Appendix F Full health economic report

Introduction

Patients with advanced and progressive disease for whom non-opioid analgesics and opioids conventionally used in the management of moderate pain have failed to control pain are indicated to receive strong opioids. However, there is uncertainty over the choice of strong opioids for the maintenance treatment of background pain.

The most commonly used therapy is oral sustained-release morphine, primarily because it is cheap and easy for the patients to take. However, recently, the use of transdermal opioids (fentanyl and buprenorphine) as a first-line approach to moderate to severe pain has increased substantially. Transdermal opioid therapies may be preferred over oral therapies because of better patient compliance, a better safety profile and the preference of the patient (Tassinari et al. 2008).

Aims

This economic evaluation aimed to assess the cost-effectiveness of first-line opioid maintenance treatments in patients with advanced and progressive disease who require strong opioids. The analysis considered the perspective of the National Health Service (NHS).

Method

Existing Economic Evidence

A systematic literature review was performed to assess the volume and quality of the current economic literature. Three relevant studies were identified; Neighbors et al. (2001), Lehmann et al. (2002) and Greiner et al. (2006). Each of these studies described the development of an economic model to assess the cost-effectiveness of oral opioids. Health effects were quantified in terms of quality adjusted life days (QALDs) and/or quality adjusted life years (QALYs). Table 1 shows the modified grade profiles for each of the three studies.

Table 1: Modified GRADE table

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Neighbors et al. 2001	Cancer and non-cancer patients with moderate to severe chronic pain	Fentanyl transdermal therapeutic system (A)	$2,491	243.62 QALDs	Reference			One-way sensitivity analysis was performed on the key variables of interest (as identified by the authors). Range of cost-effectiveness results: A vs. B: an ICER of $1,553 to A being dominated by B. A vs. C: A is dominant to an ICER of $487,474	Partially applicable	Potentially serious limitations
		Controlled release morphine (B)	$2,037	235.63 QALDs	$454	7.99 QALDs gained	$20,709 / QALY gained			
		Controlled release oxycodone (C)	$2,307	230.94 QALDs	$184	12.68 QALDs gained	$5,273 / QALY gained			
	Comments: Considers a US perspective. Sponsored by manufacturer.									

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Lehmann et al. 2002	Patients with non-malignant moderate to severe chronic pain.	Controlled release morphine	DM 6,186.48	216.16 QALDs	Reference			One-way sensitivity analysis was performed on the key variables (as identified by the authors). The ICER value varied from fentanyl being dominant to a value of DM 40,738. The authors identified the price of fentanyl as a key driver of the analysis.	Partially applicable	Potentially serious limitations
		Transdermal fentanyl	DM 6,950.19	233.67 QALDs	DM 763.71	17.51 QALDs	DM 15,920 / QALY gained			
	Comments: Considers a German perspective. Sponsored by manufacturer.									
Greiner et al. 2006	Patients with non-	Transdermal fentanyl (A)	€2,947.85	0.539 QALYs	Reference			Parameter uncertainty was	Partially applicable	Potentially serious

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
	malignant moderate to severe chronic pain.	Sustained release morphine (B)	€2,883.44	0.499 QALYs	€64.41	0.04 QALYs	€4.45 / QALD gained €1,625.65 / QALY gained	assessed using probabilistic sensitivity analyses (PSA). Results were reported as robust to changes, with an ICER of €10,000 or less in 93% of runs. Additionally, one-way sensitivity analysis was carried out on the probability of skin irritation with Fentanyl TTS. However, the effect on the ICER was found to be minimal.		limitations
		Transdermal buprenorphine (C)	€3,151.13	0.537 QALYs	-€267.69	0.002 QALYs	A is dominant			
		Controlled release oxycodone (D)	€2,911.13	0.502 QALYs	€240.00	0.037 QALYs	€2.75 / QALD gained €1,003.03 / QALY gained			
		Additional scenario: D vs B	NA	NA	€27.69	0.003 QALYs	€19.79 / QALD gained €7,224.62 / QALY gained			
	Comments: Considers a German perspective. Sponsored by manufacturer									

All the studies were based around the same model structure. Lehmann et al. (2002) and Greiner et al. (2006) used the same basic model structure employed in the study by Neighbors et al. (2001). Of the three papers, two considered a German perspective (Lehmann et al. 2002 and Greiner et al. 2006) while the remaining study considered a US perspective (Neighbors et al. 2001). Reflecting the growing use of opioids in patients with non-malignant diseases, two of the three studies consider non-cancer patient populations with the remaining study considering a cancer and non-cancer population.

All the studies found transdermal fentanyl to be cost-effective against oral sustained-release morphine with incremental cost-effectiveness ratios (ICERs) of £17,798, £14,487 and £1,406 per QALY in the studies by Neighbors et al. (2001), Lehmann et al. (2002) and Greiner et al. (2006), respectively. In addition, Greiner et al. (2006) showed transdermal buprenorphine to be cost-effective against oral sustained-release morphine with an ICER of £6,248 per QALY.

All three of the studies were deemed only partially applicable to the guideline. This was mostly a result of the studies considering countries other than the UK. In some instances, there were also concerns about the applicability of the quality of life data because they were often based on assumptions by a panel of clinical experts rather than reported directly from patients. Furthermore, potentially serious limitations were identified with all of the included studies. Many of the key model parameters, such as efficacy and resource use were estimated using the opinion of a panel of clinical experts. In addition, potential conflicts of interest were identified in all of the studies, as the analyses were sponsored by pharmaceutical companies.

