Epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for the treatment of pulmonary arterial hypertension in adults

Assessment Group Additional Work

West Midlands Health Technology Assessment Collaboration

January 2008

1. Question: What is the effect on cost-effectiveness of altering the assumption that patients receive supportive care including epoprostenol once they have progressed to FCIV in both the active and supportive care arms of the model?

Analysis requested by NICE: Based on the reference case in the Assessment Report, conduct an extreme case analysis (for all the five technologies) by modifying the model to remove epoprostenol from supportive care in the FCIV state for the active treatment and supportive treatment arms. Thus patients in FCIV only receive supportive care.

To explore this, the assessment model was run for all therapies assuming that patients receive supportive care alone in FCIV. This is in contrast with the reference case where epoprostenol is assumed to be prescribed. The findings are presented below. No analysis is presented for epoprostenol in FCIV as the reference case analysis already assumes supportive care only in the comparator arm.

1.1 Epoprostenol in addition to supportive care versus supportive care alone, FCIII

Table 1 shows the results of the analysis for epoprostenol in FCIII. Compared with supportive care alone, epoprostenol alongside supportive care is more expensive but generates more QALYs, giving an ICER of £273,000 per QALY gained. The CEAC presented in Figure 1 shows that at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, epoprostenol has a zero probability of being cost-effective.

Table 1 Epoprostenol with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	115,000		1.091		
Epoprostenol	344,000	229,000	1.927	0.837	273,000

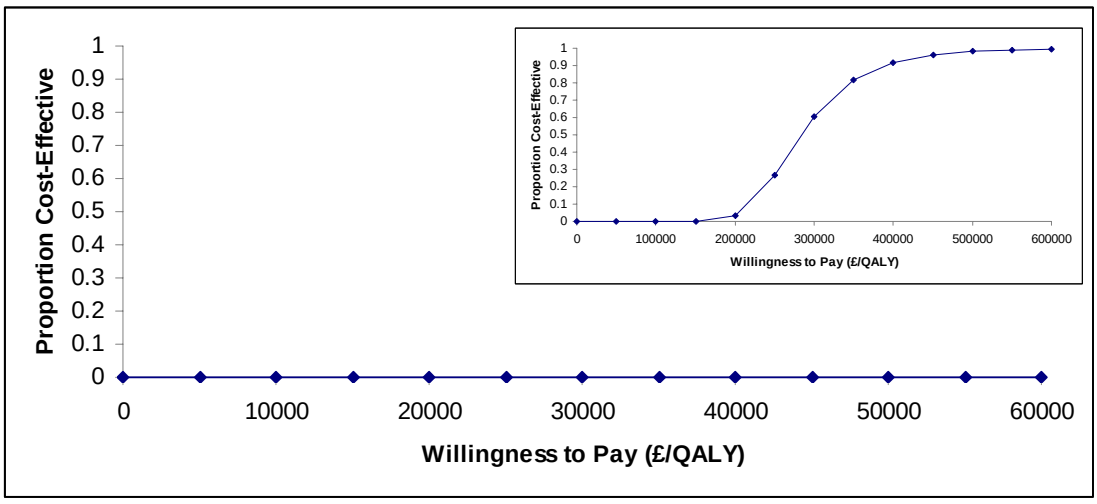

Figure 1 CEAC for epoprostenol with supportive care versus supportive care alone, FCIII

Inset graph shows larger X-axis scale

1.2 Iloprost with supportive care versus supportive care alone, FCIII

Table 2 shows the results of the analysis for iloprost in FCIII. Iloprost alongside supportive care is more costly than supportive care alone but yields more QALYs, giving an ICER of £98,000 per QALY gained. The CEAC presented in Figure 2 shows that at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, iloprost has a zero probability of being cost-effective.

Table 2 Iloprost with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	105,000		1.086		
Iloprost	207,000	102,000	2.131	1.045	98,000

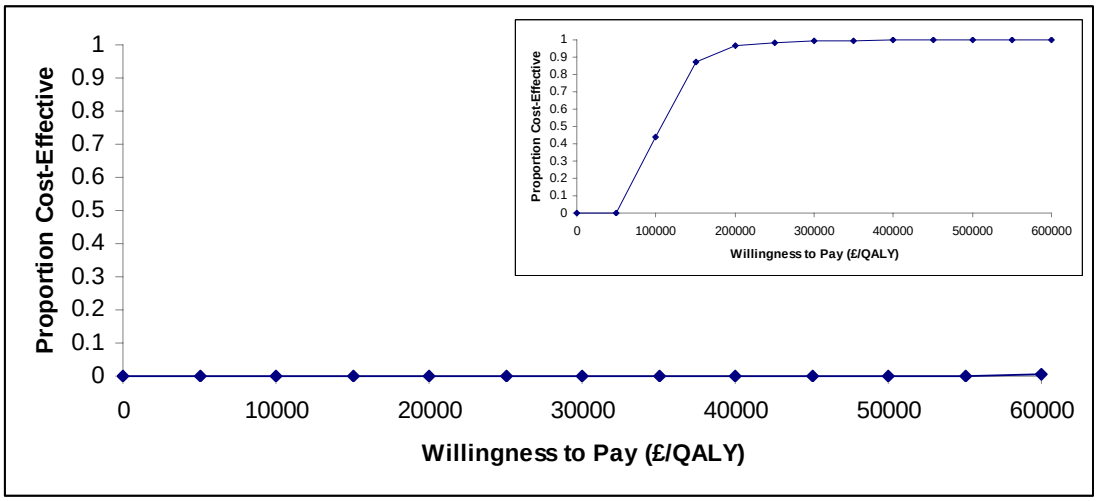

Figure 2 CEAC for iloprost with supportive care versus supportive care alone, FCIII

Inset graph shows larger X-axis scale

1.3 Bosentan in addition to supportive care versus supportive care alone, FCIII

Table 3 shows the results for bosentan, with the intervention more expensive than supportive care alone and producing a greater amount of QALYs, resulting in an ICER of £42,000 per QALY gained. The CEAC in Figure 3 demonstrates that bosentan has a zero chance of being cost-effective at £20,000 per QALY and a 3% chance at £30,000 per QALY.

Table 3 Bosentan with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	84,000		1.532		
Bosentan	239,000	155,000	5.209	3.677	42,000

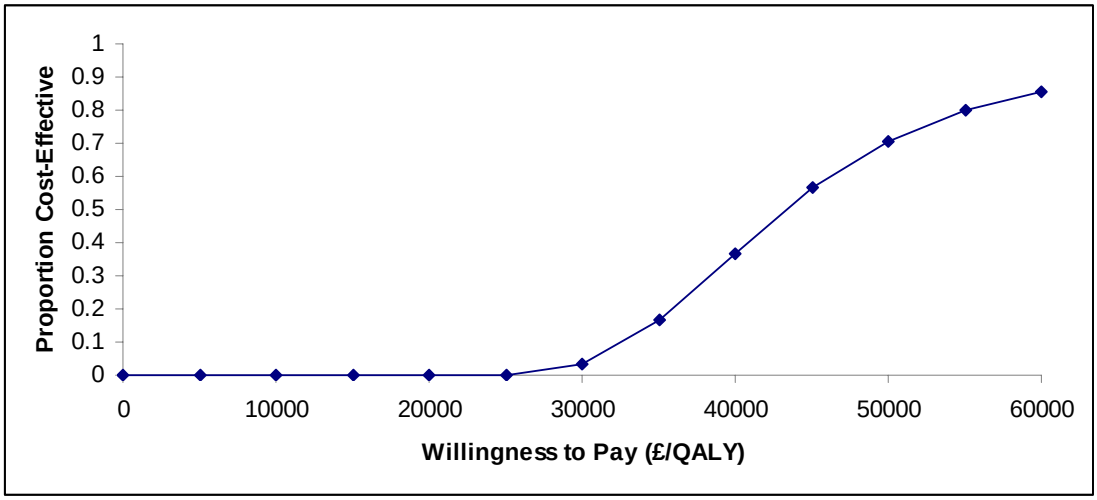

Figure 3 CEAC for bosentan with supportive care versus supportive care alone, FCIII

1.4 Sitaxentan in addition to supportive care versus supportive care alone, FCIII

Table 4 shows the results for sitaxentan, with the intervention more expensive than supportive care alone and producing greater amount of QALYs, resulting in an ICER of £44,000 per QALY gained (Table 4). The CEAC presented in Figure 4 demonstrates that at thresholds of £20,000 and £30,000 per QALY gained, the probability of sitaxentan of being cost-effective is zero and 3% respectively.

