected costs and QALYs are close to a linear function of the parameter values.

Table 95: Deterministic base-case cost–utility results

	Independent LOS						VAS-dependent LOS					
	Single complication rate (Scenario 1A)			Dynamic Complications (Scenario 1B)			Single complication rate (Scenario 2A)			Dynamic Complications (Scenario 2B)		
	C-IV	PCA	Δ	C-IV	PCA	Δ	C-IV	PCA	Δ	C-IV	PCA	Δ
Costs												
Acute episode:												
Inpatient care	£4,301	£3,043	-£1,258	£4,270	£2,974	-£1,296	£1,106	£929	-£178	£909	£712	-£197
PCA consumables	£0.00	£32.14	£32.14	£0.00	£31.54	£31.54	£0.00	£15.78	£15.78	£0.00	£13.87	£13.87
Morphine	£26.00	£3.30	-£22.70	£26.00	£3.30	-£22.70	£27.00	£18.84	-£8.16	£27.00	£18.84	-£8.16
Subtotal	£4,327	£3,078	-£1,249	£4,296	£3,009	-£1,287	£1,133	£963	-£170	£936	£745	-£191
Long-term costs:												
Stroke rehabilitation	£532.69	£532.69	£0.00	£134.29	£92.52	-£41.76	£532.69	£532.69	£0.00	£58.46	£44.63	-£13.83
Total	£4,860	£3,611	-£1,249	£4,431	£3,102	-£1,329	£1,666	£1,496	-£170	£994	£789	-£205
Effects												
Episodes of ACS	6.26%	6.26%		1.58%	1.09%		6.26%	6.26%		0.69%	0.52%	
Strokes	0.23%	0.23%		0.06%	0.04%		0.23%	0.23%		0.03%	0.02%	
Deaths	0.18%	0.18%		0.05%	0.03%		0.18%	0.18%		0.02%	0.02%	
Mean LOS (days)	9.440	6.678		9.372	6.528		2.428	2.038		1.994	1.562	
QALYs:												
Acute episode	0.062	0.063	0.002	0.062	0.064	0.002	0.062	0.063	0.002	0.063	0.064	0.002
Subsequent LE (discounted)	13.029	13.029	0.000	13.040	13.042	0.001	13.029	13.029	0.000	13.043	13.043	0.000
Total	**13.090**	**13.092**	**0.002**	**13.103**	**13.106**	**0.003**	**13.090**	**13.092**	**0.002**	**13.105**	**13.107**	**0.002**
ICER	**PCA dominates**			**PCA dominates**			**PCA dominates**			**PCA dominates**		
Incremental NMB:												
WTP=£20, 000 / QALY	£1,282.04			£1,388.03			£202.27			£245.81		
WTP=£30, 000 / QALY	£1,298.60			£1,417.62			£218.43			£266.28		

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Sensitivity analysis

One-way deterministic sensitivity analysis

One-way sensitivity analyses were conducted to illustrate which model inputs have the greatest impact on the cost–utility results, and also to show areas where further exploration of uncertainty may be instructive. Figure 18 and Figure 19 show the impact on model results of each change in single parameter values (that is, changing the value of a single parameter while keeping all other parameters constant).Results are shown for scenarios 1A and 2A only, in terms of INMB assuming a threshold value of £20,000 per QALY gained. The B scenarios are extremely similar to the A scenarios, so have not been shown.

For scenarios 1A and 1B (Figure 18), the model appears to be sensitive to changes in the median length of stay and, to a lesser extent, the relative reduction in VAS, the daily cost of inpatient care and the mean VAS at baseline. However, it appears that none of the changes in these parameters affected the cost–utility conclusions (that is, INMB remained positive with all values tested). The model was not sensitive to all other parameters.

In scenarios 2A and 2B (Figure 19), the model was most sensitive to the relative reduction in VAS and, to a lesser extent, the mean VAS at baseline and VAS threshold for discharge. The cost–utility conclusions were altered when parameters for the relative reduction in VAS were changed to low values (in the PCA arm) or high values (in the C-IV arm). The model was not sensitive to all other parameters.

In all scenarios, adopting a linear rather than polynomial fit to characterise the functional relationship between VAS score and health-state utility (see ‘Health-related quality of life’, under ‘Generic model parameters’, above) had a trivial effect on results.

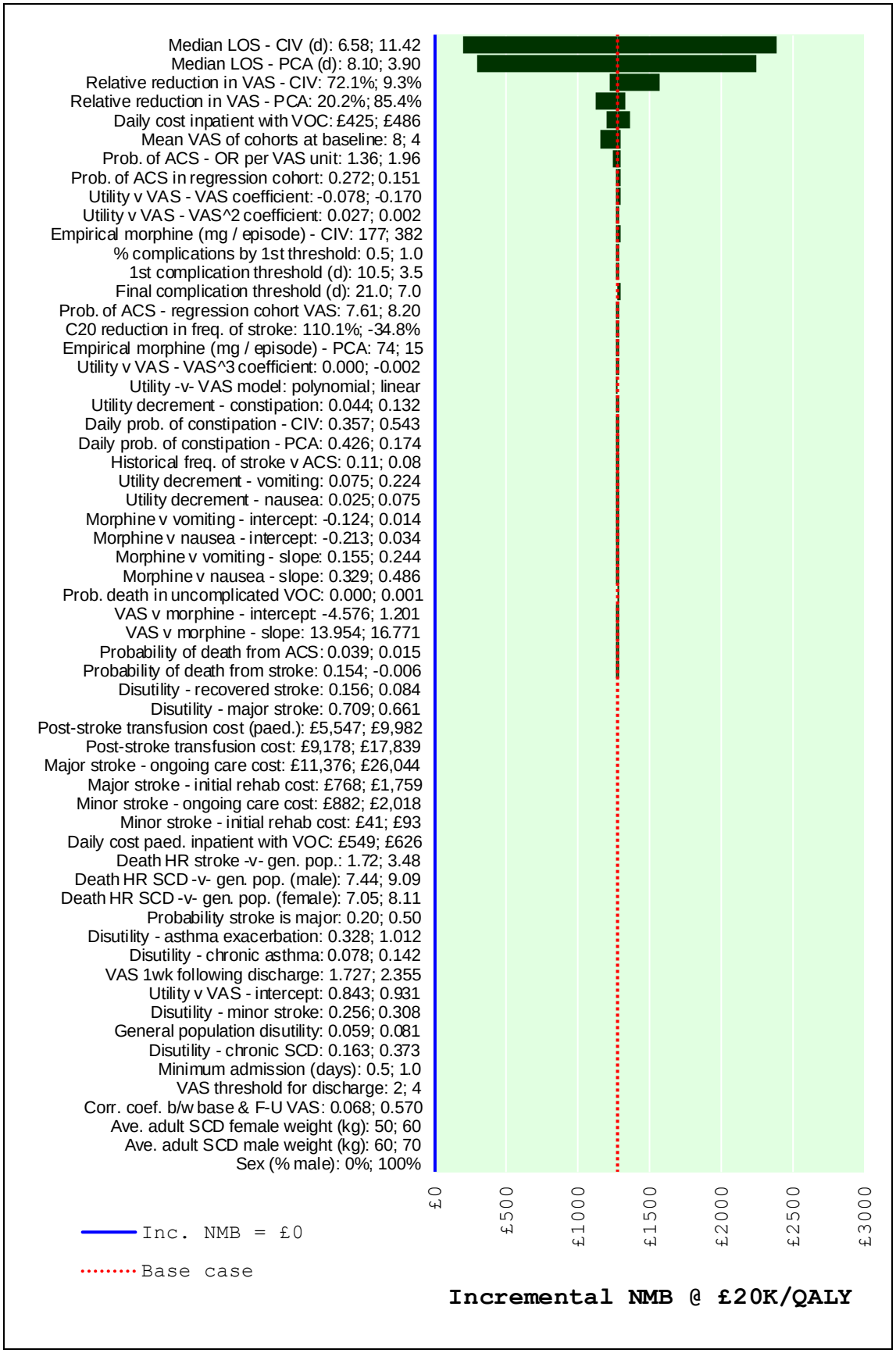

Figure 18: One-way deterministic sensitivity analysis – tornado plot (scenario 1A)

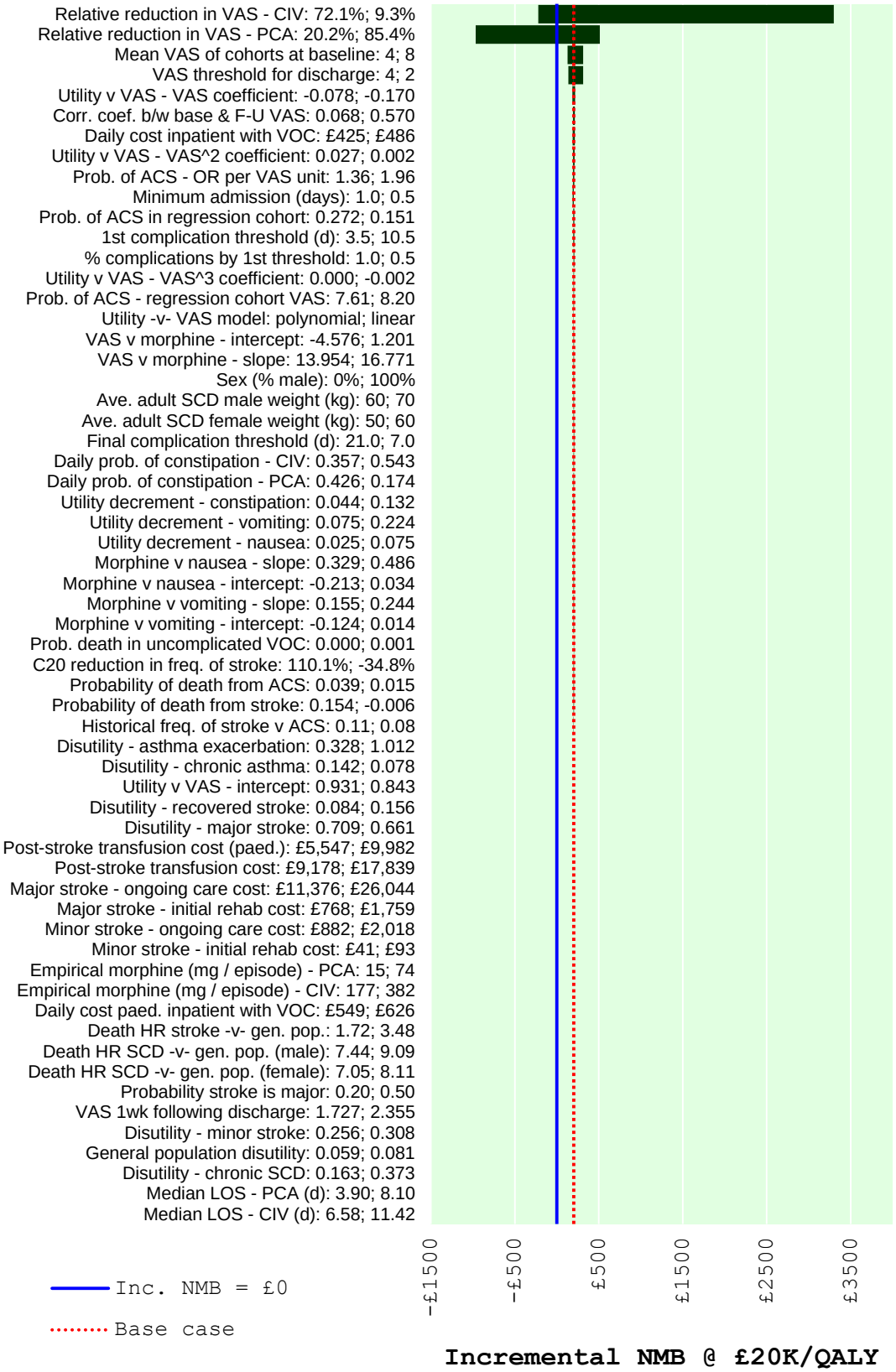

Figure 19: One-way deterministic sensitivity analysis – tornado plot (scenario 2A)

Threshold Analysis

Threshold analysis was conducted on the parameters which had the potential to affect cost–utility conclusions (that is, the relative reduction in VAS in scenarios 2A and B), with the aim of identifying the point at which those conclusions would be altered (Figure 20). The assumed value of each parameter was varied over a broad range, assuming a conventional threshold of £20,000 per QALY. These analyses suggest that providing PCA remains the most cost-effective option with a few exceptions:

- C-IV would become the preferred option if
  - the relative reduction in VAS for people on C-IV exceeds 51.7% (base case: 40.7%), or
  - the relative reduction in VAS for people on PCA drops below 41.5% (base case: 52.8%)

