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Clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for pulmonary arterial hypertension within their licensed indications: a systematic review and economic evaluation

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Clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for pulmonary arterial hypertension within their licensed indications: a systematic review and economic evaluation

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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Abstract

Clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for pulmonary arterial hypertension within their licensed indications: a systematic review and economic evaluation

Y-F Chen,[1*] S Jowett,[2] P Barton,[2] K Malottki,[1] C Hyde,[1] JSR Gibbs,[3] J Pepke-Zaba,[4] A Fry-Smith,[1] J Roberts[1] and D Moore[1]

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Objective(s): To investigate the clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for the treatment of adults with pulmonary arterial hypertension (PAH) within their licensed indications.

Data sources: Major electronic databases (including the Cochrane Library, MEDLINE and EMBASE) were searched up to February 2007. Further data were obtained from dossiers submitted to NICE by the manufacturers of the technologies.

Review methods: The systematic clinical and economic reviews were conducted according to accepted procedures. Model-based economic evaluations of the cost-effectiveness of the technologies from the perspective of the UK NHS and personal social services were carried out.

Results: In total, 20 randomised controlled trials (RCTs) were included in this assessment, mostly of 12–18 weeks duration and comparing one of the technologies added to supportive treatment with supportive treatment alone. Four published economic evaluations were identified. None produced results generalisable to the NHS. There was no consensus in the industry submissions on the most appropriate model structure for the technology assessment. Improvement in 6-minute walk distance (6MWD) was seen with intravenous epoprostenol in primary pulmonary hypertension (PPH) patients with mixed functional class (FC) (mainly III and IV, licensed indication) compared with supportive care (58 metres; 95% CI 6–110). For bosentan compared with supportive care, the pooled result for improvement in 6MWD for FCIII patients with mixed PAH (licensed indication) was 59 metres (95% CI 20–99). For inhaled iloprost, sitaxentan and sildenafil no stratified data for improvement in 6MWD were available. The odds ratio (OR) for FC deterioration at 12 weeks was 0.40 (95% CI 0.13–1.20) for intravenous epoprostenol compared with supportive care. The corresponding values for inhaled iloprost (FCIII PPH patients; licensed indication), bosentan, sitaxentan (FCIII patients with mixed PAH; licensed indication) and sildenafil (FCIII patients with mixed PAH; licensed indication) were 0.29 (95% CI 0.07–1.18), 0.21 (95% CI 0.03–1.76), 0.18 (95% CI 0.02–1.64) and [Commercial-in-confidence information has been removed] respectively. The incremental cost-effectiveness ratios (ICERs) for the technologies plus supportive care compared with supportive care alone, determined by independent economic evaluation, were £277,000/quality-adjusted life-year (QALY) for FCIII and £343,000/QALY for FCIV patients for epoprostenol, £101,000/QALY for iloprost, £27,000/QALY for bosentan and £25,000/QALY for sitaxentan. For the most part sildenafil plus supportive care was more effective and less costly than supportive care alone and therefore dominated supportive care. In the case of epoprostenol the ICERs were sensitive to the price of epoprostenol and for bosentan and sitaxentan the ICERs were sensitive to running the model over a shorter time horizon and with a lower cost of epoprostenol. Two RCTs directly compared the technologies against each other with no significant differences observed between the technologies. Combinations of technologies were investigated in four RCTs, with some showing conflicting results.

Conclusion(s): All five technologies when added to

supportive treatment and used at licensed dose(s) were more effective than supportive treatment alone in RCTs that included patients of mixed FC and types of PAH. Current evidence does not allow adequate comparisons between the technologies nor for the use of combinations of the technologies. Independent economic evaluation suggests that bosentan, sitaxentan and sildenafil may be cost-effective by standard thresholds and that iloprost and epoprostenol may not. If confirmed, the use of the most cost-effective treatment would result in a reduction in costs for the NHS. Long-term, double-blind RCTs of sufficient sample size that directly compare bosentan, sitaxentan and sildenafil, and evaluate outcomes including survival, quality of life, maintenance on treatment and impact on the use of resources for NHS and personal social services are needed.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the content, but a glossary and list of abbreviations are provided for the non-specialist reader.

Glossary

6MWT – 6-minute walk test The 6MWT measures the distance that a patient can walk unencouraged on a flat, hard surface in a time of 6 minutes.

Borg dyspnoea index A measure of perceived breathlessness on a scale of 0–10, in which 0 = no breathlessness. Initially designed to measure exertion.

Cardiac index The cardiac index relates the volume of blood pumped by the heart in a unit of time (cardiac output) to the body surface area. It is calculated as: (stroke volume × heart rate)/body surface area. The cardiac index is usually expressed in l/min/m^2.

Functional class (FC) A classification of functional capacity initially developed by the New York Heart Association (NYHA) for patients with cardiac diseases based on clinical severity and prognosis. It was later adapted specifically for patients with pulmonary hypertension (see Chapter 1, Clinical classification). Briefly, patients are classified into one of the following four categories: FCI (asymptomatic), FCII (mild), FCIII (moderate), FCIV (severe).

Pulmonary arterial hypertension (PAH) Throughout this report PAH refers to category 1 (excluding subcategory 1.5) of the Venice 2003 classification for pulmonary hypertension (see Chapter 1, Clinical classification). Subcategories of PAH, such as idiopathic PAH (IPAH) and associated PAH (APAH), were defined in line with this classification. However, it is acknowledged that the term primary pulmonary hypertension (PPH) was widely used before the advent of the Venice 2003 classification and a decision was made to retain this term in this report if it was used in the original publications/reports of individual studies. When the term PPH is retained it is regarded as being interchangeable with IPAH.