Table 4 Sitaxentan with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	84,000		1.532		
Sitaxentan	226,000	142,000	4.780	3.248	44,000

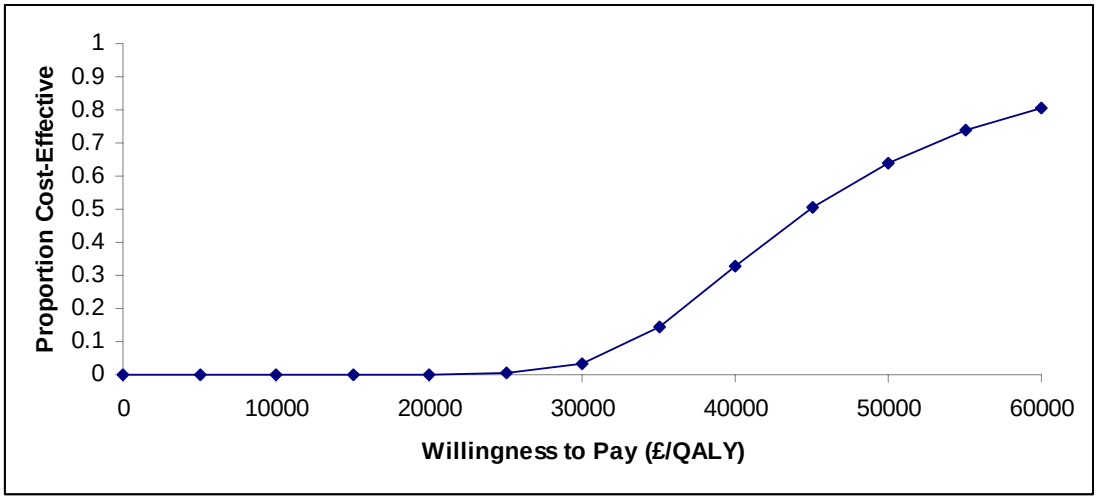

Figure 4 CEAC for sitaxentan with supportive care versus supportive care alone, FCIII

1.5 Sildenafil in addition to supportive care versus supportive care alone, FCIII

Table 5 shows the results for sildenafil, with the intervention more expensive than supportive care alone and producing greater amount of QALYs, resulting in an ICER of £9,000 per QALY gained. The CEAC presented in Figure 5 shows that sildenafil has a probability of being cost-effective of 83% at £20,000 per QALY and 92% at £30,000 per QALY.

Table 5 Sildenafil with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	84,000		1.532		
Sildenafil	115,000	31,000	4.950	3.418	9,000

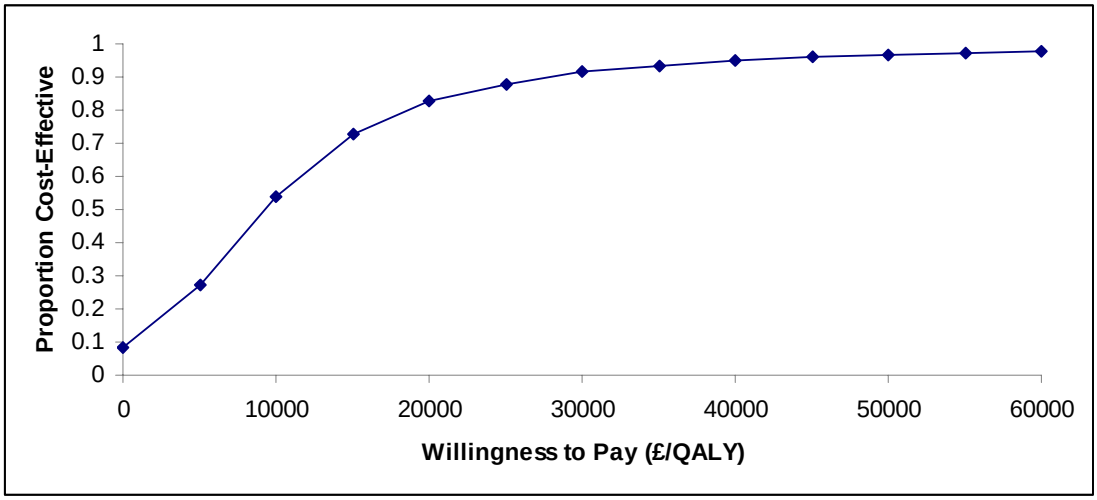

Figure 5 CEAC for sildenafil with supportive care versus supportive care alone, FCIII

1.6 Summary of results – comparison with reference case

- The ICER for epoprostenol reduced very slightly from £277,000 per QALY gained to £273,000. Although the difference in costs increases, the difference in QALYs also increases.
- The ICER for iloprost reduced very slightly from £101,000 per QALY gained to £98,000. The difference in costs changes very little but the difference in benefits is greater.
- The ICER for bosentan increased from £27,000 per QALY gained to £42,000. Although the difference in QALYs increases slightly, the difference in costs is much greater.
- The ICER for sitaxentan increased from £25,000 per QALY gained to £44,000. Although the difference in QALYs increases slightly, the difference in costs is much greater.
- The ICER for sildenafil was £9,000 per QALY gained compared with being dominant in the reference case. The difference in QALYs increases, however the direction on the difference in costs changes, so costs are now greater in the sildenafil arm.

1.7 Explanation of results

When comparing treatments which start in FCIII patients, in the reference case the main drive of cost in both the treatment and supportive care arms was epoprostenol for patients subsequently reaching FCIV. Removal of epoprostenol from FCIV substantially reduced the costs in both arms, but more so in the supportive care arm as more patients reach FCIV and they do so quicker compared to the treatment arm (i.e. treatment of FCIII patients reduces the proportion and delays progression to FCIV). The supportive care option therefore became relatively cheap. The removal of epoprostenol also meant there was greater loss of QALY (that would be saved by using epoprostenol) in the supportive care arm, but this had less impact on the ICERs compared to the change in costs.

This scenario may not reflect clinical practice, as other prostaglandins (which may not have been licensed in the UK) may be used if epoprostenol is not available for treating FCIV patients.

2. Question: What is the effect on cost effectiveness of the oral drugs if the same assumptions for mortality on treatment and best supportive care are used as those used for epoprostenol in functional class III?

Analysis requested by NICE: Based on the reference case in the Assessment Report, conduct a sensitivity analysis (for the three oral drugs) by applying the same mortality on treatment and mortality on supportive care as those used for epoprostenol in functional class III.

The data on mortality for epoprostenol (0.021 per cycle, 95% CI 0.017 to 0.025) and the corresponding mortality for supportive care (0.051 per cycle, 0.041 to 0.069) were used in the model, replacing those mortalities used in the reference case analysis for each intervention (see Appendix 9 of the main report).

2.1 Bosentan in addition to supportive care versus supportive care alone, FCIII

Table 6 shows the results of the analysis for bosentan in FCIII. Bosentan alongside supportive care is more costly than supportive care alone but yields more QALYs, giving an ICER of £6,000 per QALY gained. The CEAC presented in Figure 6 shows that at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, bosentan has a 67% and 75% probability of being cost-effective respectively.

Table 6 Bosentan with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	349,000		2.236		
Bosentan	364,000	14,000	4.857	2.620	6,000

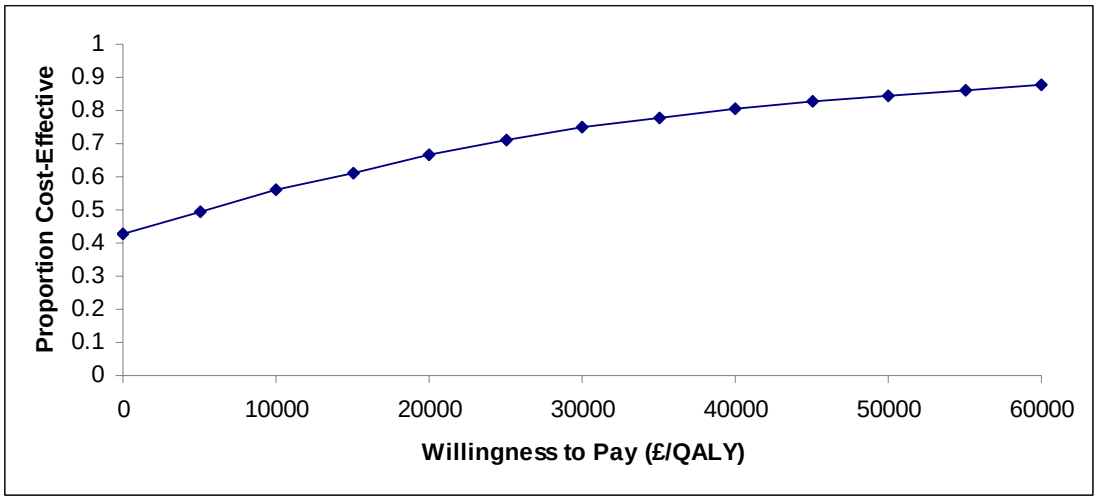

Figure 6 CEAC for bosentan with supportive care versus supportive care alone, FCIII

2.2 Sitaxentan in addition to supportive care versus supportive care alone, FCIII

Table 7 shows the results of the analysis for sitaxentan in FCIII. Sitaxentan alongside supportive care is more costly than supportive care alone but yields more QALYs, giving an ICER of £1,400 per QALY gained. The CEAC presented in Figure 7 shows that at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, bosentan has a 67% and 73% probability of being cost-effective respectively.