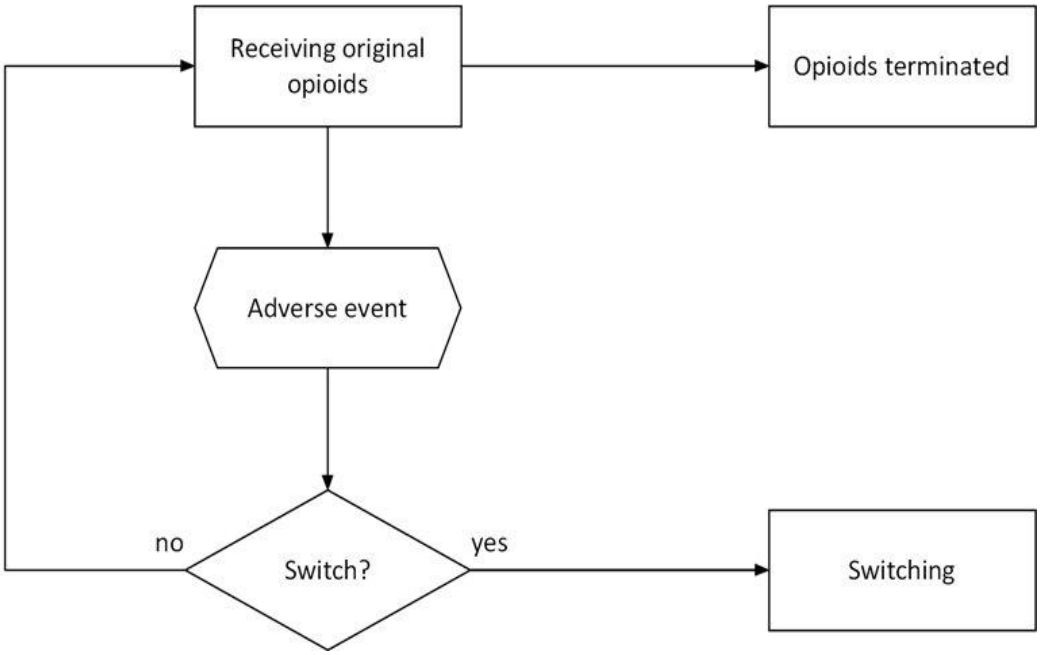
De Novo Economic Model

Since the current economic literature didn’t adequately address the decision problem, a de novo Markov model was developed to assess the cost-effectiveness of first-line strong opioid treatments. Markov models involve dividing a patients' possible prognosis into a series of discrete health states. In this case, the health states were "Receiving original opioids", "Opioids

terminated" and "Switching." The structure of the economic model is shown in figure 1.

In comparison to previous models, the structure of this model is relatively simple. In general, when building economic models, there is a trade-off between complexity and transparency with more complicated models being more poorly understood. Thus, it is good practice for economic models to be no more complicated than necessary to answer the decision problem. In this instance, the simplicity of the model reflects the results of the clinical data review whereby adverse events were identified as the only significant difference between treatments (see "Clinical data" section for more details).

Figure 1: Structure of health economic model



Patients enter the model when commencing maintenance therapy and start in the “Receiving original opioids" health state. At each weekly cycle, patients may transition to the "Switching" health state, the "Opioids terminated" health state or remain in the “Receiving original opioids” health state. Movement between the states is determined via transition probabilities (see "Clinical data" section for more details). Patients move to the "Opioids terminated" health state following spontaneous, non-treatment related resolution of pain symptoms. Patients move to the "Switching" health state following treatment discontinuation due to the occurrence of an adverse event.

Note that the "Switching" and "Opioids terminated" health states are 'absorbing' health states meaning that patients cannot leave the state once they have entered it. Thus a spontaneous resolution of pain is assumed to last for the duration of the modelled time horizon. Likewise, patients who switch remain on their second therapy for the duration of the modelled time horizon (i.e. it is assumed that the second therapy will be effective and tolerated, thus patients can only switch once).

Each of the health states have an associated cost and benefit tariff that patients accrue while in that state. The costs reflect the therapy that the patient is currently receiving as well as the cost of any other resource use that may be required (e.g. community nurse visit). Patients in the "Receiving original opioids" state incur the cost of the opioids that they started with, while there is no cost for patients in the "Opioids terminated" state. Patients in the "Switching" health state will receive the cost of an alternative therapy (calculated as the average cost of the treatments under comparison). In addition, the transition to the switching state has a “one-off” cost associated with administering the new therapy and monitoring the patient.

In terms of benefits, each health state has an associated quality of life (QoL) tariff. This reflects the model's measurement of benefits in terms of QALYs, whereby the quantity and quality of life can be expressed simultaneously. Patients in the “Receiving original opioids” and “Switching” health state will get a QoL value associated with controlled pain. Patients in the “Opioids terminated” health state will get a utility value associated with reduced pain. Utility decrements are also applied to reduce QoL in those patients that experience adverse events.

The overall costs and benefits for each treatment are then estimated on the basis of the total length of time individuals spend in each health state over the time horizon that has been modelled. The analysis considered a number of different time horizons with a maximum time horizon of 1 year. These relatively short time horizons reflect the prognosis of patients receiving palliative care, with most unlikely to live beyond 1 year. Given that the

maximum modelled time horizon was 1 year, discount rates were not necessary and so were not considered.