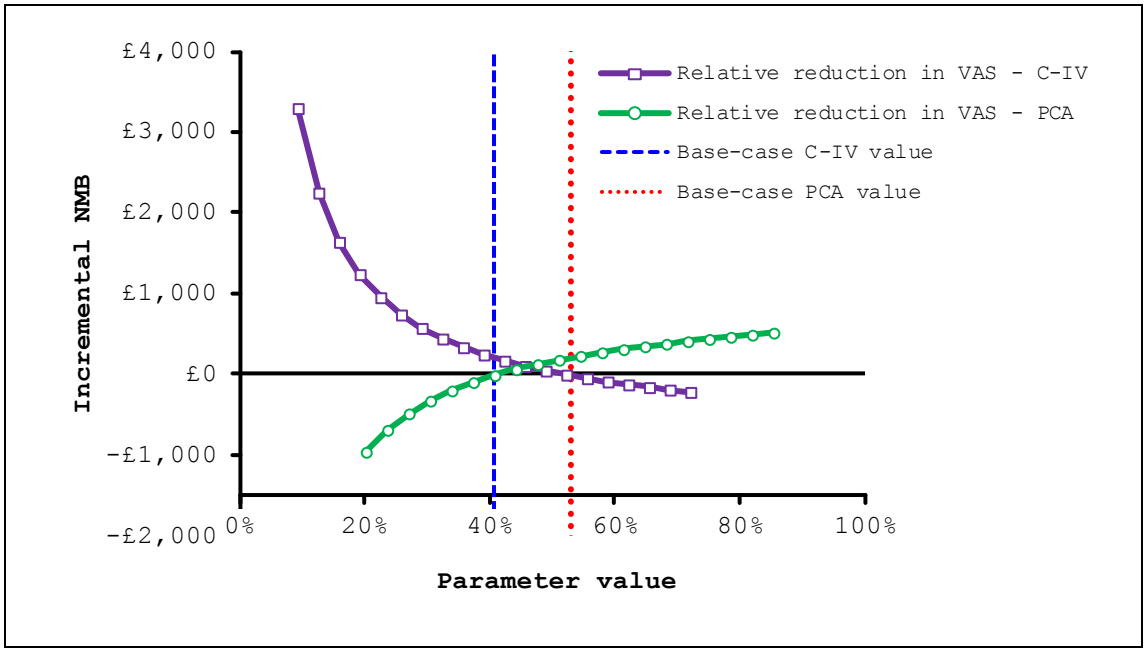

Figure 20: Threshold analyses: relative reduction in VAS (PCA and C-IV); model scenario 2A

It may be noticed that, in each analysis, the critical threshold value in one treatment arm is close to the base-case parameter for the other arm. This is a predictable finding: it is equivalent to saying that the comparator with the superior VAS reduction will be the option with a favourable cost–utility profile.

Again, this is unsurprising since, in scenarios 2A and 2B of the model, all critical cost and QALY outputs are dependent on modelled VAS.

Probabilistic sensitivity analysis (PSA)

The PSA relied on Monte-Carlo simulations with parameter values randomly sampled from distributions reflecting uncertainty around their true values. We performed 10,000 simulations per scenario – a total of 40,000 iterations overall. Table 96 Summarises mean values from these simulations. Figure 21(a) shows the joint distribution of incremental costs and incremental QALYs on the cost–utility plane. Figure 21(b) presents a cost-effectiveness acceptability curve (CEAC), indicating the probability that, when compared with C-IV, PCA provides best value for money (highest net benefit), given different ceiling thresholds of up to £100,000 per QALY gained.

Scenario 1A and 1B

In Figure 21(a), the results from scenario 1A and 1B spread to all four quadrants of the cost–utility plane. However, in around 72% of simulations, PCA was associated with greater QALY gains than C-IV (data points appear on the right-hand side of the *y*-axis) and, in over 95% of simulations, PCA was associated with lower costs than C-IV (data points below the *x*-axis).

Figure 21(b) suggests that results are entirely unrelated to the assumed ceiling value per QALY gained. PCA would have more than a nine-in-ten chance of being cost effective irrespective of the value that society is assumed to place on each QALY gained.

Scenario 2A and 2B

In Figure 21(a), the joint distribution of results from scenario 2A and 2B shows an obvious correlation between costs and QALYs. In simulations in which PCA is estimated to provide less health gain than C-IV (negative incremental QALYs), it is also highly likely to be associated with increased costs. Conversely, those simulations in which PCA appears more effective are also those in which it appears less expensive. This is a predictable finding: as

demonstrated in one-way sensitivity analysis (see Figure 19, above), the model is almost entirely driven by VAS in scenarios 2A and 2B. Accordingly, it is to be expected that probabilistic results are very heavily dependent on randomly assigned VAS values: when VAS decline is sampled to be superior in PCA than C-IV, it will dominate C-IV and *vice versa*. However, because the distributions from which the model samples favour PCA in the majority of cases, there is a preponderance of data points in the South-East (dominant) quadrant of the cost–utility plane. Figure 21(b) suggests that PCA has a little less than a seven-in-ten chance of being cost effective irrespective of the value that society is assumed to place on each QALY gained.

Table 96: PCA -v- C-IV: summary of cost–utility results (mean estimates) from probabilistic sensitivity analysis

	Independent LOS		VAS-dependent LOS		All four scenarios combined
	Single complication rate (Scenario 1A)	Dynamic Complications (Scenario 1B)	Single complication rate (Scenario 2A)	Dynamic Complications (Scenario 2B)	
C−IV					
Costs (95%CI)	£4515 (£3346, £5743)	£4367 (£3200, £5601)	£1511 (£759, £3260)	£1167 (£528, £2983)	£2890 (£623, £5491)
QALYs (95%CI)	12.986 (10.642, 14.749)	13.027 (10.705, 14.786)	13.010 (10.732, 14.768)	12.990 (10.646, 14.780)	13.003 (10.678, 14.773)
PCA					
Costs (95%CI)	£3261 (£2217, £4356)	£3065 (£1992, £4167)	£1233 (£675, £2321)	£860 (£470, £1868)	£2105 (£537, £4100)
QALYs (95%CI)	12.989 (10.643, 14.752)	13.030 (10.710, 14.791)	13.012 (10.738, 14.774)	12.992 (10.651, 14.779)	13.006 (10.679, 14.775)
Incremental					
Costs (95%CI)	−£1254 (−£2722, £191)	−£1302 (−£2902, £232)	−£278 (−£2019, £818)	−£308 (−£2241, £934)	−£786 (−£2691, £641)
QALYs (95%CI)	0.002 (−0.006, 0.014)	0.003 (−0.007, 0.015)	0.002 (−0.006, 0.013)	0.002 (−0.007, 0.015)	0.002 (−0.007, 0.014)
ICER	PCA dominates	PCA dominates	PCA dominates	PCA dominates	PCA dominates
Incremental NMB:					
WTP=£20, 000 / QALY (95%CI)	£1299 (−£163, £2778)	£1358 (−£207, £2984)	£322 (−£943, £2293)	£355 (−£1073, £2519)	£833 (−£723, £2786)
WTP=£30, 000 / QALY (95%CI)	£1322 (−£153, £2818)	£1386 (−£186, £3024)	£344 (−£1005, £2428)	£378 (−£1141, £2650)	£857 (−£765, £2851)
Probability cost effective:					
WTP=£20, 000 / QALY	0.961	0.956	0.690	0.686	0.823
WTP=£30, 000 / QALY	0.962	0.957	0.691	0.686	0.824

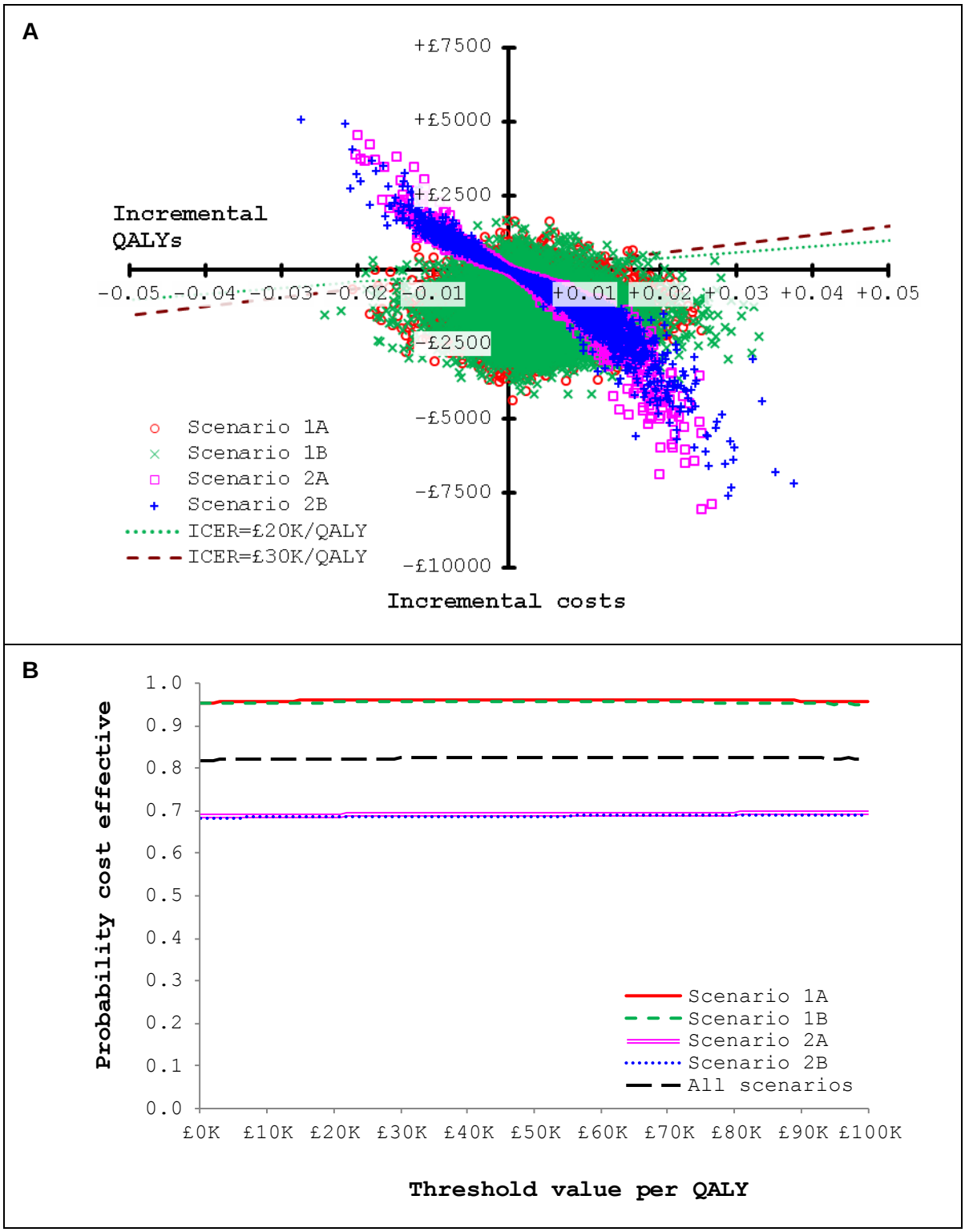

Figure 21: Probabilistic sensitivity analysis: cost–utility scatterplot (A) and cost-effectiveness acceptability curve (B)

Conclusion

Overall, the results substantiate those produced in the deterministic analysis. In all four scenarios, the CEAC produced almost entirely horizontal lines – consistent with dominance (that is, if we estimate that a technology is cheaper and more effective than its comparator, the amount we would be prepared to pay for health gains is irrelevant). Considering all four scenarios combined, PCA can be concluded as being cost effective with about 82% certainty when compared with C-IV, irrespective of the value that society is assumed to place on each QALY gained (Figure 21[b]).

Children

It was not possible to identify values that characterise the effects of PCA and C-IV in paediatric populations, so we cannot estimate the cost effectiveness of the competing alternatives in a robust manner.

However, we performed an exploratory analysis in which a cohort with a mean baseline age of 5 was simulated, using effectiveness parameters from the adult evidence-base. In this analysis, the number of model parameters that properly reflect paediatric practice is limited: the (longer) life expectancy of the population and its (higher) daily inpatient costs are incorporated. Medication costs are also reduced, where these are provided on a per-kilogram dose.

The results of this analysis are tabulated inTable 97. Although **absolute** model outputs must be seen as exploratory, it is worthwhile to note that the **relative** magnitude of benefit expected in this population is somewhat higher – both in terms of QALYs gained and costs saved with PCA compared with C-IV. This is because the additional life expectancy of a younger cohort leads to greater gains when mortality and morbidity is avoided, and daily inpatient costs are higher for children; therefore, reduced requirement for hospitalisation results in greater cost savings.