Pulmonary artery pressure (PAP) Measured directly during right heart catheterisation. Mean pulmonary artery pressure (mPAP) > 25 mmHg at rest or > 30 mmHg with exercise is one of the criteria of PAH diagnosis.

Pulmonary capillary wedge pressure (PCWP) PCWP provides an indirect estimate of left atrial pressure. The measurement is made with a balloon-tipped, multilumen catheter (Swan–Granz catheter), inserted into a peripheral vein and then advanced into the right atrium, right ventricle, pulmonary artery and into a branch of the pulmonary artery. The normal value of the PCWP is 8–10 mmHg. A PCWP ≤ 15 mmHg is one of the PAH diagnostic criteria. PCWP is used to calculate pulmonary vascular resistance.

Pulmonary hypertension When the term 'pulmonary hypertension' is used in this report it refers to all categories (1–5) of the Venice 2003 classification for pulmonary hypertension (see Chapter 1, Clinical classification). This is therefore a broader term that encompasses PAH and other forms of pulmonary hypertension.

Pulmonary vascular resistance (PVR) PVR = [mean pulmonary artery pressure (mmHg) – pulmonary capillary wedge pressure (mmHg)]/cardiac output (l/min) × 80. Units are dyn s/cm^5. A PVR > 240 dyn s/cm^5 is one of the diagnostic criteria of PAH.

Right atrial pressure (RAP) RAP is measured at right heart catheterisation. It measures the

continued

filling pressure of the right ventricle, and rises progressively as the right ventricle fails. High RAP thus identifies a failing right ventricle and a poor prognosis. Normal value is up to 5 mmHg.

Supportive treatment(s) Supportive treatment(s) or supportive care refers to anticoagulation therapy, diuretics, oxygen, digoxin and calcium channel blockers (see Chapter 1, Supportive treatment). It was commonly referred to as conventional therapy or background therapy in the literature.

Venice 2003 classification This is a clinical-based classification that groups pulmonary hypertension into five major categories based on pathophysiological mechanisms, clinical presentation and therapeutic options. PAH is one of the categories. See Chapter 1 (Clinical classification) for the full list of categories and subcategories.

Abbreviations

6MWD	6-minute walk distance
6MWT	6-minute walk test
AIR	Aerosolized Iloprost Randomized study
APAH	associated pulmonary arterial hypertension
AQoL instrument	Assessment of Quality of Life instrument
BNF	*British National Formulary*
BREATHE	Bosentan Randomized Trial of Endothelin Antagonist Therapy
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CEAC	cost-effectiveness acceptability curve
cGMP	cyclic guanosine monophosphate
CHD	congenital heart disease
CHEC	Consensus on Health Economic Criteria
CI(s)	confidence interval(s)
CTD	connective tissue disease
CTD-APAH	pulmonary arterial hypertension associated with connective tissue disease
COMBI trial	Combination Therapy of Bosentan and Aerosolised Iloprost in Idiopathic Pulmonary Arterial Hypertension trial
ESC	European Society of Cardiology
ET-1	endothelin-1
ET_A, ET_B	endothelin receptor type A, type B
FCII, FCIII, FCIV	functional class II, III, IV
FPAH	familial pulmonary arterial hypertension
ICER(s)	incremental cost-effectiveness ratio(s)
IPAH	idiopathic pulmonary arterial hypertension

continued

INR	international normalised ratio
ITT	intention to treat
MLHF questionnaire	Minnesota Living with Heart Failure questionnaire
mPAP	mean pulmonary arterial pressure
NCG	National Commissioning Group, formerly known as NSCAG.
NICE	National Institute for Health and Clinical Excellence
NNT	number needed to treat
NSCAG	National Specialist Commissioning Advisory Group
NYHA	New York Heart Association
PAH	pulmonary arterial hypertension
PAP	pulmonary artery pressure
PCTs	primary care trusts
PCWP	pulmonary capillary wedge pressure
PPH	primary pulmonary hypertension
PSA	probabilistic sensitivity analysis
PSS	personal social services
PVR	pulmonary vascular resistance
QALY(s)	quality-adjusted life-year(s)
RAP	right atrial pressure
RCT	randomised controlled trial
RR(s)	relative risk(s)
SAE(s)	serious adverse event(s)
SEM	standard error of the mean
SD(s)	standard deviation(s)
SF-36	Short-Form 36
STEP	*S*afety and Pilot Efficacy *T*rial in Combination with Bosentan for *E*valuation in *P*AH
STRIDE	*S*itaxsentan *t*o *R*elieve *I*mpair*ed* *E*xercise study
SUPER	Sildenafil Use in Pulmonary Arterial Hypertension study
TTO	time trade-off
VAS	visual analogue scale
WHO	World Health Organization
WMD	weighted mean differences

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable amount of data that was deemed commercial-in-confidence or academic-in-confidence. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of commercial-in-confidence or academic-in-confidence data removed and replaced by the statement 'commercial-in-confidence removed' or 'academic-in-confidence removed' and is available on the NICE website www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all of the data considered in the original full NICE report.