The GDG expressed particular interest in a time horizon of 4 weeks since this was the time period over which they expected the therapies to differ most.

Clinical data

The results of the clinical review were used to inform the economic model. The review suggested that the proportion of patients experiencing pain relief could be higher with oral sustained-release morphine than with oral sustained-release oxycodone, transdermal fentanyl and transdermal buprenorphine (Bekkering et al. 2011). However, this was not the case in all patient populations or at all time points. Indeed, in the case of the comparison of oral sustained-release morphine with transdermal buprenorphine, the opposite was true (in patients with cancer pain or a treatment duration greater than 1 month, pain relief was lower with oral sustained-release morphine than with transdermal buprenorphine). Furthermore, the review showed that there were no statistically significant differences in the proportion of patients who discontinue as a result of a lack of efficacy. Thus, in the base-case analysis, it was assumed that all therapies were equally effective (in terms of pain relief).

The selection of the adverse events to be considered in the model was informed by the clinical evidence review. Side effect differences were reported for the comparison of oral sustained-release morphine and oral sustained-release oxycodone. According to Reid et al. (2006), oral sustained-release oxycodone was associated with a reduction in the occurrence of dry mouth. However, this aspect was not considered in the cost-effectiveness analysis as it's unlikely to have any meaningful impact on costs and benefits. Lauretti et al. (2003) reported fewer nausea events with oral sustained-release oxycodone but this was based on a very small study population (N = 22). Other studies in larger populations didn't show significant differences in nausea (four out of five studies showed no statistically significant differences in side effects).

Given that oral sustained-release morphine and oral sustained-release oxycodone were equivalent in effectiveness terms, it was decided that this comparison would not need to be modelled. A decision on the most cost-effective treatment option could instead be based on the therapy costs associated with each treatment.

Statistically significant reductions in constipation were observed in those patients receiving transdermal therapies compared with oral sustained-release morphine(Tassinari et al 2008). In addition, patients receiving transdermal buprenorphine had significantly fewer gastrointestinal side effects than patients receiving oral sustained-release morphine. However, the comparison of oral sustained-release morphine and transdermal buprenorphine was based on a study with low patient numbers (N=52) and was judged to be of very low quality.

Given the limitations of the evidence base for oral sustained-release morphine and transdermal buprenorphine, it was decided that this comparison would not be considered in the economic evaluation.

Thus, only the comparison of transdermal fentanyl and oral sustained-release morphine were considered in the economic model. Table 2 shows the weekly adverse event occurrence and discontinuation probabilities that were applied in the model for each treatment.

Table 2: Adverse event occurrence and discontinuation

Adverse event	Adverse event occurrence		Discontinuation following adverse event
	Morphine	Fentanyl	
Constipation	12.26%	6.24%	4.06%

Since there was a lack of reliable evidence describing discontinuations resulting from individual adverse events, discontinuations as a result of constipation were estimated using data from the Bekkering study. The weighted average weekly discontinuation rate due to adverse events was calculated for each therapy. Differences in discontinuations by therapy were assumed to be attributed to the differences in the occurrence of constipation

by therapy (under the rationale that there were no significant differences in other adverse events).

Following the advice of the GDG, discontinuations following adverse events were assumed to only occur in the first 4 weeks of treatment. This reflects the experiences of the GDG in clinical practice whereby discontinuations in the first 4 weeks are driven by safety concerns while discontinuations thereafter are driven by a lack of adequate pain relief (not considered in the model since treatments are assumed to be equal in terms of pain relief).

In the absence of data, the GDG estimated that there would be a spontaneous, non-treatment related, resolution of pain in 5% of patients in the 1-year period. Thus, the model assumes that 0.10% of patients would transition to the "Opioids terminated" at each weekly cycle.

Mortality was not considered in the economic model. This decision was made because of the difficulty of sourcing mortality data appropriate for the population under consideration. A suitable mortality rate would have to reflect the wide range of possible disease areas that may cause a patient to require strong opioids and this was considered to be unfeasible. Thus, an alternative approach was adopted in the model whereby different time horizons were used to reflect a patient that lives for 1 month, 2 months, 3 months, 6 months and 12 months.

Cost data

The unit costs of the drugs considered in the model were sourced from the British National Formulary (BNF 61). Table 3 shows the doses and weekly therapy costs of the interventions of interest in the economic evaluation.

Table 3: Therapy costs and doses

Therapy	Dose	Unit	Average weekly cost (£)
Morphine*	60	mg/day	2.33
Oxycodone^	30	mg/day	10.49
Fentanyl†	25	µg/hour	11.84
Buprenorphine‡	35	µg/hour	6.88

*Morphgesic® SR, MST Continus® and Zomorph®

^OxyNorm® and OxyContin®

†Fentanyl (non-proprietary) and Durogesic DTrans®

‡Transtec®

The 60mg starting dose of oral sustained-release morphine was sourced from a published study by Brooks et al. (1995) who conducted a regional survey of opioid use by patients receiving specialist palliative care. This dose is in accordance with the BNF's recommendation that a starting maintenance dose of 20-30mg should be given every 12 hours. The equivalent dose of oral sustained-release oxycodone, transdermal fentanyl and transdermal buprenorphine were calculated using a dose equivalence table from the BNF combined with advice from the GDG.