887 **Table 97: Scenario analysis: results in children (mean baseline age 5 years)**

	Independent LOS						VAS-dependent LOS					
	Single complication rate (Scenario 1A)			Dynamic Complications (Scenario 1B)			Single complication rate (Scenario 2A)			Dynamic Complications (Scenario 2B)		
	C-IV	PCA	Δ	C-IV	PCA	Δ	C-IV	PCA	Δ	C-IV	PCA	Δ
Costs												
Acute episode:												
Inpatient care	£5,556	£3,930	-£1,625	£5,516	£3,842	-£1,674	£1,429	£1,199	-£229	£1,174	£919	-£254
PCA consumables	£0.00	£32.14	£32.14	£0.00	£31.54	£31.54	£0.00	£15.78	£15.78	£0.00	£13.87	£13.87
Morphine	£26.00	£3.30	-£22.70	£26.00	£3.30	-£22.70	£7.11	£4.96	-£2.15	£7.11	£4.96	-£2.15
Subtotal	£5,582	£3,966	-£1,616	£5,542	£3,877	-£1,665	£1,436	£1,220	-£216	£1,181	£938	-£242
Long-term costs:												
Stroke rehabilitation	£697.37	£697.37	£0.00	£175.80	£121.12	-£54.68	£697.37	£697.37	£0.00	£76.53	£58.43	-£18.11
Total	**£6,279**	**£4,663**	**-£1,616**	**£5,718**	**£3,998**	**-£1,720**	**£2,133**	**£1,918**	**-£216**	**£1,257**	**£997**	**-£260**
Effects												
Episodes of ACS	6.26%	6.26%		1.58%	1.09%		6.26%	6.26%		0.69%	0.52%	
Strokes	0.23%	0.23%		0.06%	0.04%		0.23%	0.23%		0.03%	0.02%	
Deaths	0.18%	0.18%		0.05%	0.03%		0.18%	0.18%		0.02%	0.02%	
Mean LOS (days)	9.440	6.678		9.372	6.528		2.428	2.038		1.994	1.562	
QALYs:												
Acute episode	0.062	0.063	0.002	0.062	0.064	0.002	0.062	0.063	0.002	0.063	0.064	0.002
Subsequent LE (discounted)	17.569	17.569	0.000	17.583	17.585	0.001	17.569	17.569	0.000	17.586	17.586	0.000
Total	**17.631**	**17.633**	**0.002**	**17.646**	**17.649**	**0.003**	**17.631**	**17.633**	**0.002**	**17.648**	**17.651**	**0.002**
ICER	**PCA dominates**			**PCA dominates**			**PCA dominates**			**PCA dominates**		
Incremental NMB:												
WTP=£20, 000 / QALY	£1,649.02			£1,783.43			£248.05			£302.95		
WTP=£30, 000 / QALY	£1,665.59			£1,815.29			£264.21			£324.18		

Results: low-molecular-weight heparin

Model outputs

The model simulated four different scenarios, as in the previous analysis of PCA:

- **1A** Independent LOS with a fixed complication rate at baseline (Figure 24)
- **1B** Independent LOS with a dynamic complication rate (Figure 25)
- **2A** Pain predicts LOS with a fixed complication rate at baseline (Figure 26)
- **2B** Pain predicts LOS with a dynamic complication rate (Figure 27)

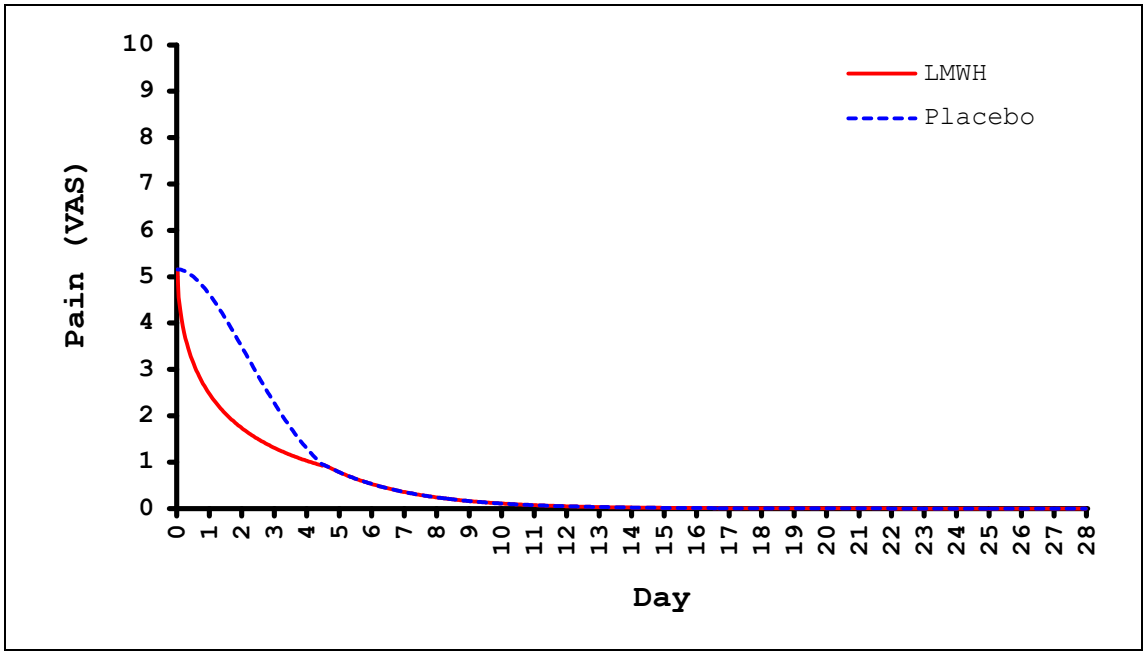

Figure 22: Modelled average pain score over time for people taking LMWH or placebo (applies to all scenarios)

Model outputs reflect the input data suggesting that, on average, patients who receive a therapeutic dose of LMWH in addition to standard care experience considerably less pain in the first few days of treatment than those who do not (Figure 22). The effect of LMWH becomes apparent from the first day on admission but, as per the base-case assumption that the two arms follow the same VAS profile after the initial treatment period (see Parameters particular to LMWH model, above), the advantage is limited to the first 4.5 days of

treatment only. This can be seen in (Figures 22 and 23). The same VAS profile is adopted in all four scenarios.

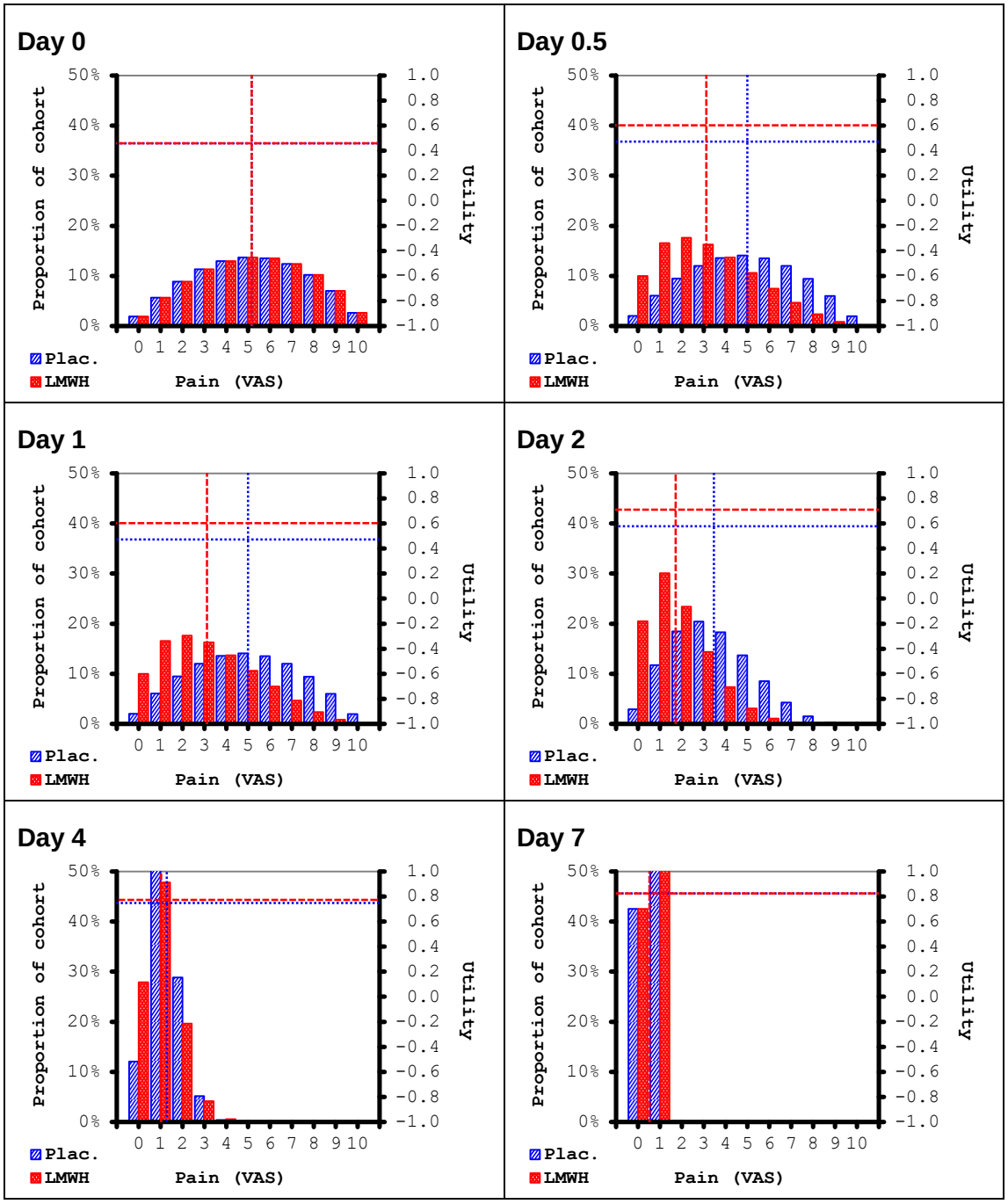

Figure 23: Modelled distribution of pain scores over time for people taking LMWH or placebo (applies to all scenarios)

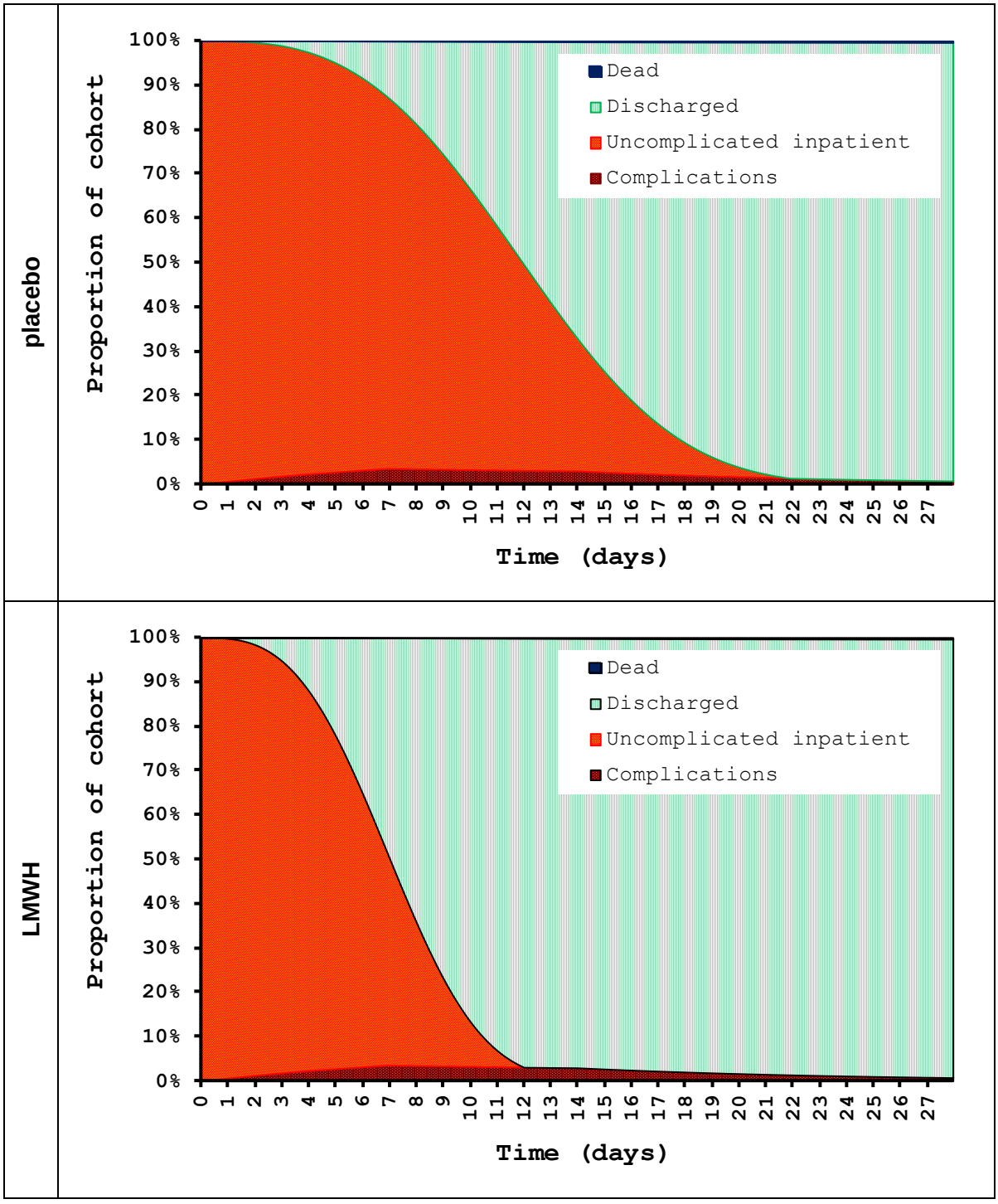

Figure 24: Modelled cohort composition – scenario 1A

In scenario 1A (Figure 24), where LOS is independent of pain score and the likelihood of complication is derived as a function of baseline pain score, the model predicts that people with an uncomplicated acute episode remain on admission for as long as 22 days in the standard care (placebo) group,

compared with a maximum of about 12 days in the LMWH group. Complication rates in both arms remain the same but the point beyond which all remaining inpatients are assumed to have incurred a complication is about 10 days shorter in the LMWH arm than in the standard care arm. This suggests that, on average, patients with an uncomplicated episode who have received LMWH will experience a shorter duration of hospital stay, compared with those who have not.