Executive summary

Background

Pulmonary arterial hypertension (PAH) is a diverse group of diseases with similar pathophysiology and clinical presentation. It is characterised by a progressive increase of pulmonary vascular resistance, leading to right ventricular heart failure and premature death. PAH can occur with no identifiable cause. This was previously referred to as primary pulmonary hypertension (PPH) but was renamed as idiopathic PAH (IPAH). PAH is also commonly associated with various conditions including connective tissue disease (CTD-APAH) and congenital heart disease (CHD). Symptoms of PAH include dyspnoea (breathlessness), fatigue, chest pain, syncope (fainting) and oedema, which can result in loss of capacity to perform exercise and eventually activity of daily living. It therefore has a devastating impact on both the quality and duration of patients' life. PAH is a rare disease with an estimated incidence of two to four cases per million per year, which approximates 100 to 200 new cases in England and Wales per year.

Until the 1990s, PAH was managed by supportive treatments, which include anticoagulation therapy, diuretics, oxygen and digoxin that mainly aim at controlling symptoms. In addition, calcium channel blockers (CCBs) were found to be effective for treating a small proportion of patients with PAH. More recently, new technologies specifically licensed for treating PAH have become available in the UK. These include intravenous epoprostenol, inhaled iloprost, and three oral treatments: bosentan, sitaxentan and sildenafil. The licenses differ between the technologies in terms of type of PAH and severity of disease measured by functional class (FC). These technologies are believed to not only relieve symptoms but also to potentially modify disease progress. Once initiated the technologies are given repeatedly and only when inevitably the disease progresses are additional treatments or (more rarely) switching considered. The costs for these technologies vary but are very high (≈£12–£400 per patient per day, list price of drug only).

Objectives

The objectives of the assessment report were:

- To assess as far as available data from randomised controlled trials (RCTs) would allow, whether the five technologies named above (alone or in combination) are clinically effective when used within their licensed indications for the treatment of adults with PAH for whom CCBs are inappropriate or no longer effective compared to supportive treatment (and/or intravenous iloprost), and whether the clinical effectiveness differs significantly between PAH of various causes.
- To assess whether the clinical effectiveness differs significantly between the technologies (alone or in combination) if head-to-head RCTs exist.
- To assess whether each of the five technologies are cost-effective when used within their licensed indications for treating adults with PAH for whom CCBs are inappropriate or no longer effective compared to supportive treatment.

Methods

Clinical effectiveness

A systematic review of RCTs was undertaken. Databases searched included the Cochrane Library, MEDLINE, and EMBASE along with other sources up to February 2007. Further data were obtained from dossiers submitted to the National Institute for Health and Clinical Excellence (NICE) by the manufacturers of the technologies. RCTs of longer than one week duration that compared any of the five technologies (alone or in combination) to placebo, supportive care, any other technologies (alone or in combination) and/or non-licensed drugs in adult PAH patients were included. Inclusion decisions, quality assessment and data extraction were undertaken according to predefined criteria. Where sufficient data were available, meta-analyses were undertaken for each technology using a random effects model. Primary analysis included data from FCIII patients (and FCIV patients for epoprostenol) for licensed doses only. Extensive sensitivity analyses were carried out.

Cost-effectiveness

A systematic review of published studies on the costs and cost-effectiveness of the technologies in PAH, and a review of the dossiers submitted to

NICE by the manufacturers of the technologies were undertaken. In addition, model-based economic evaluations of the cost-effectiveness of the technologies from the perspective of the UK National Health Service (NHS) and Personal Social Service (PSS) were carried out.

Results

Clinical effectiveness and cost-effectiveness

A total of 20 RCTs, most of good quality, were included in this assessment. The majority had durations of 12 to 18 weeks and compared one of the technologies added to supportive treatment versus supportive treatment alone. Only a small number of trials compared the technologies against each other or investigated the use of combinations of technologies.

Many of the trials included patient populations (in terms of FC and types of PAH) and doses that were outside the licensed indication of the technologies. Only very limited data examining specific types (subcategories) of PAH were available. Existing data do not suggest significant differences in treatment effects between subcategories of PAH, but studies are likely to be under-powered to detect clinically important differences.

Data stratified by FC were scant, as such an assessment of treatment effects stratified by FC could not be reliably conducted with the available evidence. This is particularly problematic when findings from the clinical effectiveness review were to be used to inform the economic modelling.

Monotherapy added to supportive treatment versus supportive treatment

All the technologies, when added to supportive treatment at their licensed doses, have been shown to be more effective than supportive treatment alone in improving exercise capacity, symptoms of PAH and haemodynamic measures. The volume of evidence and patient populations included in the trials varied between technologies. The incremental cost-effectiveness ratio (ICER) for each technology added to supportive treatment compared to supportive treatment varies considerably between the technologies according to the independent economic evaluation conducted for this report.

The effectiveness of intravenous epoprostenol has been shown in open-label RCTs that included both patients with PPH and patients with scleroderma. Pooled results for PPH patients with mixed FC (mainly III & IV, licensed indication) for improvement in 6-minute walk distance (6MWD) was 58 metres (95% confidence interval 6 to 110) and the odds ratio (OR) for FC deterioration at 12 weeks was 0.40 (0.13 to 1.20) compared to supportive care. Independent economic evaluation gave ICERs for the reference case for epoprostenol plus supportive care compared to supportive care alone of £277,000/quality-adjusted life-year (QALY) for FCIII and £343,000/QALY for FCIV patients. In non-reference case analyses the lowest of these ICERs became £106,000/QALY and £96,000/QALY respectively when the manufacturer's reduced price was used. Most other non-reference case analyses did not appreciably alter the magnitude of the reference case ICERs.