Note that since the model starts when patients commence maintenance therapy, the costs incurred when titrating to an effective dose are not considered. Furthermore, the average doses applied in the above table are assumed to be effective for the duration of the modelled time horizon. Thus, dose increases are not considered in the model.

To reflect clinical practice, patients were assumed to receive laxatives concomitantly for the prevention of constipation. Based on the advice of the GDG, patients receive an average cost of the laxatives that are typically given to patients receiving opioids. Average costs were calculated using cost and dose information from the BNF and are shown in table 4.

Table 4: Concomitant laxatives for the prevention of constipation

Therapy	Medications and doses	Average weekly cost (£)
Co-danthramer	Non-proprietary: 25/200† capsules; 1-2 times daily, 37.5/500† strong capsules; 1-2 times daily, 25/200†* suspension; 5ml and 10ml daily, 75/1000†* strong suspension;: 5ml daily	2.61
Co-danthrusate	Non-proprietary: 50/60‡ capsules; 1-3 daily, 50/60‡^ suspension, 5-15ml daily	3.29
Lactulose solution	Non-proprietary: solution 15ml twice daily	1.28
Senna	Non-proprietary: 7.5mg tablets; 2-4 daily, Senokot: syrup 7.5mg^ 10-20ml daily	0.54
Movicol	Oral powder: macrogol ‘3350’ sachet˜; 1-3 daily	3.12
Laxido	Oral powder: macrogol ‘3350’ sachet˜; 1-3 daily	3.12
Dulcolax	Perles® (=capsules); 5-10mg daily	1.59
Magnesium hydroxide	Non-proprietary: 20ml twice daily	1.26

Therapy	Medications and doses	Average weekly cost (£)
Overall		2.10

† Dantron to poloxamer ratio, e.g. 25/200 = dantron 25 mg, poloxamer '188' 200 mg

‡Dantron to docusate sodium ratio, e.g. 50/60 = dantron 50 mg, docusate sodium 60 mg

* Dose per 5ml

^Dose per ml

˜ 13.125g sodium bicarbonate, 178.5mg sodium chloride, 350.7mg potassium chloride, 46.6mg per sachet

Despite receiving concomitant laxatives to prevent constipation, patients in the model may still experience a constipation "event" (see the occurrence probabilities in table 1). Only the medication costs associated with a constipation event were considered in the model. It was assumed that patients will regularly make visits to the GP while receiving opioid therapy and additional visits would not be made in response to an adverse event.

The GDG advised that in the occurrence of a constipation event, patients would most likely receive strong oral laxatives or suppositories. However, in some 10% of patients (estimated by the GDG) an enema would be required. Table 5 shows the estimated cost of a constipation event that was applied in the model (using unit cost and dose information from the BNF).

Table 5: Constipation event costs

Therapy	Resource use	Average weekly cost (£)
Senna and docusate	Non-proprietary: 7.5mg tablets; 2-4 daily, Senokot: 7.5mg† syrup l 10-20ml daily	4.86
Bisacodyl suppositories	Non-proprietary: suppositories 10-20mg daily	0.97
Glycerol suppositories	Glycerin: suppositories 4g‡ daily	0.86
Enema		
Drug costs	Norgalax Micro-enema® 10-g* unit, Relaxit Micro-enema® 5ml^, Micralax Micro-enema® 5ml˜, Micolette Micro-enema® 5-10ml§	0.48
Administration cost	20 minute home visit by community nurse≈	24.00
Patients requiring enema		10%∞
Overall		4.68

† Dose per 5ml

‡ Gelatin 140 mg, glycerol 700 mg, purified water to 1 g

* Docusate sodium 120mg in 10-g dose

Therapy	Resource use	Average weekly cost (£)

^ Sodium citrate 450 mg, sodium lauryl sulphate 75 mg, sorbic acid 5 mg, together with glycerol and sorbitol in a viscous solution in 5-mL single-dose

˜Sodium citrate 450 mg, sodium alkylsulphoacetate 45 mg, sorbic acid 5 mg, together with glycerol and sorbitol in a viscous solution in 5-mL single-dose

§Sodium citrate 450 mg, sodium lauryl sulphoacetate 45 mg, glycerol 625 mg, together with potassium sorbate and sorbitol in a viscous solution, in 5-mL

≈Average length of 20 minutes from PSSRU (Netten and Curtis)

∞Assumption made by guideline development group (GDG)

Patients moving into the "Switching" health state receive a one-off cost associated with the process of switching. As shown in the table 6, this cost encompassed the cost of a GP visit, advice from a medical consultant (sought by GP), community nurse visit and GP telephone consultation.

Table 6: 'One-off' switching cost

Resource	Duration (minutes)	Cost (£)
GP surgery visit	11.7*	32.00
Medical consultant	10†	24.33
Community nurse visit	20.0*	24.00
GP telephone consultation	7.1*	19.00
Total	-	99.33

* Based on the average length of consultation reported in Netten and Curtis

†Assumption

It is assumed that patients in the "Switching" health state would receive one of the treatments under consideration (oral sustained-release morphine, oral sustained-release oxycodone, transdermal fentanyl or transdermal buprenorphine) that they have not received. In the model this is estimated as the average cost of the three treatments that the patient has not received. For example, patients switching from oral sustained-release morphine would receive an average of the cost of oral sustained-release oxycodone, transdermal fentanyl and transdermal buprenorphine.