A similar trend is observed in scenario 1B (Figure 25), for which the likelihood of complications was assumed to be a dynamic function of modelled pain score. In this instance, there are fewer complications in the LMWH arm and, overall, the complications rates are much lower than those observed in scenario 1A. This is because pain-scores on admission are relatively low (VAS of 5) and decrease over time. Thus, the longer people stay in hospital, the lower their pain score becomes and the lower the likelihood of complications (which are a dynamic function of pain in this scenario).

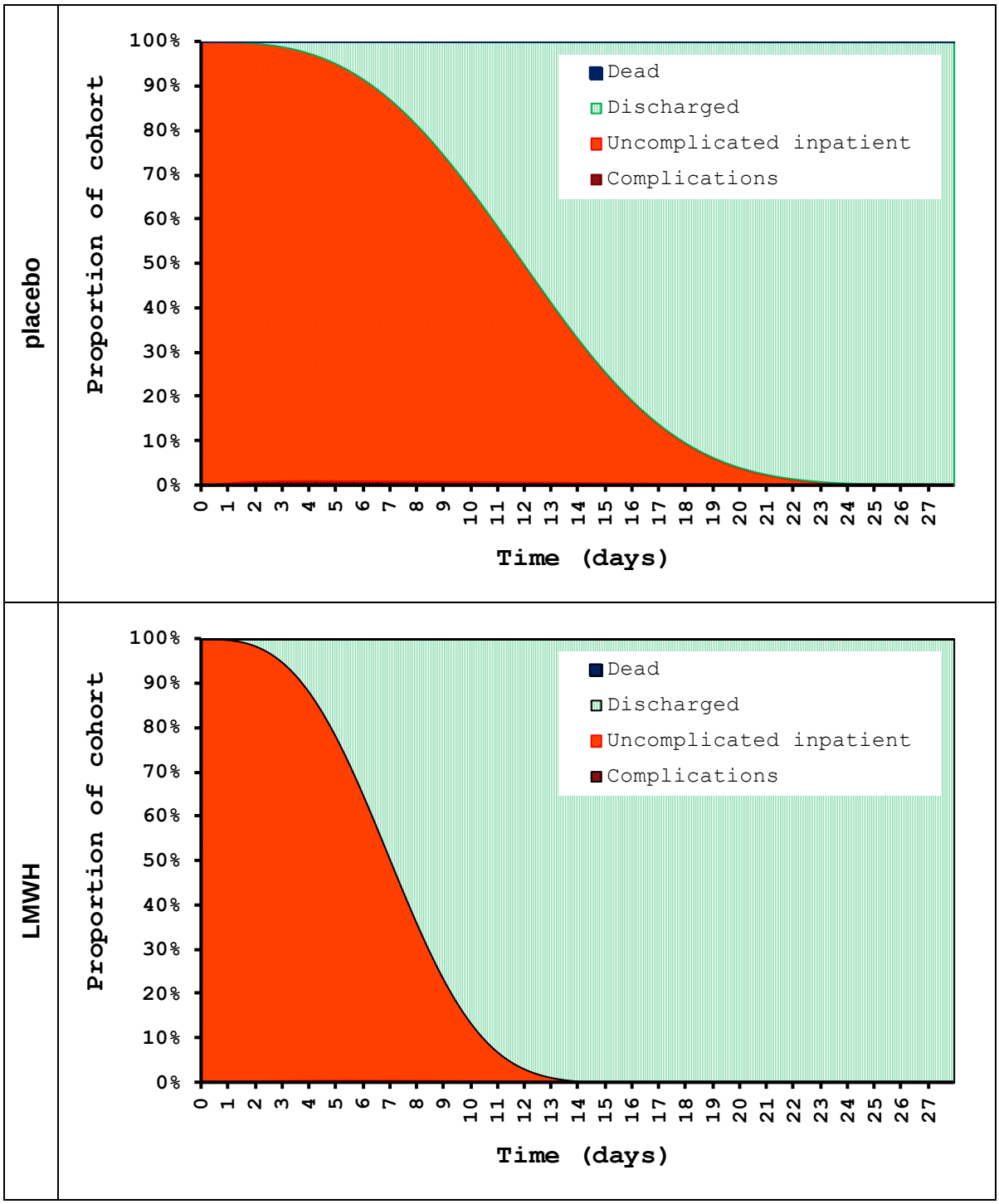

Figure 25: Modelled cohort composition – scenario 1B

In both scenarios 2A and 2B (Figures 26 and 27) – where LOS is driven by pain – the model also shows that LMWH provides quicker pain relief and on average LOS is reduced by about 1 day when compared with standard care. The complication rates in scenario 2A are the same in both LMWH and

standard-care arms and are significantly more than those in scenario 2B for the same reasons as in 1A and 1B above.

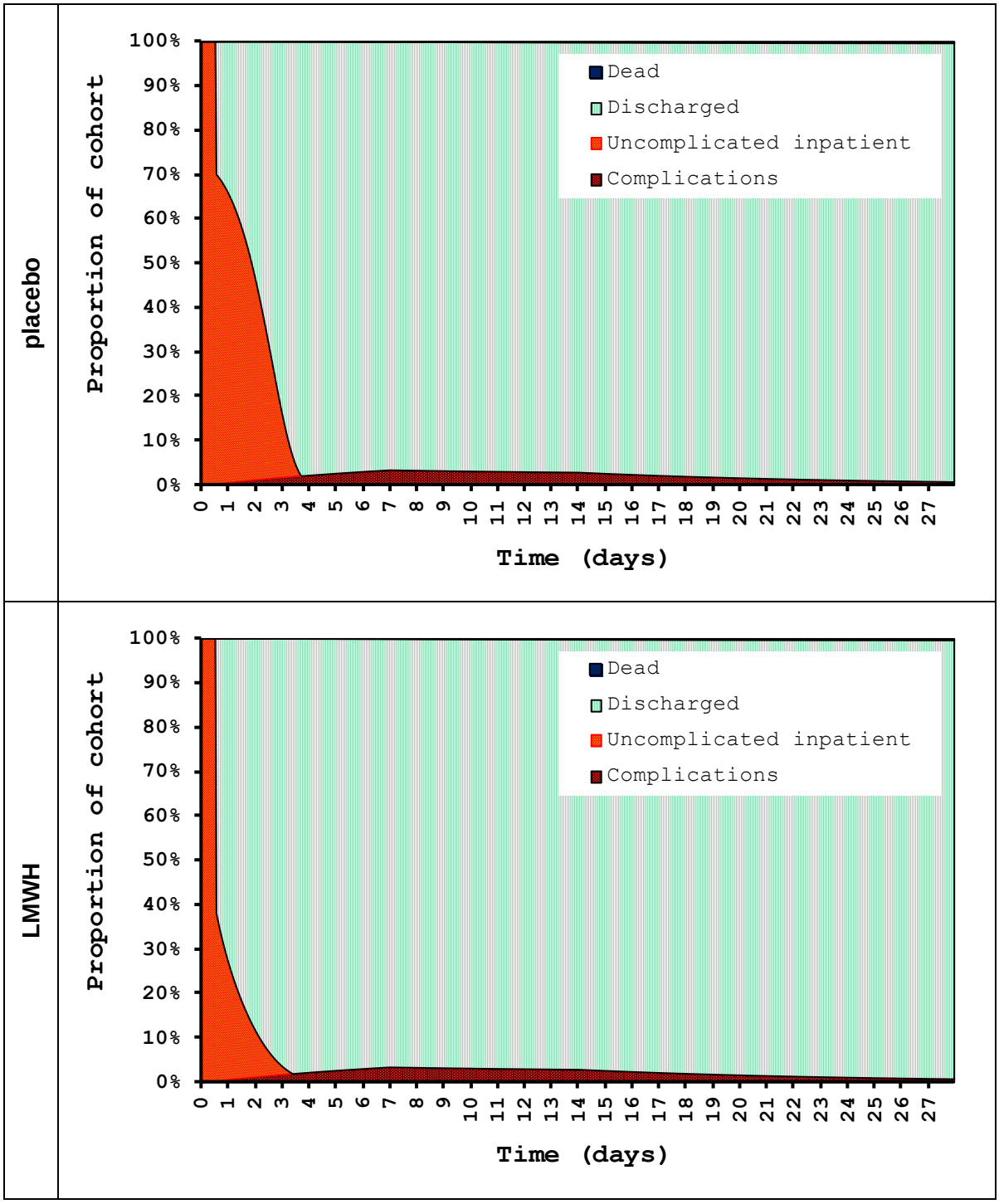

Figure 26: Modelled cohort composition – scenario 2A

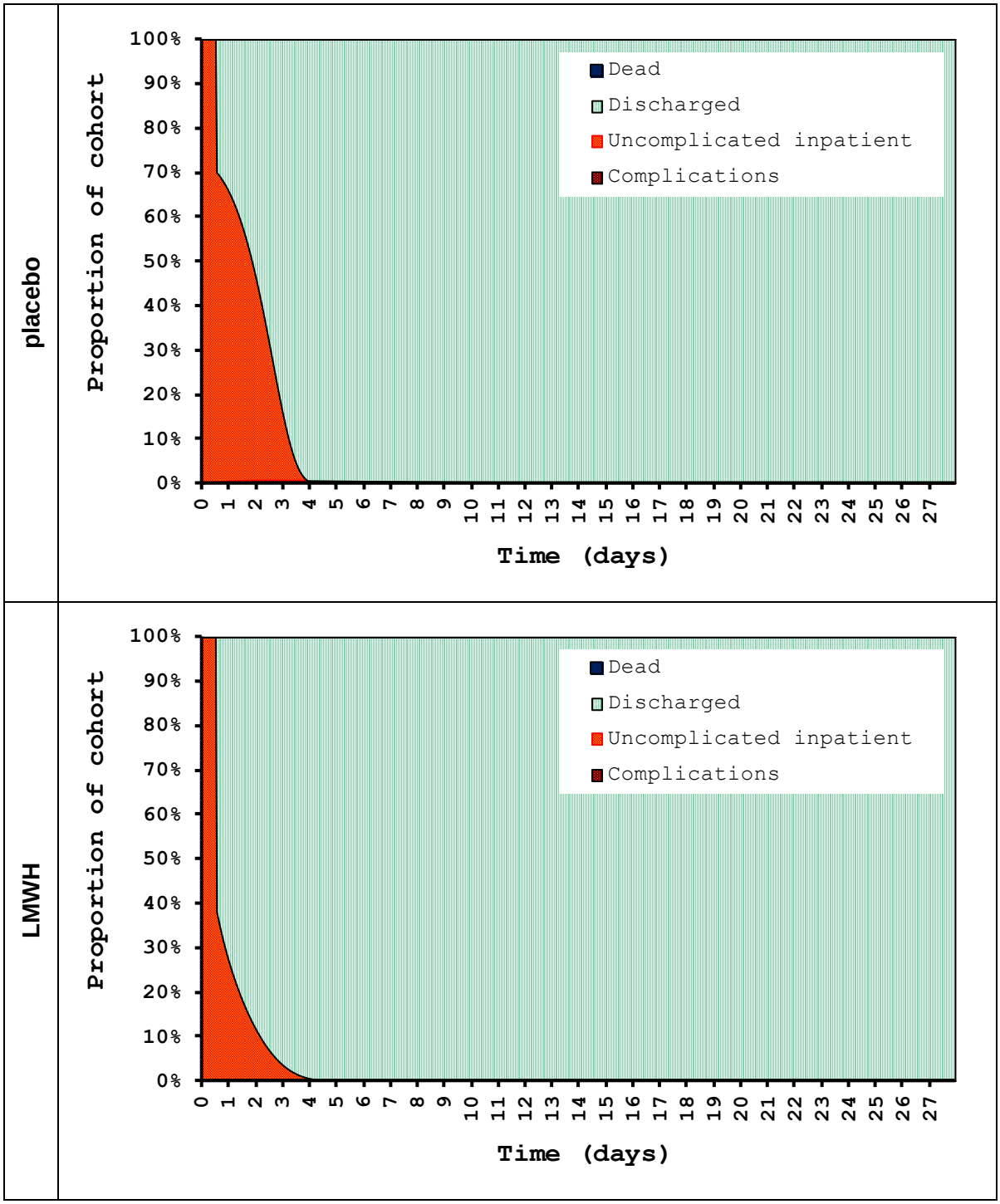

Figure 27: Modelled cohort composition – scenario 2B

Cost–utility results: deterministic base case

In its base case, the economic model suggests that LMWH – when used as an adjunct to standard care – is likely to be preferred to standard care alone for managing pain during an acute painful sickle cell episode.