The effectiveness of inhaled iloprost has been shown in one double-blind RCT that included patients of mixed FC (III and IV) with mixed types of pulmonary hypertension including non-PAH. For FCIII PPH patients (licensed indication), stratifed data for 6MWD were not available and OR for deterioration in FC at 12 weeks was 0.29 (0.07 to to 1.18) compared to supportive care. An additional open-label RCT demonstrated effectiveness in only some of the measured outcomes. Independent economic evaluation gave an ICER for the reference case for iloprost plus supportive care compared to supportive care alone of £101,000/QALY. Non-reference case analyses did not appreciably reduce the magnitude of this ICER.

The effectiveness of bosentan was demonstrated in double-blind RCTs that included patients predominantly of FC III and an additional open-label RCT. Effectiveness has been shown in mixed populations of IPAH, CTD-APAH and PAH associated with Eisenmenger syndrome, a specific type of CHD. For FCIII patients with mixed PAH (licensed indication), the pooled result for improvement in 6MWD was 59 metres (20 to 99) and the pooled OR for deterioration in FC at 12 weeks was 0.21 (0.03 to 1.76) compared to supportive care. Independent economic evaluation gave an ICER for the reference case for bosentan plus supportive care compared to supportive care alone of £27,000/QALY. Non-reference case analysis demonstrated the ICER was sensitive to running the model over a shorter time horizon and with a lower cost of epoprostenol.

The effectiveness of sitaxentan was demonstrated in double-blind RCTs that included patients of mixed FC (predominantly II and III) with mixed

PAH (IPAH, CTD-APAH and PAH associated with CHD). For FCIII patients with mixed PAH (licensed indication), no stratified data for improvement in 6MWD were available and the pooled OR for deterioration in FC at 12 weeks was 0.18 (0.02 to 1.64) compared to supportive care. Independent economic evaluation gave an ICER for the reference case for sitaxentan plus supportive care compared to supportive care of £25,000/QALY. Non-reference case analysis demonstrated the ICER was sensitive to running the model over a shorter time horizon and with a lower cost of epoprostenol.

The effectiveness of sildenafil was demonstrated in a double-blind RCT that included patients of mixed FC (predominantly II and III) with mixed PAH (IPAH, CTD-APAH and PAH associated with CHD). For FCIII patients with mixed PAH (licensed indication), no stratified data for improvement in 6MWD were available and the OR for deterioration in FC at 12 weeks was [confidential information removed] compared to supportive care. Independent economic evaluation demonstrated that for the most part sildenafil plus supportive care was more effective and less costly than supportive care alone and therefore dominated supportive care. Even when sildenafil did not dominate ICERs were on the whole still relatively low.

Direct comparison

Only two RCTs have directly compared the technologies against each other. No significant difference between the technologies was observed in any outcome in both trials. However, the conclusion was limited by small sample size in one trial and differential blinding of treatments in the other trial. No independent economic analysis was undertaken for this comparison.

Combination therapy

Use of the combinations of the technologies was investigated in four RCTs. A double-blind RCT showed no benefit for using the combination of bosentan plus epoprostenol compared to epoprostenol alone in patients of mixed FC (III and IV) with mixed types of PAH (IPAH, CTD-APAH).

A double-blind RCT showed that inhaled iloprost added to ongoing bosentan and supportive treatment was more effective than ongoing bosentan and supportive treatment in patients (mainly FCIII) with mixed types of PAH. However, a further open-label RCT that included patients of FCIII with IPAH failed to demonstrate this.

A double-blinded RCT showed that above licensed doses of sildenafil added to ongoing epoprostenol and supportive care was more effective than ongoing epoprostenol and supportive care in patients of mixed FC (predominantly II and III) with mixed types of PAH (IPAH and CTD-APAH).

No independent economic analyses were undertaken for these comparisons.

Comment on independent economic evaluation

The ICERs for one technology should not be compared to that of another technology as the model only compares each technology plus supportive care to supportive care alone. To do so would be inappropriate.

In the model epoprostenol treatment is initiated on progression to FCIV, as such the ICERs for all technologies are sensitive to the cost of epoprostenol.

Due to the lack of stratified data to populate the model, and in some cases a complete absence of data, a number of assumptions had to be made, therefore bias may have been introduced by these assumptions. In addition, the data used for the model were mostly from trials of short duration containing relatively small numbers of patients. Therefore a longitudinal dataset of a sufficient number of patients would be of great benefit to future modelling in this clinical condition.

Due to the above, the probabilistic sensitivity analysis undertaken in this report may well have underestimated the full uncertainty around each analysis.

Published economic evaluations

Four published economic evaluations were identified. None produced results generalisable to the NHS.

Review of economic evaluations submitted by manufacturers

There was no consensus in the manufacturers' submissions on the most appropriate model structure for the technology assessment, with variability seen in the type of economic evaluation, methods used and data sources. In addition, the same comparator was not used in all submissions therefore they were not all addressing the same policy question.

Discussion

Strengths, limitations of the analyses and uncertainties

The strengths of this assessment report include a systematic review focusing on the most robust evidence from RCTs, comprehensive literature search, inclusion of unpublished data, comprehensive analyses highlighting the mismatch between licensed indications and available evidence, independent assessment of published economic evaluations and manufacturer submissions, a de novo model-based economic evaluation, and use of data from the systematic review to inform the model.