This assumption was necessarily made because of a lack of data on the treatments that patients receive following a discontinuation of treatment with oral sustained-release morphine or transdermal fentanyl. For simplicity, the treatments that patients could receive were restricted to the therapies under consideration. In reality, there is a wide range of potential treatments that the

patients may receive (including non-opioid treatments). The impact of varying the treatment to which patients will switch is assessed in the sensitivity analysis.

The switching costs for patients switching from oral sustained-release morphine and transdermal fentanyl are shown in table 7.

Table 7: Switching costs

Switching from	Switching to	Average weekly cost
Morphine	Oxycodone, fentanyl or buprenorphine	£9.58
Fentanyl	Morphine, oxycodone or buprenorphine	£6.43

Health-related quality of life data

All patients receive a baseline quality of life of 0.592, which is associated with controlled pain. This value was based on a study by Goosens et al. (1999) in patients with chronic low back pain where a standard gamble technique was used to elicit the utility values. In the absence of suitably high quality data in the direct population of interest, this value was assumed to be representative of patients requiring strong opioids. This value was also used in the cost-effectiveness analysis by Greiner et al. (2006).

Patients who experience a constipation event incur a utility decrement of 0.072. This value was derived from SF-36 data from a systematic review of constipation on quality of life in adults and children (Belsey et al. 2010). Since NICE typically expresses a preference for the EQ-5D classification system when measuring quality of life (see NICE's 'Guide to the methods of technology appraisal'), a published mapping equation (Ara et al. 2008) was used to convert the SF-36 data to EQ-5D data. This particular mapping equation was chosen because it performed effectively in the validation exercise carried out by the authors (whereby mean statistics from published studies were used to validate the results).

Sensitivity analysis

To estimate uncertainty and determine the key drivers of the model, a series of one-way sensitivity analyses were conducted. One-way sensitivity analysis involves changing one input parameter, re-running the model and recording

the new cost-effectiveness result. Analyses were conducted where the value of an input variable was uncertain and the influence of changes to this variable on the cost-effectiveness result could be substantial.

Since the main benefit of transdermal fentanyl over oral sustained-release morphine is the reduction in constipation, changes to constipation-related variables could have a considerable influence on the cost-effectiveness result. Thus, changes to the discontinuation rate following constipation, the disutility associated with constipation and the proportion of patients requiring an enema following constipation were considered. In the absence of alternative evidence on the discontinuation associated with constipation, the discontinuation rate was increased to 50% and 100%. An alternative constipation utility decrement of 0.20 was sourced from a study by Penning Van Beest et al. (2010). Given the lack of evidence on the proportion of patients requiring an enema, alternative values of 50% and 100% were assumed.

Differences in constipation between the two treatments also manifest themselves in differences in the number of patients that switch. Therefore, changes to the cost of switching (i.e. the switching event) and the weekly cost associated with the "Switching" health state could have a considerable impact on the cost-effectiveness result. In the absence of alternative evidence on the switching cost, a scenario where the base case switching cost was doubled was considered. Changes were made to the weekly cost associated with the "Switching" health state by changing the assumption about the treatment that patients receive following a switch. Scenarios were considered whereby patients switch to buprenorphine, oxycodone or the direct comparator (e.g. if discontinuing oral sustained-release morphine, then switch to transdermal fentanyl).

An area of concern for the GDG was the potential for higher average maintenance doses than those assumed in the base case. Thus, based on a study by Lundorff et al. (2007), an oral sustained-release morphine dose of 120mg/day and transdermal fentanyl dose of 50µg/hour were considered.

To further estimate uncertainty in the model, probabilistic sensitivity analysis (PSA) was performed. PSA involves running a series of simulations where the values of the model's input parameters are randomly sampled from a distribution around their mean value (informed, where possible, by some measure of variance reported in the relevant study). This analysis is useful for assessing the uncertainty around all parameter values simultaneously.

Table 8 shows the input parameters that were included in the PSA along with the standard deviations (SD) that were used to model the distribution. Note that it was assumed that cost inputs follow a gamma distribution while other input parameters were normally distributed.

Table 8: Parameters and distribution values for the PSA

Parameter	Mean	SD
Constipation occurrence: Morphine	12.26%	7.92%*
Constipation occurrence: Fentanyl	6.24%	3.96%*
Constipation utility decrement	0.072	0.018†
Constipation cost	£4.68	£2.34‡
Switching cost	£99.33	£49.67‡
Therapy costs: Morphine	£2.33	£1.17‡
Therapy costs: Fentanyl	£11.84	£5.92‡

* Estimated using data from the systematic review and meta-analysis by Bekkering et al. (2011).**Error! Bookmark not defined.**

†Estimated by applying alternative mapping equations**Error! Bookmark not defined.** to the SF-36 data reported by Belsey et al. (2010)**Error! Bookmark not defined.**

‡ SDs could not be sourced, so these values were assumed to be equal to 50% of the mean value

Results

The results of the economic model are presented as expected costs and QALYs for each treatment arm along with an incremental cost-effectiveness ratio (ICER) for each treatment comparison. The ICER is used to measure the cost-effectiveness of one treatment over another; it is calculated as shown in figure 2.