Table 7 Sitaxentan with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	349,000		2.236		
Sitaxentan	352,000	3,000	4.409	2.173	1,400

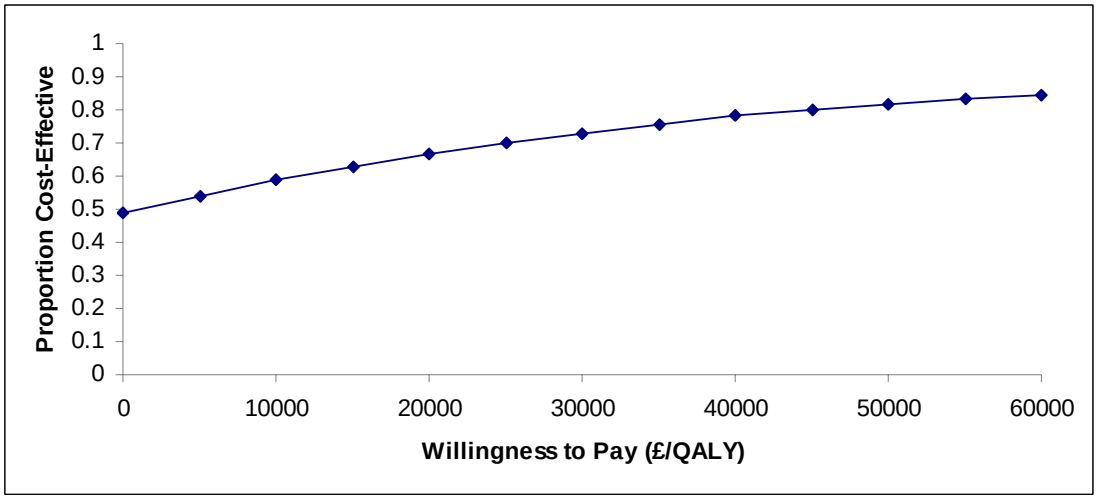

Figure 7 CEAC for sitaxentan with supportive care versus supportive care alone, FCIII

2.3 Sildenafil in addition to supportive care versus supportive care alone, FCIII

Compared with supportive care alone, sildenafil is less costly and more effective resulting in dominance for the intervention (Table 8). The CEAC presented in Figure 8 shows that sildenafil has a probability of being cost-effective of 86% at £20,000 per QALY and 89% at £30,000 per QALY.

Table 8 Sildenafil with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	349,000		2.236		
Sildenafil	259,000	-90,000	4.618	2.381	Dominant

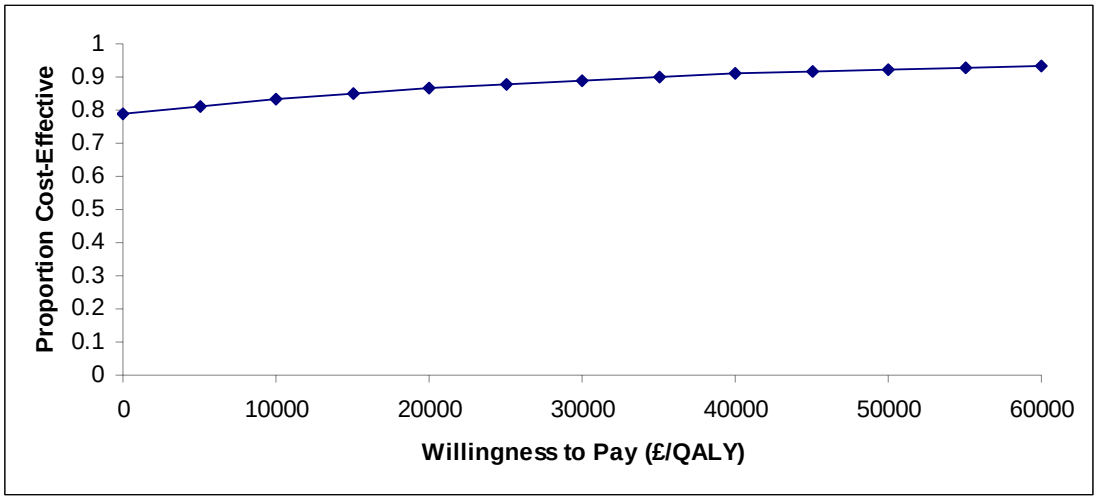

Figure 8 CEAC for sildenafil with supportive care versus supportive care alone, FCIII

2.4 Summary of results – comparison with reference case

- The ICER for bosentan is much lower, dropping from £27,000 per QALY gained in the reference case to £6,000. Although the difference in QALYs decreases, the difference in costs is much reduced.
- The ICER for sitaxentan is greatly reduced from £25,000 per QALY gained to £1,400. Although the difference in QALYs decreases, the difference in costs is now very small.
- In both the reference case and this additional analysis, sildenafil is dominant when compared to supportive care. However, the probability of being cost-effective at thresholds of £20,000 and £30,000 per QALY gained is greater in the additional analysis compared to the reference case.

2.5 Explanation of results

This sensitivity analysis explored a scenario in which the mortality on treatment and mortality on supportive care in FCIII for the three oral treatments are the same as those for epoprostenol, i.e. if these treatments offer the same survival benefit **and** there is no difference in 'baseline mortality' between patients treated with different drugs. Compared to the reference case, the mortality in the treatment arm for the oral treatments was almost doubled (per cycle mortality on treatment in FCIII was increased from 0.011 to 0.021), whilst the mortality in the supportive care arm was slightly reduced (from 0.058 to 0.051). This reduced the proportion of patients surviving to reach FCIV (which would incur expensive epoprostenol treatment) in the oral treatment arms, whist slightly increasing the proportion of patients surviving to reach FCIV in the supportive care arms. The oral treatment options therefore became comparatively cheaper compared to the reference case. Although the QALY gain in the oral treatment groups was reduced and the QALY gain in the supportive care was slightly increased compared to the reference case, the changes in cost appear to have a greater impact than the changes in QALY.

3. Question: What would be the minimum survival benefit required for the oral drugs to meet cost effectiveness thresholds of 20k, 30k and 40k per QALY?

Analysis requested by NICE: Based on the reference case in the Assessment Report, conduct a sensitivity analysis (for the three oral drugs) on the minimum survival benefit (in terms of the odds ratio for the risk of death on treatment over the risk of death on supportive care) required to meet incremental cost effectiveness thresholds of 20k, 30k and 40k per QALY.

Data for mortality on treatment was available for some oral therapies from long-term observational studies. There is a lack of data in the literature with regard to long-term mortality for patients who receive supportive care alone because it is considered unethical to withhold active treatments that have proven to be effective. In the model, to account for this absence of data, mortality on supportive care was derived by applying an odds ratio to the mortality on oral treatment. The odds ratio used was the same as the odds ratio for deterioration from FCIII to FCIV for each treatment relative to supportive care. This odds ratio was obtained from the RCTs on the effectiveness of the oral therapies and used under the assumption that a treatment which delays deterioration in FC in the short-term would also reduce mortality proportionately in the long-term.

In this threshold analysis, the odds ratio (which approximates the survival benefit) was varied in order to determine at what level of benefit did oral drugs reach the suggested cost-effectiveness thresholds. A smaller odds ratio (further away from 1 and towards 0) corresponds to a larger survival benefit for the active treatment; conversely, a larger odds ratio (closer to 1) corresponds to a smaller survival benefit for the active treatment compared to supportive care.