The analyses included in this report were restricted by the scope of the technology appraisal, which was to include only licensed indications for the technologies currently licensed in the UK. The analyses were also limited by the short duration of RCTs and the paucity of data stratified by types of PAH and FC. Uncertainties mainly derive from the lack of long-term data from RCTs with regard to how long treatment effects last and whether they differ significantly for patients in different FC and to what extent. Comparisons between the technologies were not planned, and were not considered appropriate given available evidence.

Generalisability of the findings

Most RCTs excluded patients with unstable conditions. The patients who are seen in clinical practice may be sicker than those included in the trials. The implication for the generalisability of the findings is uncertain. Variations in the costs of the technologies (including services) between regions/centres inevitably affect the cost-effectiveness of these technologies. Furthermore, the economic modelling suggested the cost-effectiveness of the technologies is sensitive to the costs of epoprostenol.

Conclusions

All the five technologies, when added to supportive treatment and used at licensed dose(s), have been shown to be more effective than supportive treatment alone in RCTs that included patients of mixed FC and types of PAH. The volume of evidence and patient populations included in the trials varied between the technologies. Current evidence does not allow adequate comparisons between the technologies nor for the use of combinations of the technologies.

Independent economic evaluation suggests that bosentan, sitaxentan and sildenafil may be cost-effective by standard thresholds and that iloprost and epoprostenol may not.

Implications for service provision

The findings for clinical effectiveness have minimal impact on clinical practice as these technologies are already being used in NHS. The findings from the economic evaluation suggest the possibility of differential cost-effectiveness between the oral treatments. This requires further confirmation as current analysis was not designed for directly comparing the technologies. If confirmed, the use of the most cost-effective treatment would result in reduction in costs for the NHS.

The findings from the economic evaluation suggest that epoprostenol and iloprost may not be cost-effective. Withdrawal of these technologies, however, could have substantial impact on patients who are currently treated with them and could also raise ethical issues. Any changes in costs for epoprostenol and/or licensing of new treatment for FCIV patients could have impact on the cost-effectiveness of the other technologies.

Suggested research priorities

Long-term, double-blind RCTs of sufficient sample size that directly compare bosentan, sitaxentan and sildenafil, and evaluates outcomes including survival, quality of life, maintenance on treatment and impact on the use of resources for NHS and personal social services are needed. Possible differences in treatment effects between subcategories of PAH and between patients of different FC at baseline should be investigated within and across these trials.

More RCTs that evaluate combinations of the technologies versus monotherapy, and studies investigating the feasibilities of replacing an ongoing treatment that failed to provide adequate control of the disease with a new treatment rather than adding the new treatment to the existing treatment are required.

Further methodological studies that investigate the predictive value of outcome measures such as 6MWD, FC, various haemodynamic measures and other novel measures on patients' prognosis and survival are needed. The reason for substantial variation in patient's responses seen in control groups in RCTs also needs to be established.

Chapter 1
Background

Description of the health problem

Pulmonary arterial hypertension (PAH) is a diverse group of diseases of similar pathophysiology and clinical presentation characterised by a progressive increase of pulmonary vascular resistance (PVR), which leads to right ventricular heart failure and premature death. PAH is a subset of pulmonary hypertension. It is defined by a mean pulmonary artery pressure (PAP) > 25 mmHg at rest or > 30 mmHg with exercise, a mean pulmonary capillary wedge pressure (PCWP) of < 15 mmHg and a raised PVR of ≥ 240 dyn s/cm^5.[1] The pathology of the disease is complex, but involves pulmonary artery vasoconstriction, smooth muscle cell and endothelial cell proliferation and pulmonary thrombosis. Symptoms of PAH include dyspnoea (breathlessness), fatigue, chest pain, syncope (fainting) and oedema, all of which can worsen as the disease progresses and heart failure develops.

Classification

PAH is classified according to clinical features. In addition, patients with PAH are classified according to their functional capacity. The following paragraphs describe the clinical classification and functional classification of PAH that are referred to throughout this report.

Clinical classification

PAH is one of five differing subtypes of pulmonary hypertension.

Pulmonary hypertension was traditionally classified into two categories, primary pulmonary hypertension (PPH) or secondary pulmonary hypertension, depending on the absence or presence of identifiable causes or risk factors. In 1998 the World Health Organization (WHO) co-sponsored a symposium on pulmonary hypertension, which took place in Evian, France. A new clinical classification of pulmonary hypertension based on pathophysiological mechanism, clinical presentation and therapeutic options was proposed in the symposium. This 'Evian classification' (or sometimes referred to as the WHO 1998 classification) includes five major categories, with PAH being one of the categories. The term 'primary pulmonary hypertension' was retained within this category and included subcategories of sporadic PAH and familial PAH (FPAH). It was agreed that the term 'secondary pulmonary hypertension' should be abandoned. In a subsequent symposium that took place in Venice, Italy, in 2003, the Evian classification was further modified. The term 'primary pulmonary hypertension' was removed and the subcategory of sporadic PAH was replaced by idiopathic PAH (IPAH). The details of the Venice 2003 clinical classification are listed in *Table 1*.[1]

As PPH was widely used before the advent of the Venice 2003 classification a decision was made to retain this term in this report if it was used in the original publications/reports of individual studies. Where PPH is retained it is regarded as being interchangeable with IPAH.