Figure 2: Calculation of the incremental cost-effectiveness ratio (ICER)

ICER = (Δ Cost) / (Δ QALYs)

ICER = (Cost Intervention A − Cost Intervention B) / (QALYs Intervention A − QALYs Intervention B)

It can be seen that by dividing the difference in costs of each treatment by the difference in benefits (in QALY terms), a cost per QALY can be calculated for each comparison. NICE typically adopts a threshold of £20,000 for one additional QALY gained. Thus, an intervention with ICER < £20,000 can usually be considered cost-effective. Interventions with ICER values above £30,000 are not typically considered cost-effective. For ICER values between £20,000 and £30,000, an intervention may be considered cost-effective if it is associated with significant benefits.

To aid understanding of the economic modelling results by all interested parties, the results are presented with the most expensive treatment as the reference case (i.e. intervention A in the above calculation).

Base case results

The base case results of the model are presented in table 9 for the comparison of transdermal fentanyl versus oral sustained-release morphine.

Table 9: Base case total expected costs, QALYs and ICERs for transdermal fentanyl versus oral SR morphine

Time point	Fentanyl		Morphine		Incremental		ICER
	Costs	QALYs	Costs	QALYs	Costs	QALYs	
1 month	£90	0.0452	£54	0.0449	£35	0.0003	£107,532
2 months	£178	0.0906	£107	0.0899	£71	0.0007	£109,469
3 months	£288	0.1474	£172	0.1463	£116	0.0011	£110,096
6 months	£573	0.2957	£342	0.2936	£231	0.0021	£110,268
12 months	£1,135	0.5950	£678	0.5908	£457	0.0042	£109,636

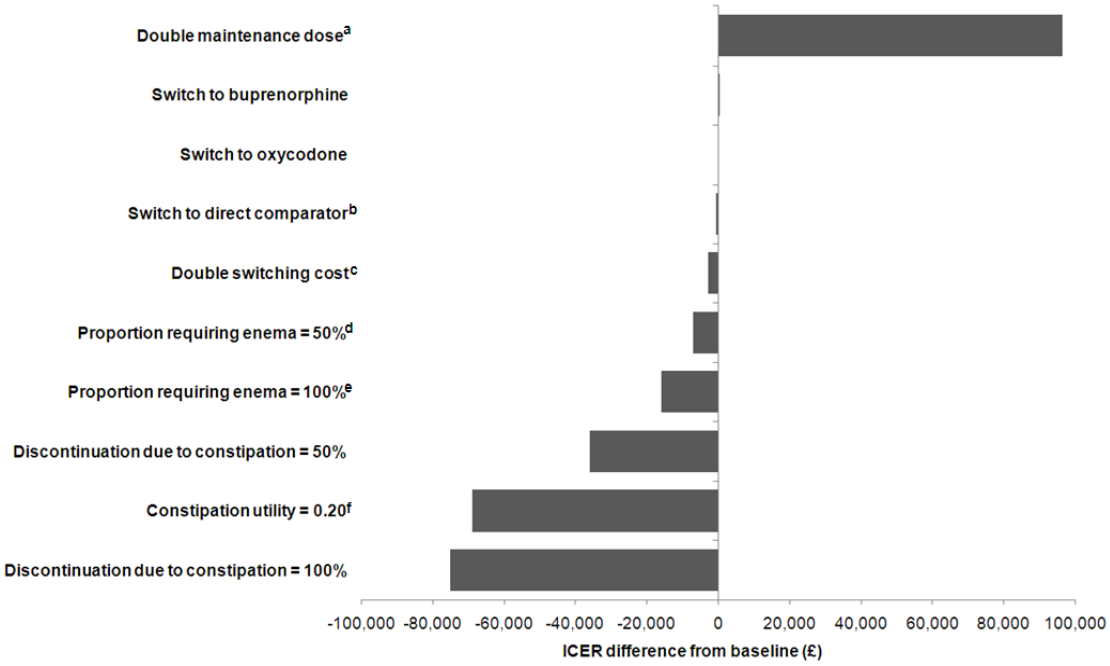
It can be seen that, at all time points, transdermal fentanyl provides an additional QALY benefit over oral sustained-release morphine but this comes at an additional cost. It can also be seen that the ICER result remains above £30,000 per QALY at all time points.

Sensitivity analysis

The results of the one-way sensitivity analyses are shown in figure 2 for the comparison of oral sustained-release morphine versus transdermal fentanyl. The x axis shows the difference in ICER value compared to the base case ICER with the vertical line representing the base case ICER result. Values to

the left of the vertical line show that the ICER is lower than in the base case (i.e. more cost-effective) and values to the right of the vertical line show that the ICER is higher than in the base case (i.e. less cost-effective).

Figure 3: Results of one-way sensitivity analysis for the comparison of transdermal fentanyl and oral sustained-release morphine



[a] Morphine dose of 120mg/day and fentanyl dose of 50µg/hour, based on Lundorff et al. (2007) and dose equivalence rates from the BNF.
[b] Patients originally receiving morphine switch to fentanyl and patients originally receiving fentanyl switch to morphine
[c] Increases switching cost to £198.66
[d] Increases constipation event cost to £14.47
[e] Increases constipation event cost to £26.71
[f] Sourced from Penning van beest et al. (2010)

The results show that the model is sensitive to changes in the discontinuation rate associated with constipation, the utility decrement assigned to constipation and the average maintenance dose that is applied in the model. The increase in the dose required for effective maintenance increases the ICER value. Conversely, the changes to the discontinuation probability or utility associated with constipation have the effect of decreasing the ICER. However note that in all cases, the ICER value remains above £30,000 per QALY.