Model runs have been conducted as per the reference case, with epoprostenol available for patients in FCIV. Results are presented for odds ratios of 0.1, 0.2 and 0.3 and for the odds ratio giving an ICER in the region of £20,000, £30,000 and £40,000 per QALY gained. As can been seen in tables 9 to 11, the ICERs increase (the treatments become less cost-effective) as the survival benefits increase (the odds ratios become smaller).

Table 9 Results for bosentan

Odds ratio	12 week cycle mortality on supportive care[a]	Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER £/QALY
0.1	0.100	Comparator	264,000		1.731		
		Active therapy	434,000	170,000	5.689	3.959	43,000
0.115	0.088	Comparator	282,000		1.838		
		Active therapy	434,000	153,000	5.688	3.849	40,000
0.165	0.063	Comparator	328,000		2.111		
		Active therapy	434,000	106,000	5.687	3.577	30,000
0.18[b]	0.058	Comparator	343,000		2.201		
		Active therapy	436,000[c]	93.000	5.969	3.494	27,000
0.2	0.053	Comparator	351,000		2.246		
		Active therapy	434,000	83,000	5.680	3.434	24,000
0.23	0.046	Comparator	367,000		2.342		
		Active therapy	434,000	67,000	5.683	3.341	20,000
0.3	0.036	Comparator	396,000		2.512		
		Active therapy	434,000	39,000	5.683	3.171	12,000

[a]The per cycle mortality on supportive care was derived assuming per cycle mortality of 0.011 on treatment.
[b]Reference case shown in the main report.
[c]Small variations in the cost for active therapy are due to the use of different random number sets.

Table 10 Results for sitaxentan

Odds ratio	12 week cycle mortality on supportive care[a]	Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER £/QALY
0.1	0.100	Comparator	264,000		1.731		
		Active therapy	420,000	157,000	5.254	3.523	44,000
0.118	0.086	Comparator	284,000		1.855		
		Active therapy	421,000	136,000	5.255	3.400	40,000
0.165	0.063	Comparator	328,000		2.111		
		Active therapy	421,000	93,000	5.262	3.151	30,000
0.18[b]	0.058	Comparator	343,000		2.201		
		Active therapy	419,000[c]	76,000	5.289	3.087	25,000
0.2	0.053	Comparator	351,000		2.246		
		Active therapy	421,000	70,000	5.268	3.022	23,000
0.22	0.048	Comparator	362,000		2.312		
		Active therapy	421,000	59,000	5.266	2.954	20,000
0.3	0.036	Comparator	396,000		2.512		
		Active therapy	421,000	25,000	5.263	2.751	9,000

[a]The per cycle mortality on supportive care was derived assuming per cycle mortality of 0.011 on treatment.
[b]Reference case shown in the main report.
[c]Small variations in the cost for active therapy are due to the use of different random number sets.

Table 11 Results for sildenafil

Odds ratio	12 week cycle mortality on supportive care[a]	Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER £/QALY
0.03	0.270	Comparator	124,000		0.895		
		Active therapy	305,000	182,000	5.459	4.563	40,000
0.05	0.182	Comparator	178,000		1.222		
		Active therapy	306,000	128,000	5.445	4.223	30,000
0.075	0.129	Comparator	227,000		1.514		
		Active therapy	307,000	80,000	5.432	3.918	20,000
0.1	0.100	Comparator	264,000		1.731		
		Active therapy	307,000	43,000	5.432	3.702	12,000
0.18[b]	0.058	Comparator	343,000		2.201		
		Active therapy	307,000	-36,000	5.436	3.235	Dominates
0.2	0.053	Comparator	351,000		2.246		
		Active therapy	307,000	-44,000	5.428	3.182	Dominates
0.3	0.036	Comparator	396,000		2.512		
		Active therapy	308,000	-88,000	5.427	2.915	Dominates

[a]The per cycle mortality on supportive care was derived assuming per cycle mortality of 0.011 on treatment.
[b]Reference case shown in the main report.
Small variations in the cost for active therapy are due to the use of different random number sets.

3.1 Explanation of results

The results are consistent with those from the sensitivity analysis described in section 2. Both analyses show that by reducing the survival benefit of the active treatment, either through increasing the mortality on treatment (as in section 2) or through increasing the odds ratio closer to one (hence reducing the mortality on supportive care as in this section), the active treatment becomes more cost-effective.

This is because when survival benefit is reduced compared to the reference case, either a smaller proportion of patients in the oral treatment arm survived to reach FCIV (which would incur expensive epoprostenol treatment), or a larger proportion of patients in the supportive care arm survived to reach FCIV. The oral treatment options therefore became comparatively cheaper. Although the QALY gain in the oral treatment groups was reduced and the QALY gain in the supportive care was increased compared to the reference case, the changes in costs appear to have a greater impact on the ICERs than the changes in QALYs.

4. Question: What is the effect on cost effectiveness of altering the assumption on mortality in FCIII, i.e. that people in the model go straight from FCIII to death rather than go through FCIV first for all drugs in this appraisal?

Analysis requested by NICE: Based on the reference case in the Assessment Report, conduct an extreme case analysis (for all the five technologies) which assumes that no death occurs while patients stay in FCIII.

The assessment model was run including the assumption that no PAH-related mortality was possible in FCIII, therefore patients had to be in FCIV before this type of mortality was possible.

4.1 Epoprostenol in addition to supportive care versus supportive care alone, FCIII

Table 12 shows the results of the analysis for epoprostenol in FCIII. Compared with supportive care alone, epoprostenol alongside supportive care is more expensive but generates more QALYs, giving an ICER of £285,000 per QALY gained. The CEAC presented in Figure 9 shows that at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, epoprostenol has a zero probability of being cost-effective.

Table 12 Epoprostenol with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	600,000		2.530		
Epoprostenol	838,000	238,000	3.367	0.837	285,000

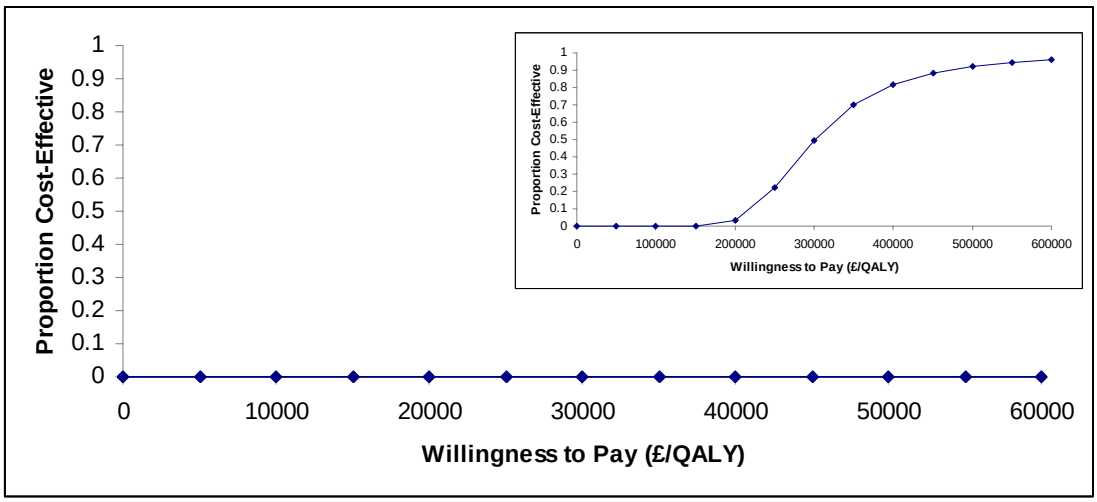

Figure 9 CEAC for epoprostenol with supportive care versus supportive care alone, FCIII

Inset graph shows larger X-axis scale

4.2 Epoprostenol in addition to supportive care versus supportive care alone, FCIV

Table 13 shows the results of the analysis for epoprostenol in FCIV. Compared with supportive care alone, epoprostenol alongside supportive care is more expensive but generates more QALYs, giving an ICER of £337,000 per QALY gained. The CEAC presented in Figure 10 shows that at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, epoprostenol has a zero probability of being cost-effective.