The results show that, on average, providing LMWH is associated with modest health gains of between 0.001 to 0.004 QALYs (depending on the assumption adopted), which is equivalent to between 0.435 and 1.425 quality-adjusted life-**days** gained per person. Treatment is also associated with cost savings ranging from £373 to £2,218 per person when compared with standard care (Table 98). These cost savings are primarily as a result of reduction in length of hospital stay in all four scenarios, and also due a reduction in complication rates in scenarios 1B and 2B. Therefore, standard care is dominated by (that is, is more expensive and less effective than) LMWH in all four scenarios and so would not be considered a viable option in an incremental analysis. This means that LMWH is likely to be considered excellent value for money irrespective of what the threshold for a QALY gain is set at.

The results also show that, compared with standard care alone, LMWH has a positive INMB at conventional thresholds per QALY in all four scenarios, likewise implying that LMWH represents an effective use of NHS resources.

The deterministic base-case results (Table 98) are very similar the probabilistic results (Table 99), indicating that the expected costs and QALYs are close to a linear function of the parameter values.

Table 98: Deterministic base-case cost–utility results

	Independent LOS						VAS-dependent LOS					
	Single complication rate (Scenario 1A)			Dynamic Complications (Scenario 1B)			Single complication rate (Scenario 2A)			Dynamic Complications (Scenario 2B)		
	Placebo	LMWH	Δ	Placebo	LMWH	Δ	Placebo	LMWH	Δ	Placebo	LMWH	Δ
Costs												
Acute episode:												
Inpatient care	£5,524	£3,355	-£2,169	£5,507	£3,245	-£2,262	£1,067	£686	-£381	£853	£451	-£402
LMWH	£0.00	£68.27	£68.27	£0.00	£66.21	£66.21	£0.00	£17.05	£17.05	£0.00	£12.57	£12.57
Morphine	£26.00	£3.30	-£22.70	£26.00	£3.30	-£22.70	£23.16	£14.53	-£8.63	£23.16	£14.53	-£8.63
Subtotal	£5,550	£3,427	-£2,124	£5,533	£3,314	-£2,218	£1,090	£717	-£373	£876	£478	-£398
Long-term costs:												
Stroke rehabilitation	£532.69	£532.69	£0.00	£158.47	£72.15	-£86.31	£532.69	£532.69	£0.00	£72.96	£22.72	-£50.24
Total	£6,083	£3,959	-£2,124	£5,691	£3,386	-£2,305	£1,623	£1,250	-£373	£949	£500	-£448
Effects												
Episodes of ACS	6.26%	6.26%		1.86%	0.85%		6.26%	6.26%		0.86%	0.27%	
Strokes	0.23%	0.23%		0.07%	0.03%		0.23%	0.23%		0.03%	0.01%	
Deaths	0.18%	0.18%		0.06%	0.03%		0.18%	0.18%		0.03%	0.01%	
Mean LOS (days)	12.125	7.363		12.086	7.122		2.342	1.505		1.871	0.989	
QALYs:												
Acute episode	0.063	0.064	0.001	0.063	0.065	0.001	0.063	0.064	0.001	0.064	0.065	0.001
Subsequent LE (discounted)	13.029	13.029	0.000	13.040	13.042	0.003	13.029	13.029	0.000	13.042	13.044	0.001
Total	13.091	13.093	0.001	13.103	13.107	0.004	13.091	13.093	0.001	13.106	13.108	0.003
ICER	**LMWH dominates**			**LMWH dominates**			**LMWH dominates**			**LMWH dominates**		
Incremental NMB:												
WTP=£20, 000 / QALY	£2,148.15			£2,382.79			£396.66			£503.71		
WTP=£30, 000 / QALY	£2,160.27			£2,421.84			£408.58			£531.35		

ACS = acute chest syndrome; ICER = incremental cost-effectiveness ratio; LE = life expectancy; LMWH = low-molecular-weight heparin; LOS = length of (hospital) stay; NMB = net monetary benefit; QALY = quality-adjusted life-years; VAS = visual analogue scale

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Sensitivity analysis

One-way deterministic sensitivity analysis

One-way sensitivity analyses were conducted to illustrate which model inputs have the greatest impact on the cost–utility results, and also to show areas where further exploration of uncertainty may be instructive. Figures 28 and 29 show the impact on model results of each change in single parameter values (that is, changing the value of a single parameter while keeping all other parameters constant).Results are shown for scenarios 1A and 2A only, in terms of INMB assuming a threshold value of £20,000 per QALY gained. The B scenarios are extremely similar to the A scenarios, so have not been shown.

For scenarios 1A and 1B (Figure 28), the model appears to be most sensitive to changes in the parameters influencing modelled length of stay (particularly the shape parameter applied to both arms, as well as the mean LOS used for each arm). To a lesser extent, the model is also sensitive to mean VAS at baseline and the daily cost of inpatient care. However, it appears that none of the changes in these parameters affected the cost–utility conclusions (that is, INMB remained positive with all values tested). The model was not sensitive to all other parameters.

In scenarios 2A and 2B (Figure 29), the model was sensitive to all VAS parameters and, in particular, the threshold for shared VAS (that is, the point in the model at which separate VAS profiles for each arm are discontinued and a common distribution is assumed). This is the only parameter which might, on its own, have an important influence on cost–utility conclusions. INMB became negative – implying LMWH would not be considered a cost-effective strategy – when the threshold for shared VAS was set to 0. This relationship was explored further in threshold analysis; see below.

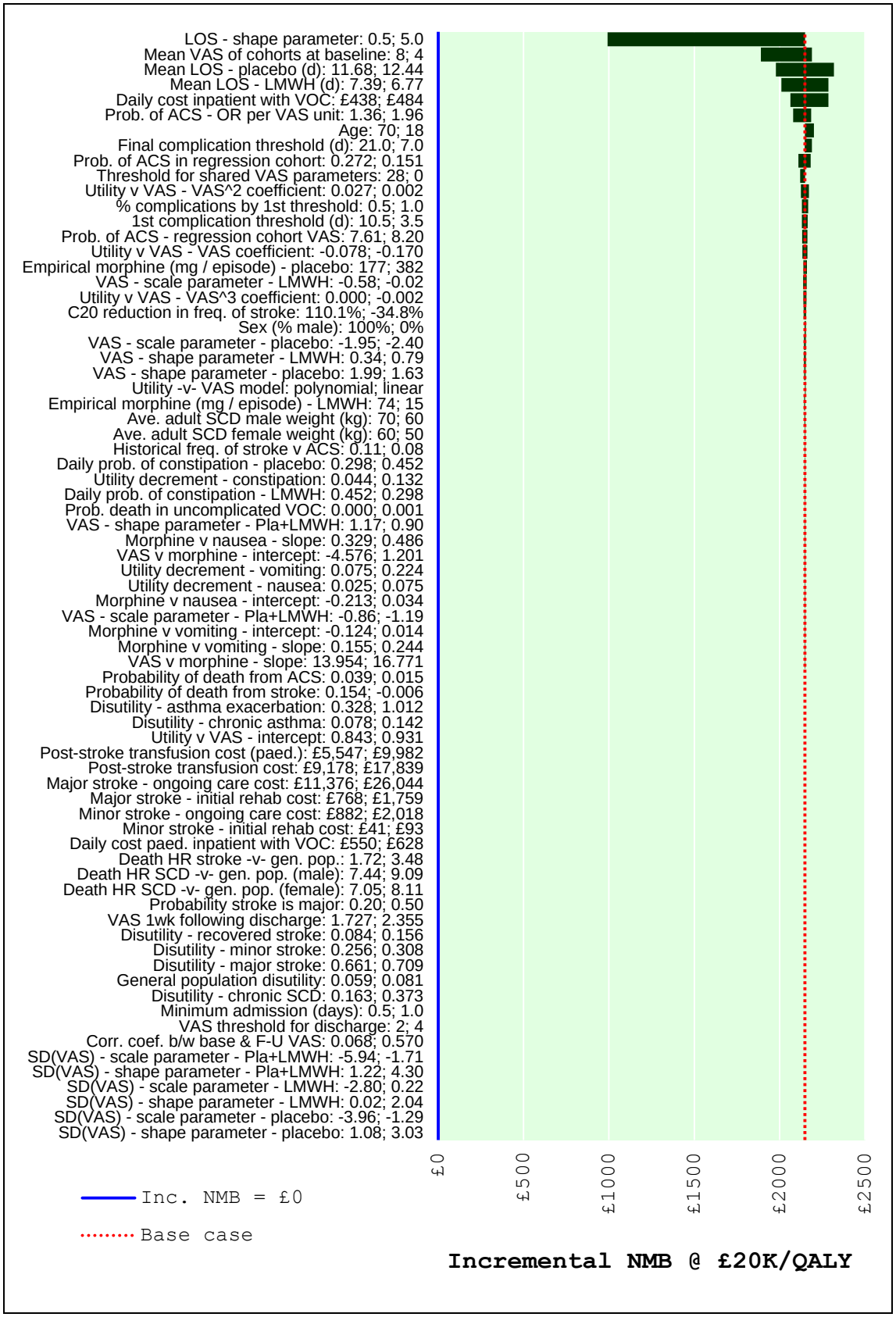

Figure 28: One-way deterministic sensitivity analysis – tornado plot (scenario 1A)

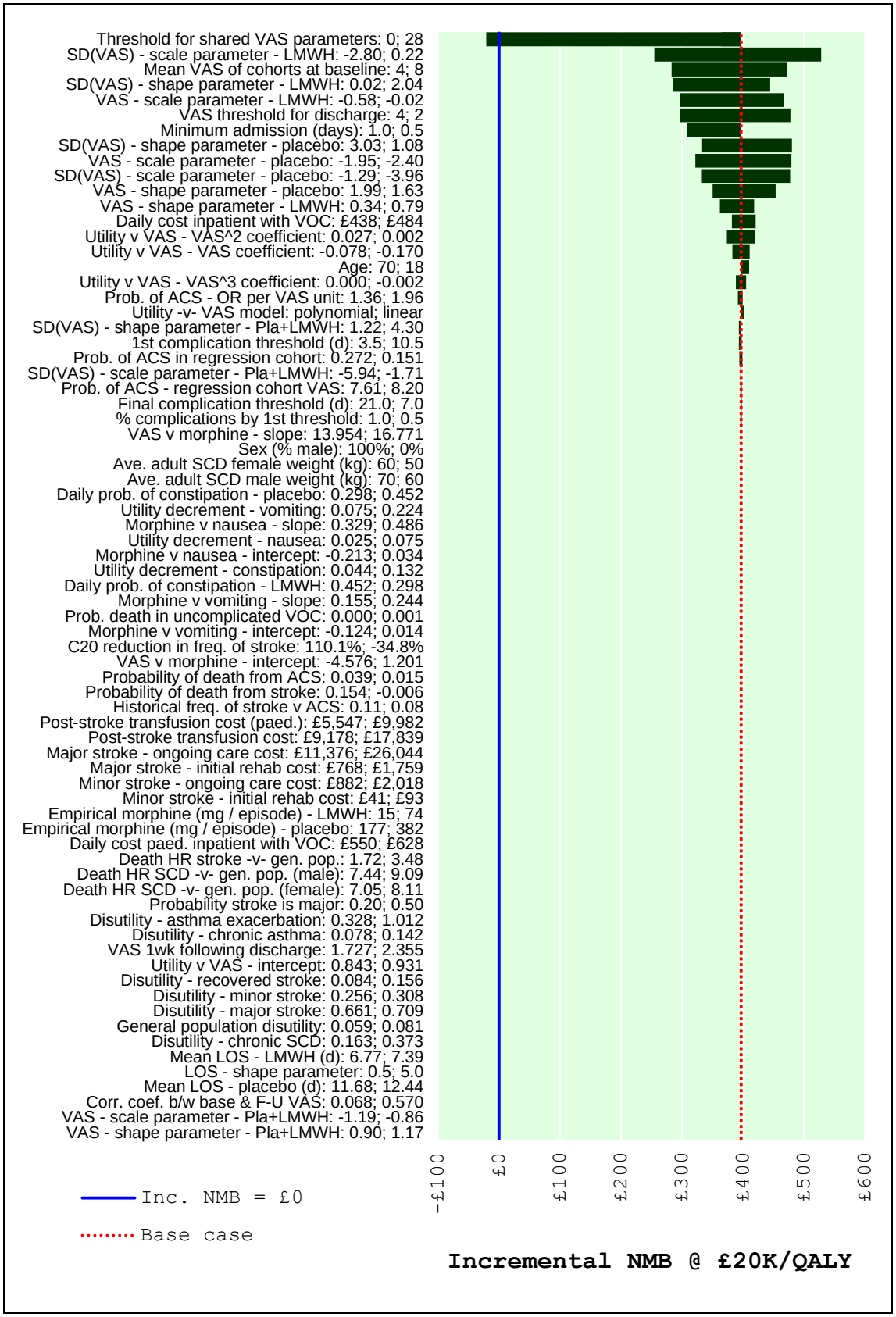

Figure 29: One-way deterministic sensitivity analysis – tornado plot (scenario 2A)

In all scenarios, adopting a linear rather than polynomial fit to characterise the functional relationship between VAS score and health-state utility (see 'Health-related quality of life', under 'Generic model parameters', above) had a trivial effect on results.