At the request of the GDG, threshold analysis was performed around the cost of switching. This was considered because of uncertainty around the amount of healthcare resources that would be utilised when patients switch. For example, there is potential for higher switching costs if the amount of

specialist advice required for a switch increases. Threshold analysis finds the value of an input that is required for the ICER value to be below a cost-effectiveness threshold of £20,000 per QALY.

Threshold analysis revealed that a switching cost of £3,086 would be required for transdermal fentanyl to be cost-effective against oral sustained-release morphine at a threshold of £20,000 per QALY. Further analysis showed that when applying a utility decrement of 0.20 for constipation events (Penning et al. 2008), a switching cost of £1,873 and would be required for transdermal fentanyl to be cost-effective against oral sustained-release morphine at a threshold of £20,000 per QALY.

The results of the PSA are shown in figure 4 and figure 5, which depict the results using a cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC), respectively.

Figure 4: Probabilistic sensitivity analysis (PSA) results shown on a cost-effectiveness plane

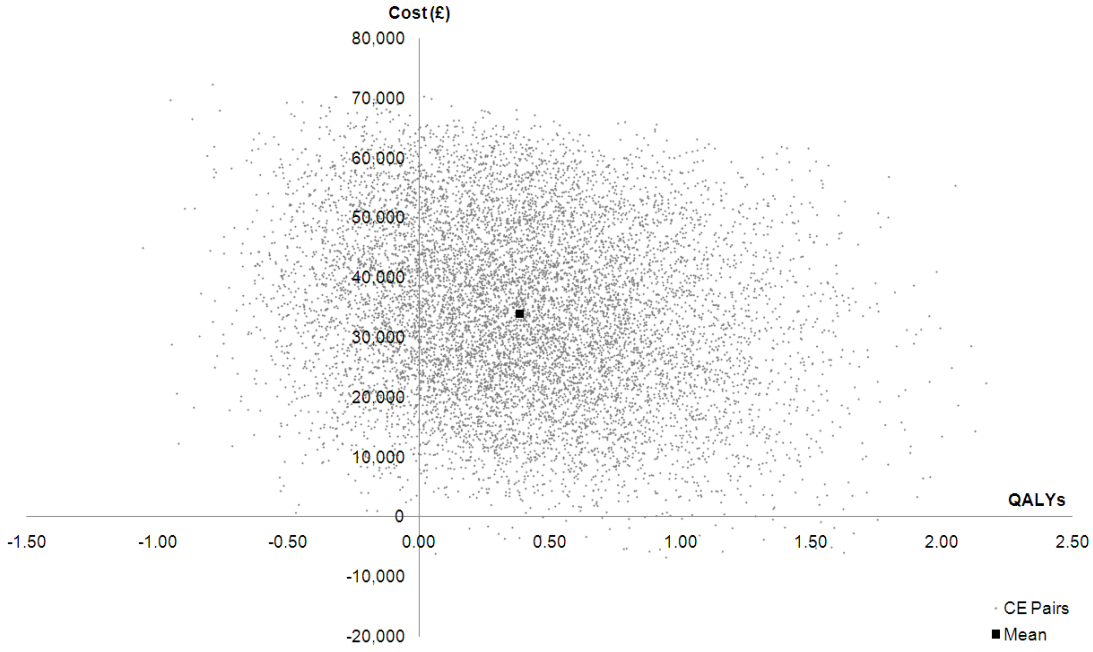


Figure 5: Probabilistic sensitivity analysis (PSA) results depicted using a cost-effectiveness acceptability curve (CEAC)