Table 13 Epoprostenol with supportive care versus supportive care alone, FCIV

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	128,000		0.826		
Epoprostenol	565,000	437,000	2.121	1.295	337,000

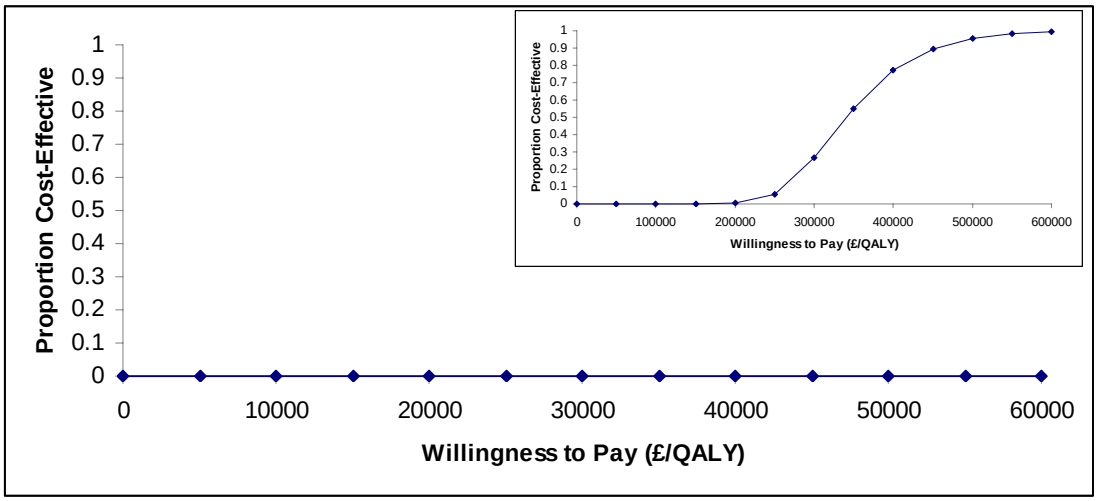

Figure 10 CEAC for epoprostenol with supportive care versus supportive care alone, FCIV

Inset graph shows larger X-axis scale

4.3 Iloprost with supportive care versus supportive care alone, FCIII

Table 14 shows the results of the analysis for iloprost in FCIII. Iloprost alongside supportive care is more costly than supportive care alone but yields more QALYs, giving an ICER of £76,000 per QALY gained. The CEAC presented in Figure 11 shows that at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, iloprost has a zero probability of being cost-effective.

Table 14 Iloprost with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	599,000		2.635		
Iloprost	682,000	83,000	3.733	1.098	76,000

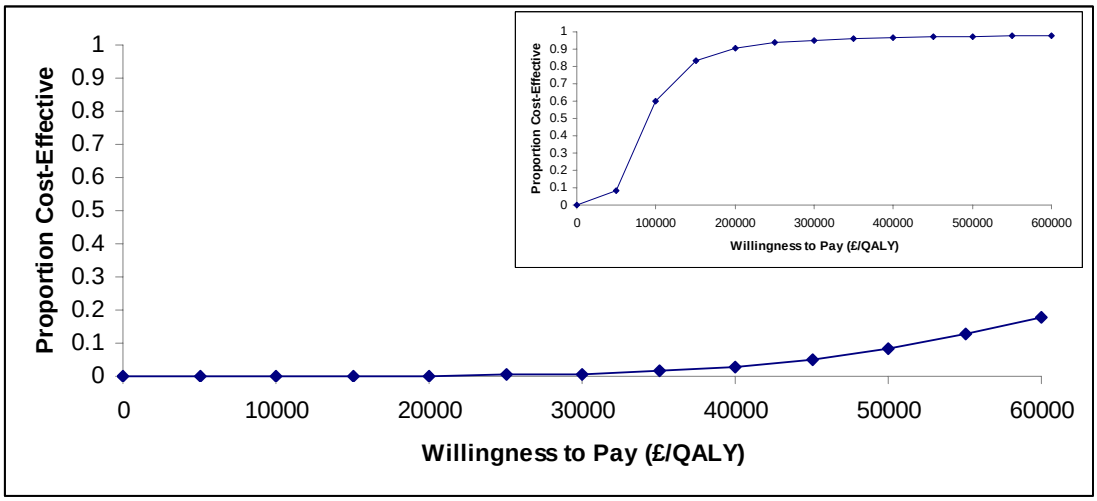

Figure 11 CEAC for iloprost with supportive care versus supportive care alone, FCIII

Inset graph shows larger X-axis scale

4.4 Bosentan in addition to supportive care versus supportive care alone, FCIII

Table 15 shows the results for bosentan, with the intervention less expensive than supportive care alone and producing a greater amount of QALYs, resulting in bosentan being dominant over supportive care. The CEAC in Figure 12 demonstrates that bosentan has an 82% chance of being cost-effective at £20,000 per QALY and an 88% chance at £30,000 per QALY.

Table 15 Bosentan with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	572,000		3.494		
Bosentan	551,000	-21,000	6.992	3.498	Dominant

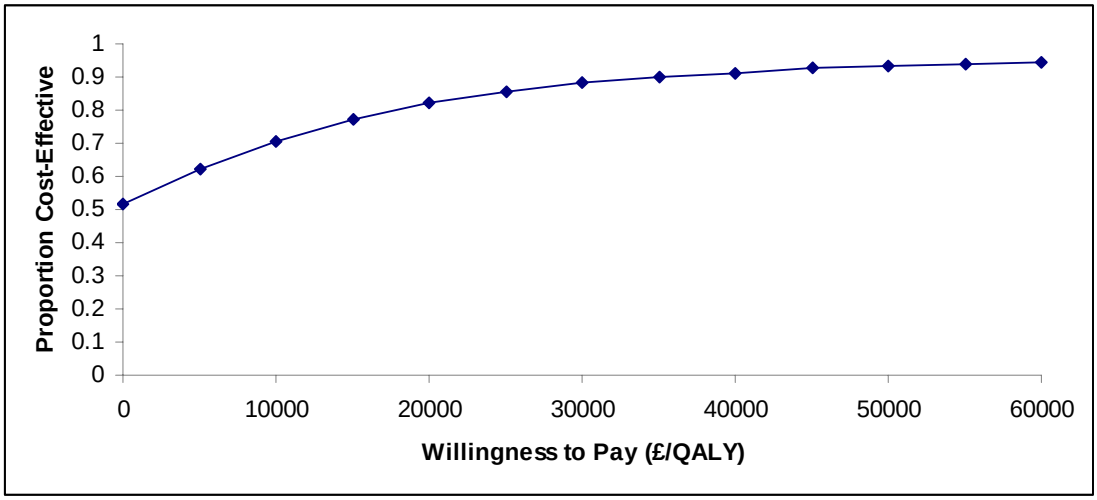

Figure 12 CEAC for bosentan with supportive care versus supportive care alone, FCIII

4.5 Sitaxentan in addition to supportive care versus supportive care alone, FCIII

Table 16 shows the results for sitaxentan, with the intervention less expensive than supportive care alone and producing a greater amount of QALYs, resulting in sitaxentan being dominant over supportive care.. The CEAC presented in Figure 13 demonstrates that at thresholds of £20,000 and £30,000 per QALY gained, the probability of sitaxentan of being cost-effective is 79%o and 85% respectively.

Table 16 Sitaxentan with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	572,000		3.494		
Sitaxentan	553,000	-19,000	6.812	3.318	Dominant

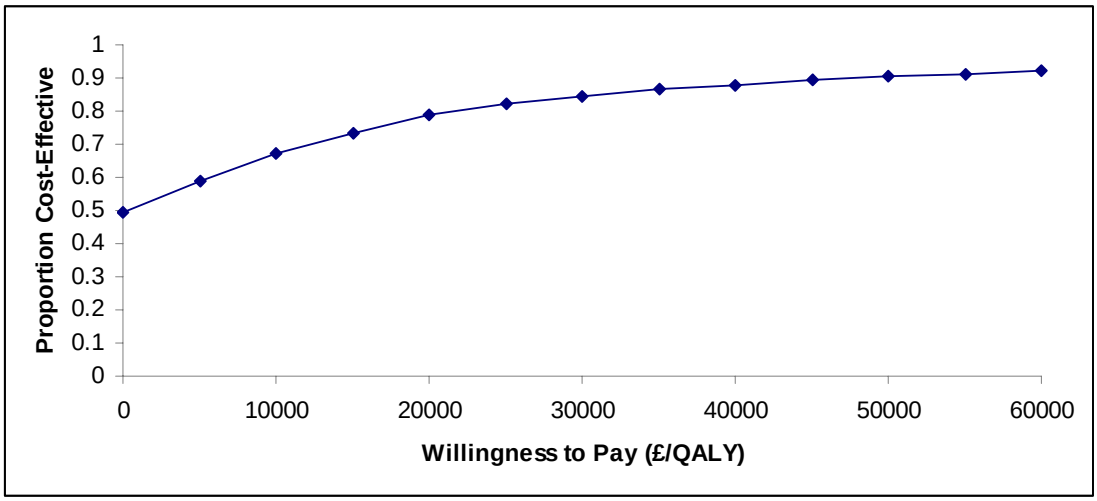

Figure 13 CEAC for sitaxentan with supportive care versus supportive care alone, FCIII

4.6 Sildenafil in addition to supportive care versus supportive care alone, FCIII

Table 17 shows the results for sildenafil, with the intervention less expensive than supportive care alone and producing a greater amount of QALYs, resulting in dominance over supportive care. The CEAC presented in Figure 14 shows that sildenafil has a probability of being cost-effective of 98% at both £20,000 and £30,000 per QALY.