Threshold Analysis

Threshold analysis was conducted on the one parameter that had the potential to affect cost–utility conclusions (that is, the threshold for shared VAS parameters in scenarios 2A and 2B), with the aim of identifying the point at which those conclusions would be altered (Figure 30). The assumed value of the parameter was varied over a broad range, assuming a conventional threshold of £20,000 per QALY. This analysis suggests that providing adjunctive treatment with LMWH would remain the most cost-effective option unless the threshold for shared VAS was set at zero (base case of 4.5 days). In other words, LMWH appears to provide slightly worse value for money than standard care alone when its effectiveness profile is set to be identical to the placebo arm. Since the use of LMWH is subject to acquisition costs, this is a predictable finding. It should be noted that LMWH appears to remain cost effective even if its benefits are assumed to accrue over one day only.

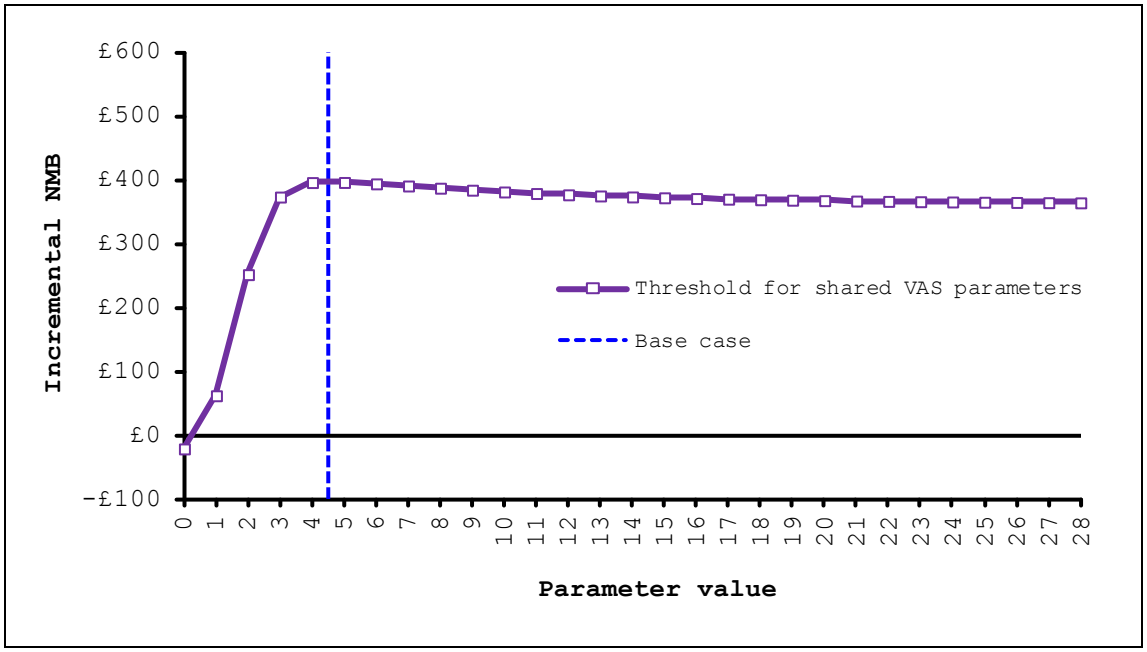

Figure 30: Threshold analysis: threshold for shared VAS parameters (days) – incremental NMB at £20,000 / QALY

Probabilistic sensitivity analysis

As for PCA, we performed 10,000 Monte-Carlo simulations per scenario – a total of 40,000 iterations overall – with parameter values randomly sampled from distributions reflecting uncertainty around their true values. Table 99 Summarises mean values from these simulations. Figure 31(a) shows the joint distribution of incremental costs and incremental QALYs on the cost–utility plane. Figure 31(b) presents a cost-effectiveness acceptability curve (CEAC), indicating the probability that, when compared with standard care alone, LMWH provides best value for money (highest net benefit), given different ceiling thresholds of up to £100,000 per QALY gained.

Scenario 1A and 1B

In Figure 31(a) (scenarios 1A and 1B), the spread of results in the South-East quadrant suggests that, in almost all cases, LMWH produces more QALYs and is cheaper than standard care. It would be highly unlikely, given the specified uncertainty across all parameters in the model, for people who receive adjunctive LMWH therapy to experience a net disadvantage in QALYs gained (across 20,000 simulations for these scenarios, only 9 resulted in higher QALYs for standard care alone).

As a consequence, Figure 31(b) suggests that LMWH is very nearly certain to be considered cost effective, regardless of the value that society is assumed to place on QALY gains.

Scenario 2A and 2B

The results in scenarios 2A and 2B are similar to those in 1A and 2B, with the exception that, in this instance, there are smaller cost savings, although QALY gains are not much reduced (Figure 31[a]). Likewise, in these two scenarios, it would be highly unlikely, given the specified uncertainty across all parameters in the model, for people who receive adjunctive LMWH therapy to experience a net disadvantage in QALYs.

Again, Figure 31(b) suggests that LMWH would almost certainly be considered cost-effective regardless of what the ceiling value per QALY gained is.

Table 99: LMWH: summary of cost–utility results (mean estimates) from probabilistic sensitivity analysis

	Independent LOS		VAS-dependent LOS		All four scenarios combined
	Single complication rate (Scenario 1A)	Dynamic Complications (Scenario 1B)	Single complication rate (Scenario 2A)	Dynamic Complications (Scenario 2B)	
C−IV					
Costs (95%CI)	£5733 (£5258, £6370)	£5610 (£5182, £6124)	£1283 (£906, £2045)	£917 (£735, £1194)	£3386 (£799, £6139)
QALYs (95%CI)	12.998 (10.651, 14.758)	13.019 (10.685, 14.797)	13.007 (10.714, 14.812)	13.018 (10.689, 14.771)	13.010 (10.685, 14.781)
LMWH					
Costs (95%CI)	£3614 (£3219, £4286)	£3361 (£3081, £3702)	£946 (£583, £1700)	£539 (£424, £805)	£2115 (£448, £3963)
QALYs (95%CI)	13.000 (10.652, 14.759)	13.020 (10.687, 14.800)	13.008 (10.716, 14.813)	13.019 (10.692, 14.772)	13.012 (10.687, 14.783)
Incremental					
Costs (95%CI)	−£2120 (−£2405, −£1842)	−£2249 (−£2553, −£1975)	−£337 (−£453, −£56)	−£378 (−£531, −£78)	−£1271 (−£2448, −£142)
QALYs (95%CI)	0.001 (0.000, 0.001)	0.002 (0.001, 0.005)	0.001 (0.000, 0.001)	0.001 (0.000, 0.003)	0.001 (0.000, 0.003)
ICER	LMWH dominates	LMWH dominates	LMWH dominates	LMWH dominates	LMWH dominates
Incremental NMB					
£20, 000 / QALY (95%CI)	£2140 (£1861, £2427)	£2289 (£2006, £2615)	£357 (£63, £477)	£408 (£88, £574)	£1298 (£154, £2490)
£30, 000 / QALY (95%CI)	£2151 (£1871, £2436)	£2308 (£2022, £2645)	£367 (£66, £490)	£422 (£93, £597)	£1312 (£160, £2511)
Probability cost effective					
£20, 000 / QALY	1.000	1.000	0.989	0.993	0.995
£30, 000 / QALY	1.000	1.000	0.989	0.993	0.996

ICER = incremental cost-effectiveness ratio; LMWH = low-molecular-weight heparin; LOS = length of (hospital) stay; NMB = net monetary benefit; QALY = quality-adjusted life-years; VAS = visual analogue scale

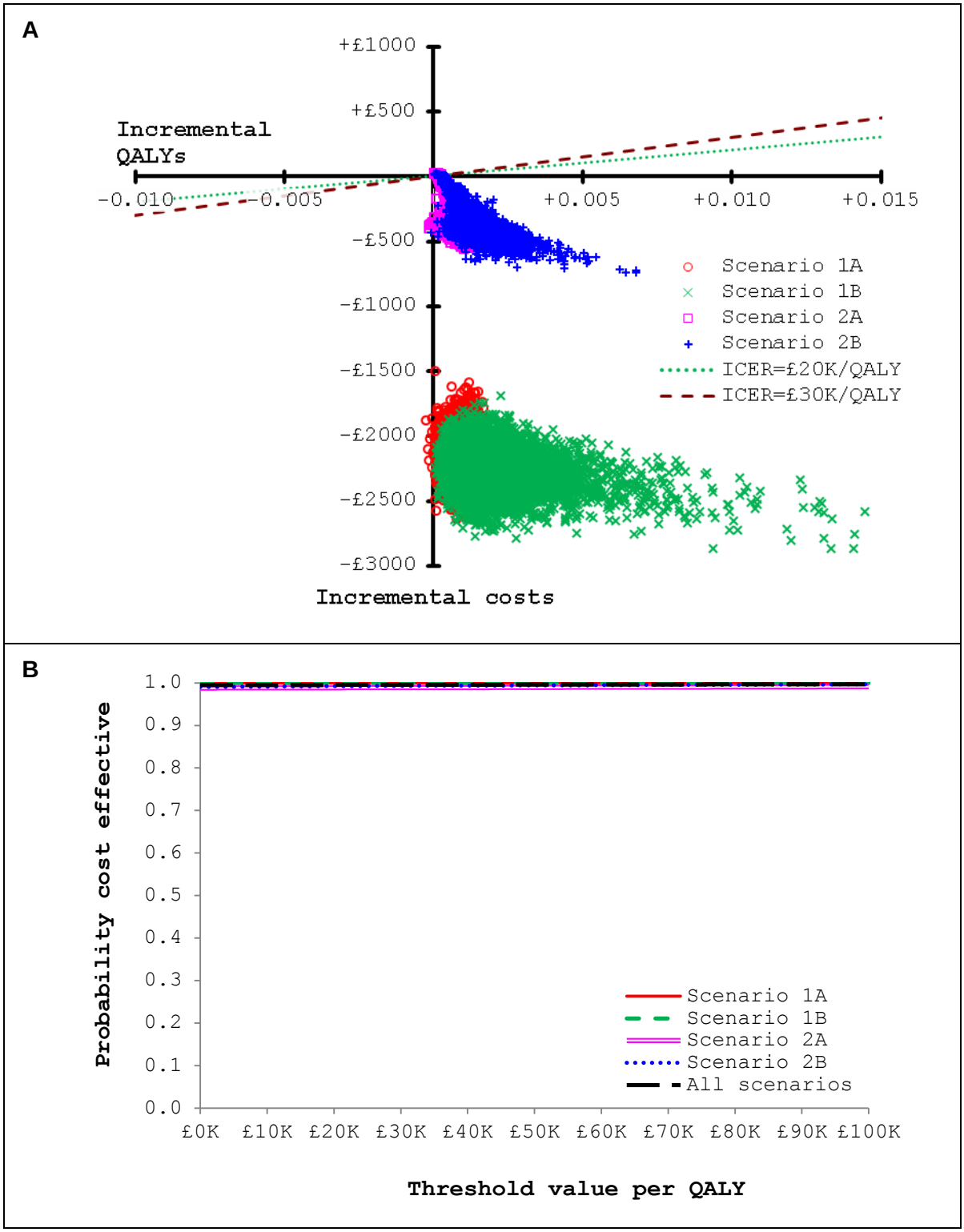

Figure 31: Probabilistic sensitivity analysis: cost–utility scatterplot (A) and cost-effectiveness acceptability curve (B)

Conclusion

Overall, the results substantiate those produced in the deterministic analysis. In all four scenarios, the CEAC produced almost entirely horizontal lines – consistent with dominance (that is, if we estimate that a technology is cheaper and more effective than its comparator, the amount we would be prepared to pay for health gains is irrelevant). Considering all four scenarios combined, LMWH can be concluded as being cost effective with greater than 99.5% certainty when compared with standard care alone, irrespective of the value that society is assumed to place on each QALY gained (Figure 31[b]).

Children

As above (see PCA results: children), we performed a simple exploratory analysis in which a cohort with a mean baseline age of 5 was simulated, because it was not possible to identify values that characterise the effects of LMWH in paediatric populations.

For effectiveness parameters, we were forced to rely on results from the adult evidence-base. Again, the number of model parameters that properly reflect paediatric practice is limited: the (longer) life expectancy of the population and its (higher) daily inpatient costs are incorporated. Medication costs – including LMWH itself – are also reduced, where doses are provided on a per-kilogram basis.