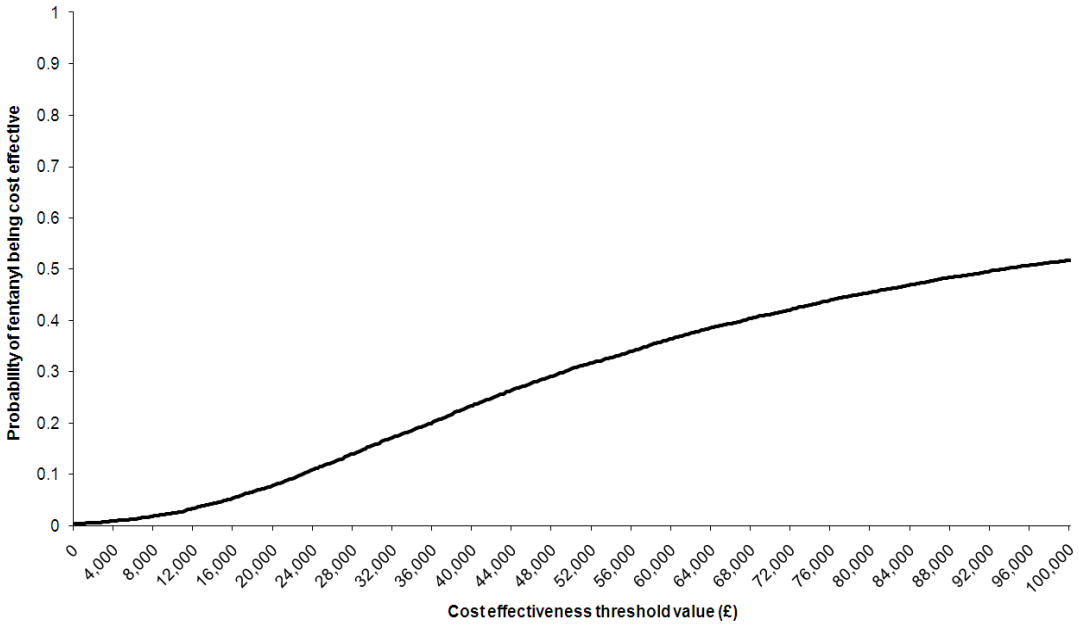


Figure 4 shows 10,000 cost-effectiveness pairs with each pair representing the result of an individual simulation in the PSA. The mean result based on these cost-effectiveness pairs is also shown. It can be seen that the mean result lies in the North East (NE) quadrant of the graph reflecting that fentanyl is more costly and more effective. It can also be seen that the majority of the cost-effectiveness pairs lie within the NE quadrant. However, note that the cost-effectiveness pairs are not tightly grouped around the mean value. Indeed, they are quite widely dispersed and span three of the four quadrants of the cost-effectiveness plane (NE, SE and NW). This suggests that there is considerable uncertainty around the mean result and that in some cases it's possible for transdermal fentanyl to be dominated or dominant in comparison to oral sustained-release morphine.

Figure 5 shows the probability that fentanyl is cost-effective against morphine at various cost-effectiveness thresholds. Thus, it gives a useful insight into how the uncertainty shown in figure 4 affects the cost-effectiveness decision. It can be seen from figure 5 that the probability of transdermal fentanyl being cost-effective increases as the cost-effectiveness threshold increases. At a cost-effectiveness threshold of £20,000 per QALY, it can be seen that the probability of transdermal fentanyl being cost-effective against oral sustained-release morphine is 8%.

Discussion

This analysis aimed to estimate the cost-effectiveness of strong opioids in patients with advanced and progressive disease for whom previous treatments have failed. The systematic review identified that there were few relevant studies conducted in this area. Furthermore, those studies that were identified had serious limitations and were considered only partially applicable to the guideline. Thus, a new economic evaluation was conducted.

The clinical evidence review showed that oral sustained-release oxycodone and oral sustained-release morphine were equal in effectiveness terms (nine out of nine studies showed no statistically significant differences in pain relief and four out of five studies showed no statistically significant differences in side effects). Thus, economic modelling was not required for this comparison and a decision on cost-effectiveness could be made purely on the basis of the cost of treatment. Thus, since oral sustained-release morphine is cheaper than oral sustained-release oxycodone, oral sustained-release morphine is the more cost-effective treatment option (i.e. provides the same benefit but at a lower cost).

The clinical review for oral sustained-release morphine versus transdermal buprenorphine did not identify any studies that were of a high enough quality to be used as the basis for an economic model.

The clinical review for oral sustained-release morphine versus transdermal fentanyl did identify significant differences in effectiveness between the studies. Thus, economic modelling was conducted for this comparison. The base case results of the model suggest that, at a cost-effectiveness threshold of £20,000 per QALY, transdermal fentanyl is not cost-effective against oral sustained-release morphine at all time points.

The one-way sensitivity analysis that was conducted showed that the model was sensitive to changes in the average maintenance dose, the utility decrement associated with constipation and the probability of discontinuation following a constipation event. However, the ICER result in all analyses

remained above £30,000 and so oral sustained-release morphine remained the more cost-effective treatment in all the analyses considered.

Threshold analysis was conducted on the switching cost required to attain cost-effectiveness at a threshold of £20,000 per QALY. The results showed that switching costs of £3,086 and £1,873 would be required when considering the base case scenario and the scenario with an increased utility decrement (0.20), respectively. These were considerably higher than even the highest switching costs expected by the GDG members.

The PSA showed considerable variation around the mean result. However, at a threshold of £20,000 per QALY there was only a 14% probability that transdermal fentanyl would be cost-effective against oral sustained-release morphine.

There are a number of limitations with the economic analysis that should be acknowledged. Firstly, the dose of strong opioids required for the effective management of pain typically increases over time. In the model, an average maintenance dose was applied for the duration of the modelled time horizon. However, the clinical evidence review didn't reveal differences in the amount of dose increases required for each treatment. Thus, given the differences in treatment costs, this assumption would most likely bias against oral sustained-release morphine. Therefore, if dose increases were to be considered in the model it would most likely only strengthen the conclusion that oral sustained-release morphine is the more cost-effective treatment.

A second limitation is the assumption that patients can only switch once. This implicitly implies that the second treatment that a patient receives is effective and well tolerated. The likely influence of this assumption on the cost-effectiveness result is somewhat difficult to ascertain. However, it is possible that allowing for multiple switches would improve the cost-effectiveness of transdermal fentanyl.

Conclusion

The results of the base-case analysis show that, in comparison with oral sustained-release morphine, transdermal fentanyl provides additional quality of life benefits to patients as a result of a reduction in adverse events. However, these benefits come at an additional cost and it was found that these benefits were not substantial enough to make transdermal fentanyl cost-effective in comparison to oral sustained-release morphine.

Oral sustained-release morphine holds a cost advantage over oral sustained-release oxycodone and transdermal buprenorphine. The clinical evidence shows that oral sustained-release morphine is equivalent to oral sustained-release oxycodone in effectiveness terms. Thus, in the average patient, oral sustained-release morphine provides the same benefit as oral sustained-release oxycodone but a lower price. It can therefore be considered the more cost-effective treatment. The clinical evidence base for the comparison of oral sustained-release morphine and transdermal buprenorphine was considered to be of very low quality. It was therefore considered inappropriate to use it as the basis for an economic evaluation.

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