Table 17 Sildenafil with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	572,000		3.494		
Sildenafil	404,000	-168,000	6.893	3.399	Dominant

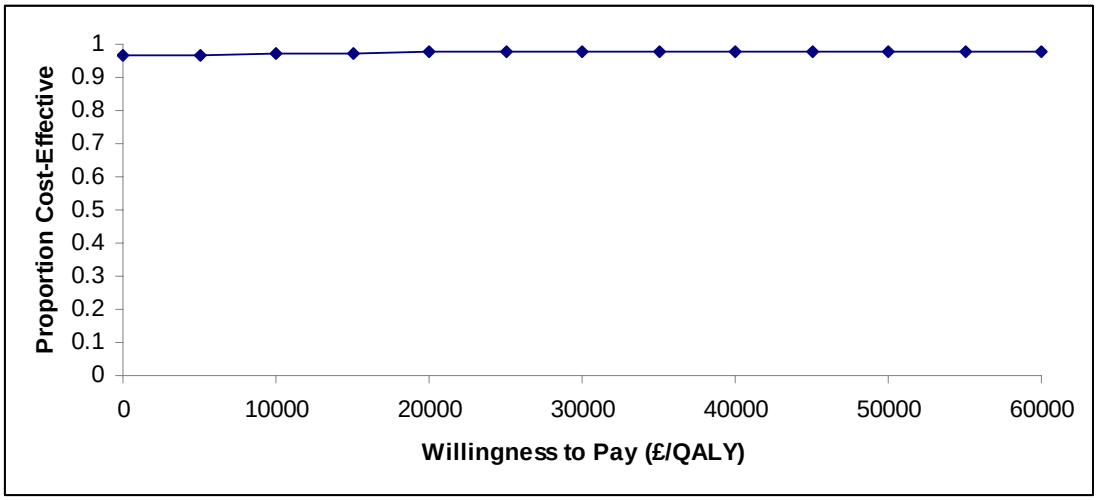

Figure 14 CEAC for sildenafil with supportive care versus supportive care alone, FCIII

4.7 Summary of results – comparison with reference case

- The ICER for epoprostenol in FCIII increased from £277,000 per QALY gained in the reference case to £285,000. Although the difference in QALYs increases, the difference in costs also increases.
- The ICER for epoprostenol in FCIV decreased slightly from £343,000 per QALY gained to £337,000. Although the difference in costs increases, the difference in QALYs also increases.
- The ICER for iloprost reduces from £101,000 per QALY gained in the reference case to £76,000. The difference in costs and difference benefits are both reduced, but more so for the costs.
- The result for bosentan changes from an ICER of £27,000 per QALY gained in the reference case to being dominant over supportive care. The difference in QALYs changes very little but costs are now lower for the intervention arm than for supportive care.
- The result for sitaxentan changes from an ICER of £25,000 per QALY to being dominant over supportive care. The difference in QALYs is slightly larger, and the costs are now lower for the intervention arm than for supportive care.
- In both the reference case and additional analysis, sildenafil is dominant when compared to supportive care, however the probability of being cost-effective at thresholds of £20,000 and £30,000 per QALY gained is greater in this additional analysis.

4.8 Explanation of results

In this extreme analysis, where no patients can die from PAH-related causes in FCIII, the oral therapies become much more cost-effective.

In the reference case the mortality on treatment for patients in FCIII for individual treatments was obtained from observational studies. In these studies patients started treatment in FCIII and were followed up for a certain period of time (e.g. one year or three years). PAH-specific mortality was calculated according to the number of patients who were followed up and the number of deaths observed during this period, taking into account the general population mortality (see Appendix 9 in the main report). The estimated PAH-specific mortality assumed that all the observed deaths occurred while the patients were in FCIII and did not take into account the possibility that some of the patients might have deteriorated to FCIV (and

incurred associated cost of epoprostenol treatment) before death. The mortality on treatment for FCIII patients in the model therefore might have been over-estimated as some of the deaths would have been accounted for through deterioration to FCIV and subsequent deaths in this FC.

Due to lack of data, it is not clear what proportion of patients would die while within a 12-week cycle in FCIII and what proportion would go through FCIV before death in the model. This sensitivity analysis therefore explored an extreme scenario in which all deaths in FCIII were removed and only deaths in FCIV were allowed. In this scenario all patients who would have died in FCIII in the reference case survived and incurred epoprostenol treatment in FCIV. The impact was greater for the supportive care arm (given its higher mortality in the reference case), making it a much more expensive option. The active treatment therefore became comparatively more cost-effective. There was greater QALY gain for supportive care arm due to proportionately greater reduction in mortality than active treatment arm under this assumption, but the impact due to the changes in cost outweighs the impact due to changes in QALY.

5. Question: What is the impact on cost effectiveness of altering the assumption that patients are hospitalised until death to only intermittent care as required for respite etc. (assumption relating to costing for patients on supportive care alone in FCIV) for all drugs in this appraisal?

Analysis requested by NICE: Based on the reference case in the Assessment Report, conduct a sensitivity analysis (for all the five technologies) which assumes that patients on supportive care alone in FCIV receive only intermittent care as required for respite until death rather than hospitalisation until death.

In the reference case it was assumed that patients in FCIV on supportive care plus epoprostenol receive intermittent care, whilst patients on supportive care alone are hospitalised until death. For this additional analysis, intermittent care rather than continuous hospitalisation is assumed for patients in FCIV on supportive care alone.

Supportive care alone in FCIV only occurs in the model as a comparator to epoprostenol plus supportive care in FCIV. This is because the reference case assumes for all the other analyses that patients are given epoprostenol plus supportive care when they reach FCIV. Consequently, only the results for epoprostenol in FCIV are presented for this additional analysis.

The only other time altering the assumption regarding continuous hospitalisation would impact on analysis is in the additional analysis in this document (section 1) when it is assumed that epoprostenol is not available and hence supportive care alone is available in FCIV. The assumption of intermittent care rather than hospitalisation to death was applied to this additional analysis and the results are also presented below.

5.1 Alternative supportive care costs in FCIV: Epoprostenol available in FCIV

5.1.1 Epoprostenol in addition to supportive care versus supportive care alone, FCIV

Table 18 shows the results of the analysis for epoprostenol in FCIV. Compared with supportive care alone, epoprostenol alongside supportive care is more expensive but generates more QALYs, giving an ICER of £427,000 per QALY gained. The CEAC presented in Figure 15 shows that at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, epoprostenol has a zero probability of being cost-effective.