The results of this analysis are tabulated inTable 100. As with our exploratory analysis of PCA -v- C-IV in children, it is worthwhile to note that the **relative** magnitude of benefit expected in this population is somewhat higher – both in terms of QALYs gained and costs saved with LMWH as an adjunct to standard care. This is because the additional life expectancy of a younger cohort leads to greater gains when mortality and morbidity is avoided, and daily inpatient costs are higher for children; therefore, reduced requirement for hospitalisation results in greater cost savings.

1086 **Table 100: Scenario analysis: results in children (mean baseline age 5 years)**

	Independent LOS						VAS−dependent LOS					
	Single complication rate (Scenario 1A)			Dynamic Complications (Scenario 1B)			Single complication rate (Scenario 2A)			Dynamic Complications (Scenario 2B)		
	Placebo	**LMWH**	**Δ**	**Placebo**	**LMWH**	**Δ**	**Placebo**	**LMWH**	**Δ**	**Placebo**	**LMWH**	**Δ**
Costs												
Acute episode:												
Inpatient care	£7,123	£4,319	−£2,804	£7,110	£4,189	−£2,921	£1,378	£886	−£492	£1,101	£582	−£519
PCA consumables	£0.00	£15.47	£15.47	£0.00	£15.04	£15.04	£0.00	£3.88	£3.88	£0.00	£2.86	£2.86
Morphine	£26.00	£3.30	−£22.70	£26.00	£3.30	−£22.70	£6.10	£3.83	−£2.27	£6.10	£3.83	−£2.27
Subtotal	£7,149	£4,338	−£2,811	£7,136	£4,208	−£2,928	£1,384	£894	−£491	£1,107	£589	−£519
Long−term costs:												
Stroke rehabilitation	£697.37	£697.37	£0.00	£207.07	£94.09	−£112.98	£697.37	£697.37	£0.00	£95.52	£29.74	−£65.78
Total	£7,847	£5,035	−£2,811	£7,343	£4,302	−£3,041	£2,082	£1,591	−£491	£1,203	£618	−£585
Effects												
Episodes of ACS	6.26%	6.26%		1.86%	0.84%		6.26%	6.26%		0.86%	0.27%	
Strokes	0.23%	0.23%		0.07%	0.03%		0.23%	0.23%		0.03%	0.01%	
Deaths	0.18%	0.18%		0.06%	0.03%		0.18%	0.18%		0.03%	0.01%	
Mean LOS (days)	12.104	7.339		12.081	7.118		2.342	1.505		1.871	0.989	
QALYs:												
Acute episode	0.063	0.064	0.001	0.063	0.065	0.001	0.063	0.064	0.001	0.064	0.065	0.001
Subsequent LE (discounted)	17.569	17.569	0.000	17.582	17.585	0.003	17.569	17.569	0.000	17.585	17.587	0.002
Total	**17.632**	**17.633**	**0.001**	**17.646**	**17.650**	**0.004**	**17.632**	**17.633**	**0.001**	**17.649**	**17.652**	**0.003**
ICER	**LMWH dominates**			**LMWH dominates**			**LMWH dominates**			**LMWH dominates**		
Incremental NMB:												
WTP=£20, 000 / QALY	£2,835.74			£3,128.63			£514.67			£645.35		
WTP=£30, 000 / QALY	£2,847.86			£3,172.36			£526.59			£675.72		

Discussion

Issues relevant to generic model (PCA -v- C-IV and LMWH)

Strengths of the model

This is the first cost–utility model – indeed, the first economic analysis of any type – to address the health economics of acute painful sickle cell episodes. It has been developed by an independent team with expert input and validation from the GDG.

In both its applications, the model generates results that appear relatively robust to the underlying structural and parameter uncertainty, as demonstrated in a series of scenario analyses and deterministic and probabilistic sensitivity analyses.

Limitations

We developed our model in the context of an extremely limited evidence-base, and this has necessitated reliance on a number of assumptions and extrapolations.

In particular, the model is highly dependent on estimated pain (VAS), from which HRQoL, likelihood of complications and resource-use are extrapolated. In scenarios 2A and 2B, LOS is also dependent on estimated VAS. With a fuller evidence-base, it might be possible to derive empirical estimates for these parameters; however, no such data were available to us.

In one instance, we have relied on unpublished evidence – to define our estimate of HRQoL on the basis of VAS. This was a necessary step, since we did not identify any relevant published evidence. The dataset used has the advantage of representing a relatively largely, UK-based population experiencing an acute painful sickle cell episode. However, the study on which it is based has not, at the time of writing, been published in a peer-reviewed journal (although publication is planned). We acknowledge that this is a weakness.

Limited data were available to us on the costs of treating an acute painful sickle cell episode. We based daily inpatient costs on NHS Reference Costs for 2010/11, using an aggregate of multiple ‘department’ and ‘currency’ codes. This introduced additional uncertainty, especially where the cost estimates for adult inpatients were concerned. This is because adult acute painful sickle cell episodes have been recorded under two separate codes, both of which will also have been used to record some unrelated incidents. However, we drew reassurance from the fact that, in both models, sensitivity analysis demonstrated that any inaccuracy in the true daily cost of inpatient treatment is unlikely to have a critical effect on model outputs.

Relatedly, we did not include any additional costs to represent the acute treatment of complications during the episode, other than as a result of extended hospitalisation. It is undoubtedly the case that the average costs reported in the NHS Reference Costs encompass clinical courses of a range of severities; if it were possible to unpick daily costs for complicated and uncomplicated cases, we could have applied these differentially in the model. This would have the effect of increasing the cost effectiveness of interventions that are predicted to prevent complications. Therefore, in scenarios 1B and 2B of the model, PCA and LMWH would represent better value for money than estimated in our analysis.

We acknowledge that the range of acute complications experienced by people undergoing an acute painful sickle cell episode is substantially broader than our model reflects. For example, infections, splenic sequestration and osteomyelitis are recognised complications of acute painful sickle cell episodes. However, no suitable data were available to us on the incidence and effects of these events, so reflecting all possible events would have entailed reliance on a range of tenuous assumptions and extrapolations. Rather than adopting this approach, we chose to focus our attention on the complication that is most commonly reported (ACS) and the one with most serious consequences (stroke). We believe that this represents an acceptable simplification of a complex clinical picture.

With the exception of the HRQoL associated with ongoing, chronic sickle cell disease, we found no published evidence on the utility weights that should be applied to the various health states encompassed in our model. Consequently, we relied on values that had been reported either in other populations experiencing the events of interest (for example, nausea in pregnant women and stroke in the general population) or in settings that the GDG agreed represented a fair analogy to the health state for which data were unavailable (for example, the utility of experiencing ACS was judged to be comparable to that associated with an acute asthma exacerbation requiring hospitalisation). This is an imperfect approach; however, in both models, sensitivity analysis demonstrated that it is unlikely to have a critical effect on model outputs.

Issues relevant to analysis of PCA -v- C-IV

Principle findings

Deterministic and probabilistic analyses strongly suggest that, when compared with morphine delivered by C-IV, morphine delivered by PCA is likely to be the cheapest and most effective (dominant) approach.

Limitations

For its clinical effectiveness parameters, our model relies exclusively on a single Dutch study (van Beers et al. 2007) reporting the experience of only 19 people (26 episodes). The generalisability of this evidence to an NHS setting is unclear. Inevitably, results from such a small sample are subject to wide uncertainty; however, this is appropriately reflected in our probabilistic analysis.

The model is heavily dependent on two clinical outcomes:

- **LOS:** in scenarios 1A and 1B, LOS is directly based on evidence from van Beers et al., in which median LOS was 6 days in the PCA group and 9 days in the C-IV group. GDG opinion suggests that this is a longer duration of hospitalisation than would be expected in UK practice, so it is possible that the model exaggerates the additional benefit it ascribes to PCA. However,

this potential bias is not present in scenarios 2A and 2B of the model, which broadly confirm the findings of scenarios 1A and 1B. It should also be noted that the difference between LOS in van Beers et al.'s two arms fell short of statistical significance. By adopting the point estimates and measures of dispersion reported in the trial (in scenarios 1A and 1B), our model effectively assumes that there probably is a benefit in LOS for PCA compared with C-IV. This is a recognised issue in health economics and, because our probabilistic analysis properly reflects parameter uncertainty, it is appropriate to rely on its outputs for decision-making (Claxton [1999] demonstrates that the objective of maximising health gain for a given budget is best met by optimising mean net benefit irrespective of whether any differences underpinning the calculation are, in themselves, regarded as statistically significant).

- **Pain (VAS)**: Similar to the above, the difference in VAS reduction extracted from van Beers et al. and applied in the model was not reported to be statistically significant by the authors. This may partially be because there was a notable difference in baseline VAS between the cohorts (the C-IV arm started at 5.9, whereas the PCA arm began at 7.2), meaning a larger (relative and absolute) reduction in the PCA arm led to similar VAS scores at two days' follow-up. We chose to rely on the relative reduction in VAS in the base-case of our model; however, sensitivity analysis showed that similar results are generated when an absolute reduction is assumed. The considerations outlined above apply here, as well: by accounting for uncertainty in its probabilistic analyses, our model appropriately incorporates and quantifies decision uncertainty based on parameter imprecision.

The analysis did not account for the purchase price of PCA pumps, as prices are variable, and the GDG agreed that many hospital units already have access to pumps that have been acquired for other indications. However, it was calculated that the expected cost savings would offset an average purchase price of around £2500, if it was assumed that each pump would be used for a minimum of between two and nine acute painful sickle cell

episodes (depending on the scenario adopted in the analyses). GDG opinion suggested that the number of episodes on which a PCA pump would be used can be expected substantially to exceed these figures; therefore, it appears reasonable to conclude that their acquisition, where necessary, would be justified by future cost savings.

Finally, GDG opinion suggests that C-IV administration of morphine is not very common in UK practice, and that a more realistic comparator for PCA would be the intermittent injection of morphine via an intramuscular or subcutaneous route. It cannot be assumed that the additional benefits and saved costs estimated in the economic model can be generalised to this comparison.

Issues relevant to analysis of LMWH

Principle findings

Deterministic and probabilistic analyses strongly suggest that the use of LMWH would both reduce costs and improve outcomes, making it excellent value for money.

Limitations

For its clinical effectiveness parameters, our model relies exclusively on a single Saudi Arabian RCT (Qari et al. 2007). The provision of health care in Saudi Arabia and the characteristics of trial participants are likely to be very different from those encountered in the UK.

Uncertainty was introduced into modelling of both LOS and VAS due to reporting of data in Qari et al.'s RCT that was imperfect for our purposes. Where LOS is concerned, there was no information on the distribution observed in the trial; to address this problem, we fitted a parametric distribution with a scale parameter calculated to match mean LOS in Qari et al.'s data and a shape value imputed from another study reporting relevant time-to-event data (Orringer et al. 2001). With regard to VAS, because we did not have the opportunity to perform a regression analysis on individual patient-level data, we chose a base-case approach that assumed a shared

distribution of pain beyond a given threshold (4.5 days). However, this assumption only had a critical impact on cost–utility results (and only then in scenarios 2A and 2B) when it was assumed that both arms had an identical pain profile throughout the simulated episode. As long as it was assumed that LMWH is associated with some degree of benefit in VAS – as the trial evidence strongly suggests – model results suggested it is likely to be a cost-effective addition to standard care.

However, the GDG advised that, in the UK, adult patients who are admitted for an acute painful sickle cell episode routinely receive a low dose of LMWH as prophylaxis against venous thrombo-embolism. Therefore a placebo-controlled RCT does not provide directly applicable evidence for the UK decision-making context: prophylactic-dose LMWH would be the relevant comparator against which to assess the clinical and cost effectiveness of therapeutic-dose LMWH in UK practice. For this reason, the effectiveness of therapeutic-dose LMWH in this analysis may have been substantially overestimated. Nevertheless, the model shows that, even if relatively modest health gains could be achieved by therapeutic-dose LMWH in comparison with prophylactic-dose LMWH, the routine use of the higher dose could be expected to represent an effective use of NHS resources.

Although prophylactic-dose LMWH is not routinely given to children in the UK, the effectiveness – and, hence, cost effectiveness – of therapeutic-dose LMWH in this population is unknown.

Cost-minimisation analysis of dedicated sickle cell centres for the management of an acute painful sickle cell episode

Decision problem

- Dedicated sickle cell centres in addition to standard care

Comparator(s)

- Standard care only

Introduction

Patients presenting with an acute episode can be treated under day-care in hospitals which have sickle cell day centres, or are admitted into hospital wards (haematology or medical) – usually via A&E – if patients present outside the centres' opening hours. In hospitals which do not have these day centres, patients are admitted into the A&E or hospital wards (haematology or medical).