Functional classification

Traditionally, patients with PAH are classified according to the classification of functional capacity developed by the New York Heart Association (NYHA) for patients with cardiac diseases based on clinical severity and prognosis. An adaptation of the NYHA functional classification specifically for patients with pulmonary hypertension was proposed in the aforementioned WHO symposium in Evian. The WHO classification and the NYHA classification are nearly identical and are sometimes referred to as the NYHA/WHO classification, which is listed in *Table 2*.[1]

Aetiology

The pulmonary vasculature is normally a low pressure system with little resistance to flow.[2] In pulmonary hypertension pulmonary arterial pressure is elevated. As indicated in the clinical classification system above, PAH frequently originates as the result of an underlying condition (disease, genetic disposition) or interaction with an inciting stimuli (e.g. toxins) or a combination of both. Whatever the underlying trigger, pathological mechanisms are activated that lead to constriction, cellular proliferation and potentially elevated blood clotting in the pulmonary microcirculation. This results in progressively increased pulmonary

TABLE 1 *Clinical classification of pulmonary hypertension – Venice 2003*

1. Pulmonary arterial hypertension (PAH):
    - 1.1. Idiopathic (IPAH)
    - 1.2. Familial (FPAH)
    - 1.3. Associated with (APAH):
        - 1.3.1. Connective tissue disease (CTD)
        - 1.3.2. Congenital systemic to pulmonary shunts
        - 1.3.3. Portal hypertension
        - 1.3.4. HIV infection
        - 1.3.5. Drugs and toxins
        - 1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)
    - 1.4. Associated with significant venous or capillary involvement:
        - 1.4.1. Pulmonary veno-occlusive disease (PVOD)
        - 1.4.2. Pulmonary capillary haemangiomatosis (PCH)
    - 1.5. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension associated with left heart diseases:
    - 2.1. Left-sided atrial or ventricular heart disease
    - 2.2. Left-sided valvular heart disease

3. Pulmonary hypertension associated with lung respiratory diseases and/or hypoxia:
    - 3.1. Chronic obstructive pulmonary disease
    - 3.2. Interstitial lung disease
    - 3.3. Sleep-disordered breathing
    - 3.4. Alveolar hypoventilation disorders
    - 3.5. Chronic exposure to high altitude
    - 3.6. Developmental abnormalities

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease:
    - 4.1. Thromboembolic obstruction of proximal pulmonary arteries
    - 4.2. Thromboembolic obstruction of distal pulmonary arteries
    - 4.3. Non-thrombotic pulmonary embolism (tumour, parasites, foreign material)

5. Miscellaneous: sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)

Reproduced from Galiè *et al*. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. *European Heart Journal* (2004;**25**:2243–78) by kind permission of the European Society of Cardiology.[1]

TABLE 2 *New York Heart Association (NYHA)/World Health Organization (WHO) classification of functional status of patients with pulmonary hypertension*

Class	Description
I	Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnoea, fatigue, chest pain or presyncope
II	Patients with pulmonary hypertension who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain or presyncope
III	Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain or presyncope
IV	Patients with pulmonary hypertension who are unable to perform any physical activity and who may have signs of right ventricular failure at rest. Dyspnoea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity

Reproduced from Galiè *et al*. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. *European Heart Journal* (2004;**25**:2243–78) by kind permission of the European Society of Cardiology.[1]

vascular resistance, elevated PAP and the clinical sequelae of PAH, ultimately leading to right ventricular failure and premature death.[1,2] The molecular mechanisms behind these changes are still being investigated and thus will only be briefly mentioned when necessary in this report.

Significance for patients in terms of ill health

People with PAH may remain relatively asymptomatic until the underlying disease process is advanced. The key initial symptoms are breathlessness on exertion, and possibly chest pain (angina) and fainting (syncope). Accurate diagnosis can often be difficult as symptoms may appear non-specific, and therefore there is often a long delay from the onset of symptoms to definitive diagnosis. This delay can be several years and thus patients can have severe disease (and possibly signs and symptoms of right heart failure) by the time that appropriate treatment is commenced. Loss of exercise capacity and latterly capacity for daily living can be devastating to a patient's quality of life and can also lead to depression and further deterioration in the quality of remaining life. Oedema and ascites are associated with severe PAH and in situ thromboses may occur in the pulmonary circulation.

PAH and IPAH in particular can occur at a relatively young age, elevating the impact of the disease on the patient and carers.

Heart–lung transplantation is an option for severe PAH; however, the number of available donors is very small and thus very few patients receive such transplants (probably less than 10 patients per year in the UK).

Significance to the NHS

Given the severity of PAH and its relatively rapid progression from diagnosis to premature death there is a considerable impact on the NHS, particularly towards the end of life when patients enter right heart failure.

According to UK Hospital Episode Statistics,[3] in 2005–6 IPAH accounted for nearly 4000 hospital admissions, nearly 4500 consultant episodes and over 17,000 bed days.

Because of the severity of the disease, including the risk of early death, close monitoring and expert care are required, and it is recommended that this is undertaken at specialist centres (see Current guideline for use in the NHS).

Risk factors

Numerous factors have been identified as possibly increasing the risk of developing PAH. *Table 3* provides information on the risk factors, including conditions that might be associated with PAH and an indication of the strength of the likelihood of an association between the factor and PAH. This table is adapted from an article by Galiè *et al*.[1] Some of these risk factors are considered sufficiently important contributors to the spectrum of PAH that they have been incorporated into the clinical classification system of PAH outlined in *Table 1*. Some of the main issues around risk factors are discussed in the following sections.