Table 18 Epoprostenol with supportive care versus supportive care alone, FCIV

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	31,000		0.826		
Epoprostenol	530,000	498,000	1.994	1.167	427,000

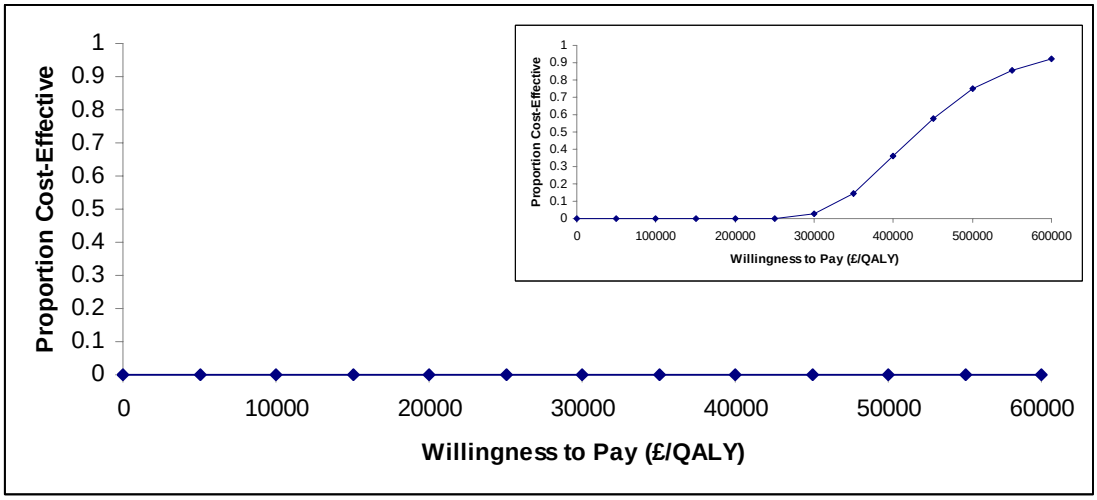

Figure 15 CEAC for epoprostenol with supportive care versus supportive care alone, FCIV

Inset graph shows larger X-axis scale

5.2 Alternative supportive care costs in FCIV: Supportive care only in FCIV

5.2.1 Epoprostenol in addition to supportive care versus supportive care alone, FCIII

Table 19 shows the results of the analysis for epoprostenol in FCIII. Compared with supportive care alone, epoprostenol alongside supportive care is more expensive but generates more QALYs, giving an ICER of £278,000 per QALY gained. The CEAC presented in Figure 16 shows that at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, epoprostenol has a zero probability of being cost-effective.

Table 19 Epoprostenol with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	30,000		1.091		
Epoprostenol	263,000	232,000	1.927	0.837	278,000

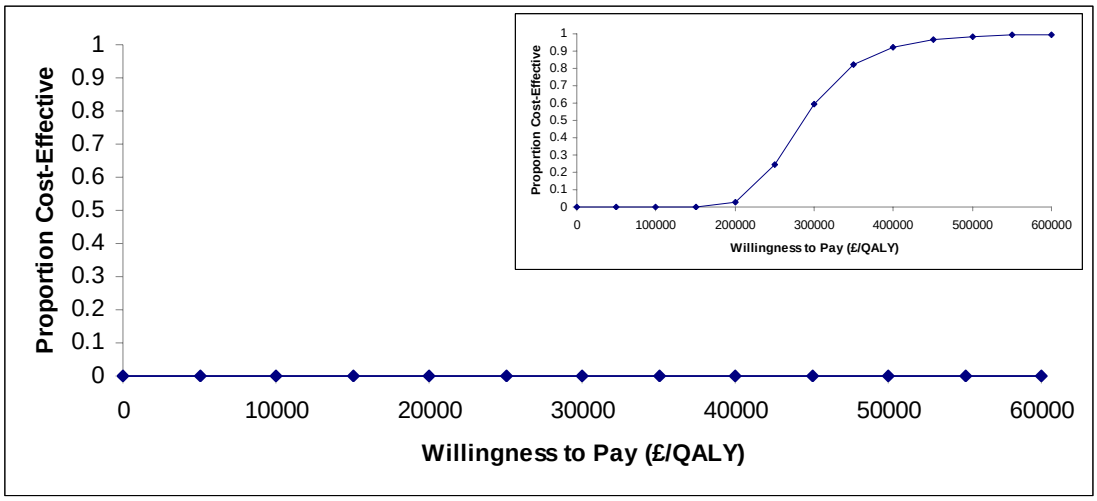

Figure 16 CEAC for epoprostenol with supportive care versus supportive care alone, FCIII

Inset graph shows larger X-axis scale

5.2.2 Iloprost with supportive care versus supportive care alone, FCIII

Table 20 shows the results of the analysis for iloprost in FCIII. Iloprost alongside supportive care is more costly than supportive care alone but yields more QALYs, giving an ICER of £99,000 per QALY gained. The CEAC presented in Figure 17 shows that at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, iloprost has a zero probability of being cost-effective.

Table 20 Iloprost with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	28,000		1.086		
Iloprost	132,000	104,000	2.131	1.045	99,000

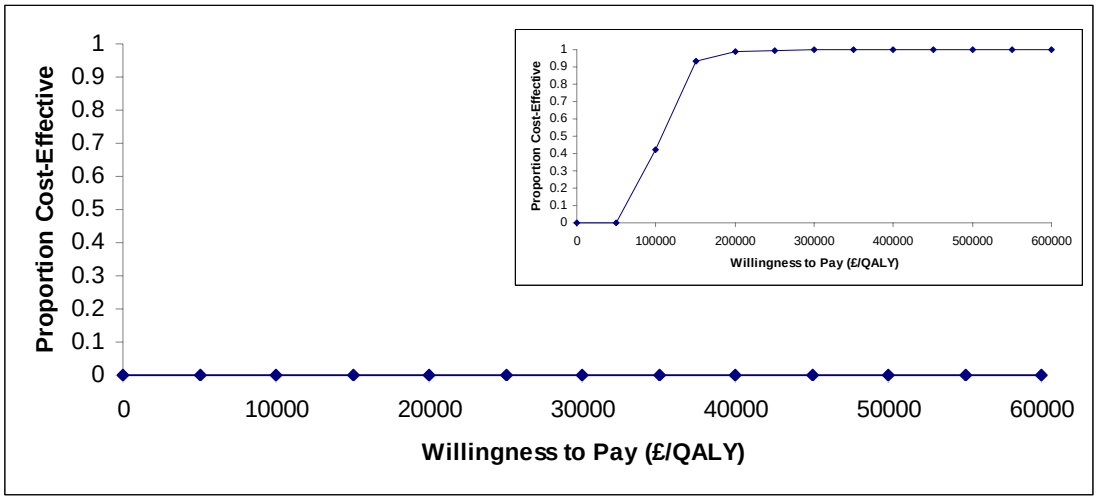

Figure 17 CEAC for iloprost with supportive care versus supportive care alone, FCIII

Inset graph shows larger X-axis scale

5.2.3 Bosentan in addition to supportive care versus supportive care alone, FCIII

Table 21 shows the results for bosentan, with the intervention more expensive than supportive care alone and producing a greater amount of QALYs, resulting in bosentan having an ICER of £46,000 per QALY gained. The CEAC in Figure 18 demonstrates that bosentan has a zero probability of being cost-effective at both £20,000 and £30,000 per QALY gained.

Table 21 Bosentan with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	25,000		1.532		
Bosentan	195,000	170,000	5.209	3.677	46,000

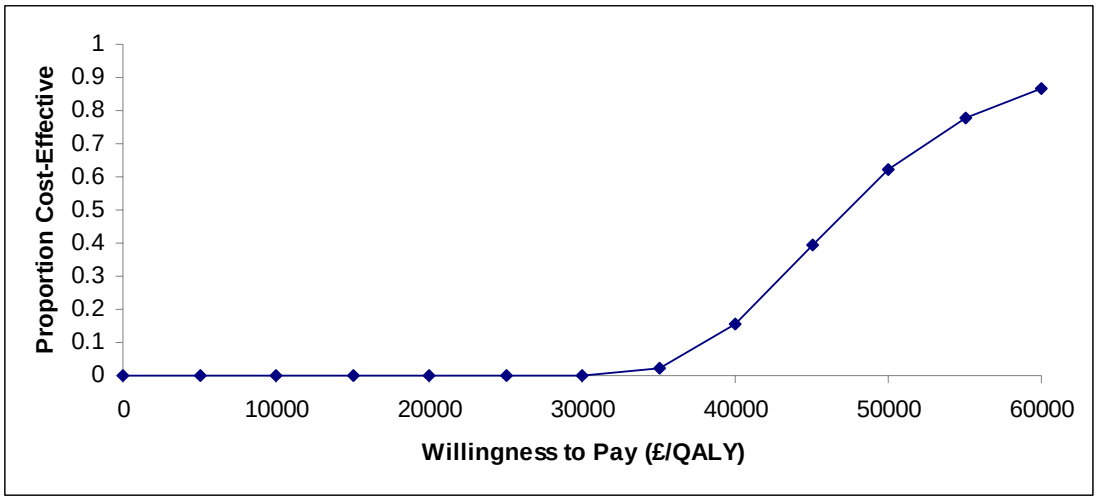

Figure 18 CEAC for bosentan with supportive care versus supportive care alone, FCIII

5.2.4 Sitaxentan in addition to supportive care versus supportive care alone, FCIII

Table 22 shows the results of the analysis for sitaxentan in FCIII. Sitaxentan alongside supportive care is more costly than supportive care alone but yields more QALYs, giving an ICER of £48,000 per QALY gained. The CEAC presented in Figure 19 shows that at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, sitaxentan has a zero probability of being cost-effective.