Methods

Very limited evidence was available to assess the economic impact of dedicated sickle cell centres for the management of an acute painful sickle episode. Only one study was identified which assessed the economic impact of a sickle cell day centre in a UK setting (Wright et al., 2004). This was a before-and-after study which explored the effects on quality of care and hospital admissions in patients with sickle cell disease 2 years before and 3 years after the establishment of a sickle cell day centre in Birmingham. The study reported cost savings per episode of commencing treatment at the day centre. The study reported only the staffing cost of the day centre (provider costs). Set-up costs, costs of inpatient admission in cases that could not be treated in day-care alone and other running costs were not included in their

analysis. Moreover, a separate analysis was not conducted for children and adults.

No data are available on HRQoL and other patient benefits that may be provided by the day-centre setting. Therefore, to explore the economic impact of dedicated sickle cell centres from an NHS perspective, we conducted an exploratory cost-minimisation analysis based on the data reported in the Wright et al. study, assuming equivalent effectiveness between a day-centre-based strategy and one consisting of A&E presentation and ward admission.

Parameters

Cost

We estimated the cost of hospital admission for an acute sickle cell episode using the same NHS Reference Cost 2010/11 values applied in our cost–utility model (see Table 90). The actual daily cost of treating an acute episode in a sickle cell day centre is uncertain because some Trusts have categorised such episodes under 'Non-Elective Inpatient (Short Stay)' code while others have categorised them under 'Day Cases' code. For this reason, we used a weighted average of the two categories. We took the average number of day centre visits per episode per patient from the study by Wright et al., 2004. This was used to estimate the cost per episode of treatment in a day centre. Those who commenced treatment at the day centre but eventually required admission into hospital within 7 days – described as 'failure of day-care' by Wright et al. – incurred both the cost of day centre treatment and the cost of hospital admission. The Wright study reported that 31% of hospital admissions were accounted for by day-care failures. The 'expected cost per episode of hospital admission' assuming there were no day-care failures (that is, standard care only) was calculated using the formula:

Observed mean cost per episode of hospital admission −
(observed mean cost per episode of day centre treatment ×
proportion of hospital admissions that were day-care failures)

Wright et al. also report that 25% of all patients treated in the day centre will require hospital admission (day-care failure). We calculated the ‘cost per episode treated in the day centre’ including day care failures using the formula:

> *Observed mean cost per episode of day centre treatment + (expected cost per episode of hospital admission assuming no day-care failures × proportion of day centre cases that end up as day-care failures).*

To calculate the cost savings per episode of commencing treatment at a day centre, we subtracted the ‘cost per episode treated in the day centre’ including day care failures from the ‘expected cost per episode of hospital admission’ assuming there were no day-care failures.

To provide validation for this calculation, we also applied current pay rates (PSSRU 2011) to the annual staff input reported by Wright et al., and calculated the cost per case of treating a sickle cell day centre, assuming the number of cases and staff requirement remained the same as that estimated in 2003.

Results

Table 101: Cost-minimisation analysis of a dedicated sickle cell unit

	Derivation	Children	Adults
NHS Reference Costs Codes		PA47Z	SA10E & SA10F
Weighted average cost of combined day cases and short stay	a	£565	£430
Average day centre visits per episode	b	1.53	1.53
Observed mean cost per episode treated in day centre	c =(a × b)	£864	£658
Observed mean cost of long-stay admission	d	£2504	£2576
Proportion of patients on admission who are day-care failures	e	0.31	0.31
Expected cost per episode of long-stay admissions without day centres	f =d− (c × e)	£2236	£2372
Expected cost per episode for day-care failures	g =(f + c)	£3100	£3030
Proportion of day-centre patients who become day-care failures	h	0.25	0.25
Total cost per patient treated in day centre (including failures)	i =c + (f × h)	£1423	£1251
Cost saving per patient treated at day centre	j =(f – i)	£813	£1121

The results (Table 101Table 101) suggest that dedicated sickle cell centres may provide cost savings of over £1100 per episode primarily by reducing the need for hospital admission. Table 102Table 102 shows the updated annual staffing cost based on the structure reported by Wright et al. The results show that the cost per episode of treatment in a day centre is about £970, which is noticeably higher than the estimate from our analysis of the NHS Reference cost data.

Table 102: Annual staffing cost for a sickle cell day unit

Description	No. FTEs required	Cost per FTE	Total	Source
Specialist nurses	3	£30,800	£92,400	PSSRU 2010
Nursing auxiliary	1	£17,003	£17,003	NHS agenda for change rates 2011
Psychologist	0.5	£38,000	£19,000	PSSRU 2010
Receptionist	1	£17,003	£17,003	NHS agenda for change rates 2011
Haematologist	0.5	£120,200	£60,100	PSSRU 2010
Total			**£205,506**	
Number of episodes in day centre (2003)			211	Wright et al. 2004
Cost per episode			**£974**	

Discussion

Overall, the analyses suggest that treating acute painful sickle episodes in dedicated sickle cell centres would be associated with cost savings primarily as result of reduction in the need for hospital ward admission.

The updated staff costs based on the structure reported by Wright et al. suggest that day centres may be somewhat more expensive on a per-episode level than estimated in our analysis (£974 per episode, compared with £658–864). However, GDG opinion suggests that the staffing requirement set out by Wright et al. is a generous one: it is likely that most sickle cell day centres operating in the NHS and contributing data to the NHS Reference Costs have a lower FTE staffing level. Furthermore, it was reported in the study by Wright et al. – and substantiated by the GDG – that day centre staff were engaged in other additional services (such as blood transfusion for people with Thalassaemia); suggesting that the costs may have been over estimated. Therefore, it is to be expected that an estimate of costs derived from the Reference Costs will be somewhat lower. Moreover, even if the updated staffing costs from Table 102 Table 102were used in the cost-minimisation analysis as an estimate of the costs to the NHS of a day-centre episode, positive cost savings would still be associated with the use of day centres.

However, it should be noted that this analysis did not take into account the set-up costs of units, which will be extremely variable, depending on the extent and nature of current provision in each locality, as well as the size of the population that is expected to benefit from the facility.

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References

1. Anie et al. Raw data provided to developers. 2011.

2. Anie KA et al. Sickle cell disease: Pain, coping and quality of life in a study of adults in the UK. Br J Health Psychol. 2002 Sep;7(Part 3):331-344. http://www.ncbi.nlm.nih.gov/pubmed/12614504

3. Ara R, Brazier J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). Value Health. 2008 Dec;11(7):1131-43. http://onlinelibrary.wiley.com/doi/10.1111/j.1524-733.2008.00352.x/pdf

4. Barden et al. Body composition in children with sickle cell disease. Am J Clin Nutr. 2002 Jul;76(1):218-25. http://www.ajcn.org/content/76/1/218.full.pdf

5. Bartolucci et al. A randomized, controlled clinical trial of ketoprofen for sickle-cell disease vaso-occlusive crises in adults. Blood. 2009 Oct 29;114(18):3742-7. http://bloodjournal.hematologylibrary.org/content/114/18/3742.full.pdf

6. Belsey J, Greenfield S, Candy D, Geraint M. Systematic review: impact of constipation on quality of life in adults and children. Aliment Pharmacol Ther. 2010;31:938–949

7. Beusterien et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health Qual Life Outcomes. 2010 May 18;8:50.

8. Bruins Slot et al. Impact of functional status at six months on long term survival in patients with ischaemic stroke: prospective cohort studies. BMJ. 2008; 336: 376-379. http://www.bmj.com/content/336/7640/376.full.pdf

9. Buchanan et al. Opioid selection during sickle cell pain crisis and its impact on the development of acute chest syndrome. Pediatr Blood Cancer. 2005 Oct 15;45(5):716-24. http://onlinelibrary.wiley.com/doi/10.1002/pbc.20403/full

10. Chambers et al. Cost-effectiveness analysis of antiplatelet therapy in the prevention of recurrent stroke in the UK. Pharmacoeconomics 1999;16:577-593.http://www.ncbi.nlm.nih.gov/pubmed/10662482/

11. Dampier C et al. Health-related quality of life in adults with sickle cell disease (SCD): a report from the comprehensive sickle cell centers

clinical trial consortium. Am J Hematol. 2011 Feb;86(2):203-5. http://onlinelibrary.wiley.com/doi/10.1002/ajh.21905/abstract

12. Department of Health. NHS Reference Costs 2010-11. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_131140

13. Dorman et al. Are the modified "simple questions" a valid and reliable measure of health related quality of life after stroke? J Neurol Neurosurg Psychiatry 2000;69:487-493. http://jnnp.bmj.com/content/69/4/487.full.pdf

14. Fox-Rushby J, Cairns J. Economic evaluation. 1st ed. Oxford,UK: Oxford University Press, 2005.

15. Fullerton et al. Declining stroke rates in Californian children with sickle cell disease. Blood. 2004 Jul 15;104(2):336-9. http://bloodjournal.hematologylibrary.org/content/104/2/336.full.pdf

16. Hong & Saver. Years of disability-adjusted life gained as a result of thrombolytic therapy. Stroke 2010, 41:471-477. http://stroke.ahajournals.org/content/41/3/471.full.pdf

17. Karl Claxton The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies; Journal of Health Economics 18 (1999). 341–364

18. Kind, P., Hardman, G. & Macran, S. (1999). UK Population norms for EQ-5D. York Centre for Health Economics Discussion Paper pp.172.

19. Lloyd et al. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. Prim Care Respir J. 2007 Feb;16(1):22-7. http://www.thepcrj.org/journ/vol16/16_1_22_27.pdf

20. McClish DK et al. Health related quality of life in sickle cell patients: the PiSCES project. Health Qual Life Outcomes. 2005 Aug 29;3:50. http://www.hqlo.com/content/pdf/1477-7525-3-50.pdf

21. Ohene-Frempong et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998 Jan 1;91(1):288-94. http://bloodjournal.hematologylibrary.org/content/91/1/288.full.pdf

22. Orringer et al. Purified poloxamer 188 for treatment of acute vaso-occlusive crisis of sickle cell disease: A randomized controlled trial.

JAMA. 2001 Nov 7;286(17):2099-106. http://jama.ama-assn.org/content/286/17/2099.full.pdf

23. Patey et al. The importance of using ethnically appropriate reference ranges for growth assessment in sickle cell disease. Arch Dis Child 2002;87:352–353. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1763031/pdf/v087p00352.pdf

24. Platt et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994 Jun 9;330(23):1639-44. http://www.nejm.org/doi/pdf/10.1056/NEJM199406093302303

25. Platt OS, Thorington BD, Brambilla DJ, et al. Pain in Sickle cell disease: rates and risk factors. N Engl J Med 1991;325:11-6.

26. Qari MH, Aljaouni SK, Alardawi MS et al. (2007) Reduction of painful vaso-occlusive crisis of sickle cell anaemia by tinzaparin in a double-blind randomized trial. Thrombosis & Haemostasis 98: 392-6.

27. Roberta Ara, Allan Wailoo NICE DSU TECHNICAL SUPPORT DOCUMENT 12: THE USE OF HEALTH STATE UTILITY VALUES IN DECISIONMODELS July 2011 http://www.nicedsu.org.uk/Utilities-TSD-series (2391676).htm

28. Roberto F. Machado and Mark T. Gladwin: Chronic sickle cell lung disease: new insights into the diagnosis, pathogenesis and treatment of pulmonary hypertension British Journal of Haematology 2005, 129, 449–464 http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2005.05432.x/pdf

29. Roberts et al. Postoperative Nausea and Vomiting Are Strongly Influenced by Postoperative Opioid Use in a Dose-Related Manner. Anesth Analg 2005;101:1343-8. http://www.anesthesia-analgesia.org/content/101/5/1343.full.pdf

30. Sebastiani et al. A network model to predict the risk of death in sickle cell disease. Blood. 2007 Oct 1;110(7):2727-35. http://bloodjournal.hematologylibrary.org/content/110/7/2727.full.pdf

31. Smith et al. The impact of nausea and vomiting on women: a burden of early pregnancy. Aust N Z J Obstet Gynaecol 2000;40:397–401. http://www.springerlink.com/content/621027305l7luv30/fulltext.pdf

32. Strouse et al. The excess burden of stroke in hospitalized adults with sickle cell disease. Am J Hematol. 2009 Sep;84(9):548-52. http://onlinelibrary.wiley.com/doi/10.1002/ajh.21476/pdf

33. Thomas et al. Height and weight reference curves for homozygous sickle cell disease. Arch Dis Child. 2000 Mar;82(3):204-8. http://adc.bmj.com/content/82/3/204.full.pdf

34. Van Beers EJ, van Tuijn CF, Nieuwkerk PT et al. (2007) Patient-controlled analgesia versus continuous infusion of morphine during vaso-occlusive crisis in sickle cell disease, a randomized controlled trial. American Journal of Hematology 82: 955-60.

35. Vishinski et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Engl J Med. 2000 Jun 22;342(25):1855-65. http://www.nejm.org/doi/pdf/10.1056/NEJM200006223422502

36. Woods KE et al. Functional status and well-being in adults with sickle cell disease. J Clin Outcomes Manag 1997;4(5):15-21.

37. Wright J, Bareford D, Wright C et al. (2004) Day case management of sickle pain: 3 years experience in a UK sickle cell unit. British Journal of Haematology 126: 878-80.