Drugs and toxins

Exposure to certain drugs and toxins might increase the risk of PAH. Evidence has been provided to associate the use of appetite suppressants structurally derived from amphetamine (aminorex, fenfluramine and dexfenfluramine) with a sixfold increase in the risk of developing PAH. Because of this adverse effect such suppressants have been removed from the market.[2]

No significant difference has been reported between patients with PAH and the general population with regard to smoking habits.[4]

Demographic and medical conditions

There is fairly clear evidence that, in adults, women tend to be more likely to develop PAH than men. Although the ratio of women to men varies from study to study it is of the order of 1.3:1 to 2.2:1.[4–6] In most trials women constitute the majority of patients.

No significant difference between PAH patients and the general population with regard to number of births per woman has been demonstrated.[4]

Diseases

PAH is frequently associated with a number of other diseases. These associations are reflected in the subclassifications of PAH (see *Table 1*).

A relationship between HIV infection and PAH has been clearly demonstrated.[1] About 0.5% of patients infected with HIV will develop PAH.[2]

Associated PAH (APAH) occurs in connective tissue diseases (CTD) and most commonly in

TABLE 3 *Risk factors and associated conditions classified according to the level of evidence*

1. Drugs and toxins:
   - 1.1. Definite: aminorex, fenfluramine, dexfenfluramine, toxic rapeseed oil
   - 1.2. Very likely: amphetamines, L-tryptophan
   - 1.3. Possible: meta-amphetamines, cocaine, chemotherapeutic agents
   - 1.4. Unlikely: antidepressants, oral contraceptives, oestrogen therapy, cigarette smoking
2. Demographic and medical conditions:
   - 2.1. Definite: gender
   - 2.2. Possible: pregnancy, systemic hypertension
   - 2.3. Unlikely: obesity
3. Diseases:
   - 3.1. Definite: HIV infection
   - 3.2 Very likely: portal hypertension/liver disease, connective tissue disease, congenital systemic–pulmonary cardiac shunts
   - 3.3. Possible: thyroid disorders, haematological conditions (asplenia secondary to surgical splenectomy, sickle cell disease, β-thalassaemia, chronic myeloproliferative disorders), rare genetic or metabolic diseases (type 1a glycogen storage disease/von Gierke's disease, Gaucher's disease, heredity haemorrhagic telangiectasia/Osler–Weber–Rendu disease)

Reproduced from Galiè *et al*. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. *European Heart Journal* (2004;**25**:2243–78) by kind permission of the European Society of Cardiology.[1]

scleroderma; around 12% of a hospital population of scleroderma patients suffer from PAH.[7] Despite similar haemodynamics survival in scleroderma APAH is worse than in IPAH, with a median survival of 1.2 years.[8]

Congenital heart disease (CHD) with non-restrictive systemic to pulmonary shunts, such as ventricular septal defects, patent ductus arteriosus and large atrial septal defects, may lead to PAH. Eisenmenger syndrome develops when such patients develop severe PAH with reversal of flow across the shunt and cyanosis. Survival in untreated Eisenmenger syndrome is much longer than in IPAH although it is still markedly reduced compared with that in the normal population.[9]

Portopulmonary hypertension, associated with liver disease and portal hypertension, is observed in 4–15% of patients who are evaluated for liver transplantation.[2]

Hereditary

In 6–10% of patients PAH is suspected or proven to be of hereditary origin. In total, 50–90% of patients diagnosed with FPAH have mutations of the bone morphogenetic protein receptor, type II (*BMPR2)* gene. Patients with FPAH tend to suffer from more severe and quickly progressing disease.[2] In 2001 in the UK there were at least 20 families known to have FPAH.[10]

Prognosis and prognostic factors

The prognosis for patients with PAH on supportive care (see Current service provision) is considered to be poor. In the 1980s median survival at the time of diagnosis for patients with IPAH (PPH) receiving supportive care was 2.8 years.[5] Percentages of patients surviving a specified period were estimated as 68% [95% confidence interval (CI) 61–75%] at 1 year, 48% (95% CI 41–55%) at 3 years and 34% (95% CI 24–44%) at 5 years.[5] One of the key factors influencing prognosis is functional class (FC). Patients with FCI or FCII PAH in the 1980s cohort had a median survival of 58.6 months, whereas those with FCIII had a median survival of 31.5 months. An extremely low median survival of 6 months was observed in patients with FCIV. [5] Given the greater awareness of PAH, the development of specialised PAH services and treatment algorithms and the potential for earlier diagnosis, median survival times from diagnosis may be longer today.

Haemodynamic variables related to decreased survival have been identified: increased mean (m) PAP, increased mean right arterial pressure (RAP) and decreased cardiac index. These variables also appeared in an equation predicting patient survival based on the results of a multivariate analysis of data from a registry established in the 1980s by the National Institutes of Health (USA).[5] The applicability of survival rates predicted by this equation, however, is questionable given the

changes in medical practice as well as in other socioeconomic factors over the past few decades.

Exercise endurance, usually measured with the 6-minute walk test (6MWT), is also considered to be an important prognostic factor. One of the earliest drug trials for PAH demonstrated that the 6-minute walk distance (6MWD) was a predicator of survival, independent of treatment.[2,11]

The progression of PAH symptoms in the context of change in clinical parameters is shown schematically in *Figure 1*.