Table 22 Sitaxentan with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	25,000		1.532		
Sitaxentan	182,000	157,000	4.780	3.248	48,000

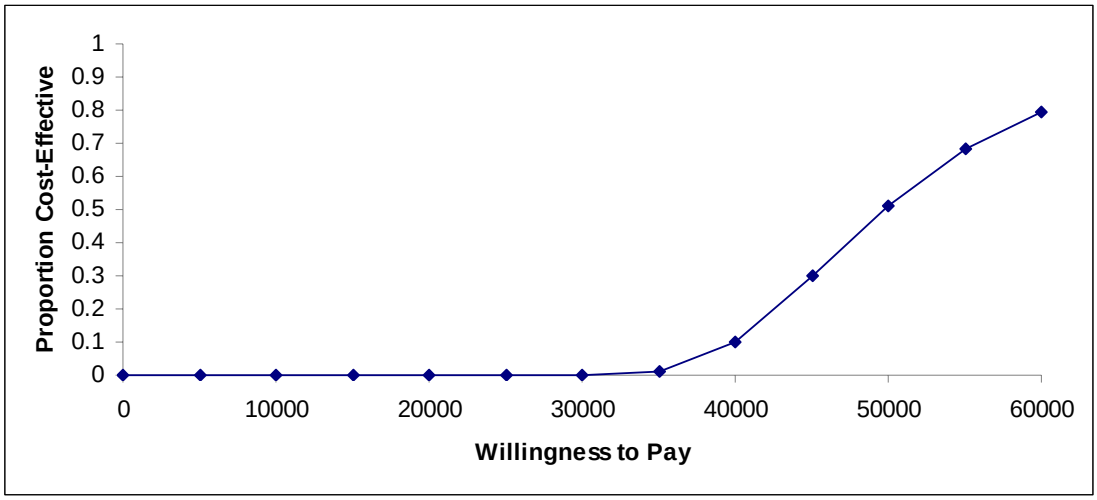

Figure 19 CEAC for sitaxentan with supportive care versus supportive care alone, FCIII

5.2.5 Sildenafil in addition to supportive care versus supportive care alone, FCIII

Table 23 shows the results of the analysis for sildenafil in FCIII. Sildenafil alongside supportive care is more costly than supportive care alone but yields more QALYs, giving an ICER of £13,000 per QALY gained. The CEAC presented in Figure 20 shows that at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, sildenafil has probabilities of being cost-effective of 90% and 98% respectively.

Table 23 Sildenafil with supportive care versus supportive care alone, FCIII

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	25,000		1.532		
Sildenafil	71,000	46,000	4.950	3.418	13,000

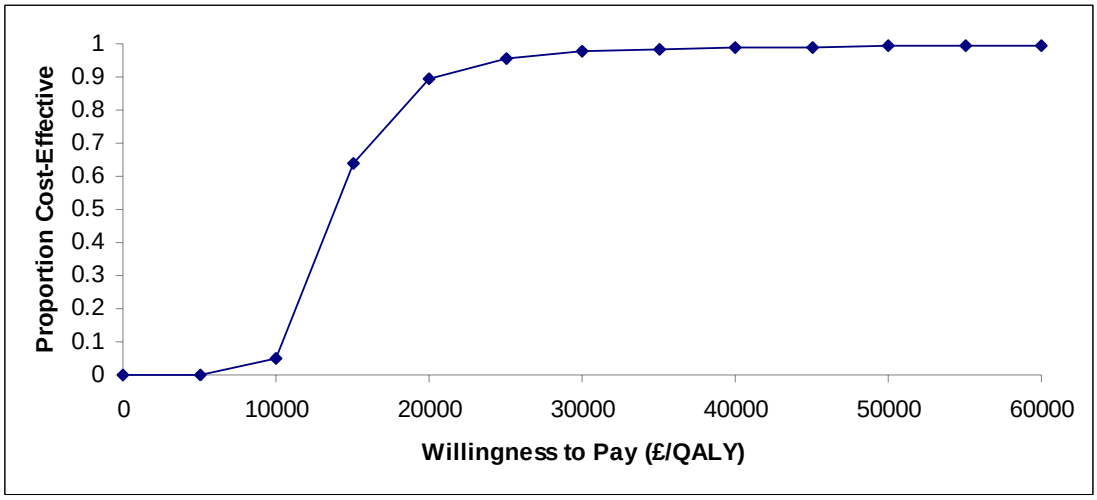

Figure 20 CEAC for sildenafil with supportive care versus supportive care alone, FCIII

5.3 Summary of results

5.3.1 Comparison with Reference Case

- The ICER for epoprostenol in FCIV increases from the reference case value of £343,000 per QALY gained to £427,000, as the difference in costs increases.

5.3.2 Comparison of results with analysis where epoprostenol is not available in FCIV (section 1)

- The ICER for epoprostenol in FCIII increases from £273,000 per QALY gained to £278,000 as the difference in costs increases very slightly.
- The ICER for iloprost increases marginally from £98,000 per QALY gained to £99,000 as the difference in costs increases very slightly.
- The result for bosentan increases from an ICER of £42,000 per QALY to £46,000 as there is a rise in the difference in costs.
- The result for bosentan increases from an ICER of £44,000 per QALY to £48,000 as there is a rise in the difference in costs.
- The ICER for sildenafil increases from £9,000 per QALY gained to £13,000 is, again because the difference in costs increases.

5.4 Explanation of results

As explained at the beginning of the section, this sensitivity analysis is only applicable to scenarios in which epoprostenol is not used in FCIV. The assumption of intermittent care instead of hospitalisation until death reduced costs associated with patients in FCIV for both the treatment and supportive care arms, but the reduction in costs was greater in supportive care arms as patients reached FCIV faster. The supportive care option thus became relatively cheap and active treatments became less cost-effective. The ICERs however only increased slightly compared to the results of the additional analysis described in section 1. This is because the differential costs between treatment options accrued in FCIV under these scenario (without epoprostenol) were small compared to the differential costs accrued in FCIII (costs of active treatment vs costs of supportive care), which drive the ICERs.

6. Overall summary of results

- A summary of ICERs for reference case and various sensitivity analyses is shown in Table 24.
- By assuming patients receive supportive care alone in FCIV, the ICERs reduce slightly for epoprostenol and iloprost compared with reference case ICERs, but are in excess of £90,000 per QALY gained. Conversely, the ICERs for bosentan and sitaxentan increase to above £40,000 per QALY gained, and sildenafil is no longer dominant but still has an ICER below a £10,000.
- Applying data on mortality for epoprostenol in FCIII to the oral therapies reduces the ICERs for all oral therapies well below £10,000 per QALY gained.
- When considering a scenario of no patients suffering PAH-related mortality in FCIII, the ICERs for epoprostenol in FCIII and FCIV increase, and the ICER decreases for iloprost, but is still in excess of £70,000 per QALY gained . All oral therapies become dominant over supportive care alone.
- Reducing the costs on supportive care alone in FCIV by reducing the intensity of hospitalisation (where treatment in FCIV is supportive care alone) increases the ICERs for all therapies, and sildenafil is the only therapy with an ICER below £40,000 per QALY gained.

Table 24 Summary of ICERs for reference case and additional analyses

	FCIV	FCIII				
	Epoprostenol	Epoprostenol	Iloprost	Bosentan	Sitaxentan	Sildenafil
Original Analyses						
Reference case	343,000	277,000	101,000	27,000	25,000	Dominates
Alternative epoprostenol price*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Additional Analyses						
Supportive care without epoprostenol in FCIV	Same as base case	273,000	98,000	42,000	44,000	9,000
Assume epoprostenol mortality on supportive care & mortality on treatment	-	-	-	6,000	1,400	Dominates
No PAH-specific death in FCIII	337,000	285,000	76,000	Dominates	Dominates	Dominates
Supportive care without epoprostenol in FCIV, intermittent care	427,000	278,000	99,000	46,000	48,000	13,000

*ICERs for the sensitivity analysis using alternative epoprostenol price are commercial in confidence.