Incidence and prevalence

PAH is a rare condition and as with such conditions the incidence and prevalence have been fairly difficult to assess. Often quoted figures for the incidence are 1–2 cases per million general population per year for IPAH and a further 1–2 cases per million population per year for other PAH aetiologies.[4,12] The likely prevalence has been estimated to be 15–50 patients per million population in the UK, with a suggestion that the estimate may be towards the upper end of the range.[6,12,13] Prevalence by FC is difficult to assess as many patients in lower FCs may not have been diagnosed yet. Thus the figures above are likely to be skewed to the more severe FCs. Assuming an adult population in England and Wales of 43.3 million this would give an approximate upper estimate of 2165 patients with PAH.

Measurement of disease

A number of measures are used clinically to monitor the severity, progression and response to treatment of PAH. Many of these can be related to exercise capacity, haemodynamics and/or cardiac performance. Clinically no single measure or composite measure is utilised to measure the disease. Severity, progression and response to treatment are assessed utilising a combination of measures. Some of the key measures are outlined in the following sections.

6-Minute walk test

The 6MWT measures the distance that a patient can walk unencouraged on a flat, hard surface in 6 minutes.[14] The absolute value of the 6MWD is predictive of survival and correlated with NYHA FC. A change from baseline is often used to assess treatment effect or patient deterioration. Conditions such as joint problems, not directly related to the pathophysiology of the pulmonary/cardiac circulation, might influence a patient's ability to walk and the results of the test.

Dyspnoea scores

A number of measures of dyspnoea are used to measure PAH. These can be related to perceived exertion and/or a combination of magnitude of task and perceived effort. These are often subjective scales, but some have been shown to correlate with physiological parameters. Examples are the Borg and Mahler scales.

Pulmonary artery pressure

PAP is measured directly during right heart catheterisation. A mPAP > 25 mmHg at rest or > 30 mmHg with exercise is one of the criteria for PAH diagnosis. Elevated mPAP, together with other haemodynamic variables, indicates patients with a poor prognosis.[1]

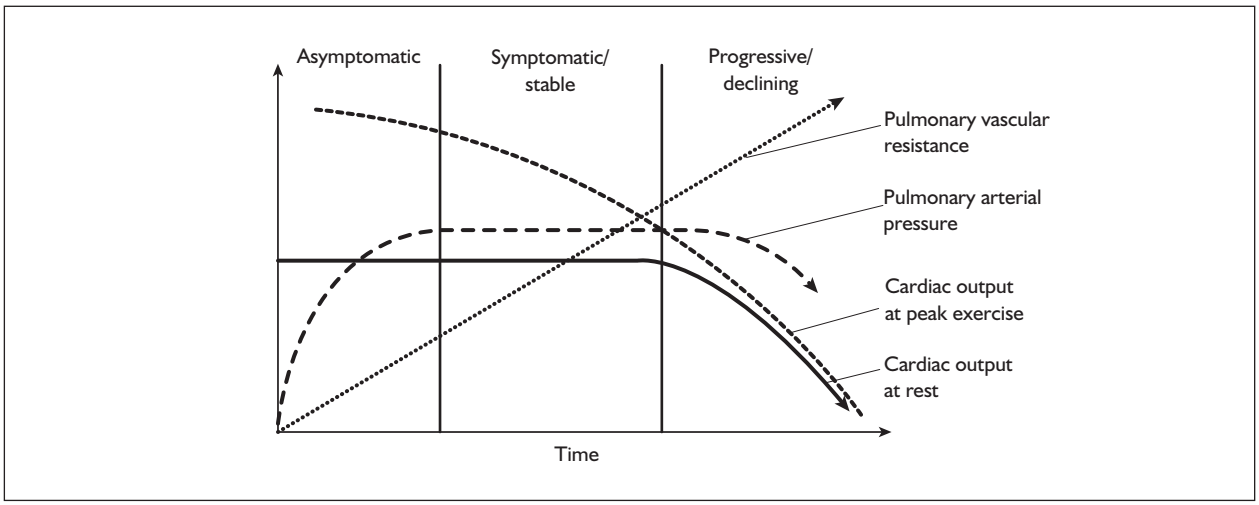

FIGURE 1 *Schematic of progression of pulmonary arterial hypertension and change in clinical parameters. Adapted from Rich S. Primary pulmonary hypertension.* Prog Cardiovasc Dis *1988;***31***:205–38. Copyright 1988, with permission from Elsevier.*

Right atrial pressure

Right atrial pressure is measured at cardiac catheterisation. RAP measures the filling pressure of the right ventricle and rises progressively as the right ventricle fails. High RAP thus identifies a failing right ventricle and a poor prognosis. The normal value of RAP is up to 5 mmHg.

Pulmonary capillary wedge pressure

Pulmonary capillary wedge pressure provides an indirect estimate of left atrial pressure. The measurement is made with a balloon-tipped, multilumen catheter inserted into a peripheral vein and then advanced into the right atrium, right ventricle and pulmonary artery and into a branch of the pulmonary artery. The normal value of PCWP is 8–10 mmHg. A PCWP ≤ 15 mmHg is one of the PAH diagnostic criteria. Elevated PCWP normally indicates left heart disease.

Pulmonary vascular resistance

PVR is a measure of the resistance of the pulmonary vascular circulation to flow. It is calculated as:

> [mean pulmonary artery pressure (mmHg) – pulmonary capillary wedge pressure (mmHg)]/ cardiac output (l/min) × 80.

A PVR > 240 dyn s/cm^5 is one of the diagnostic criteria for PAH.[15]

Cardiac output/cardiac index

Cardiac output measures the amount of blood pumped around the circulation per minute. It is usually measured by cardiac catheterisation in PAH. Non-invasive methods of measuring cardiac output are also available. The cardiac index is calculated by dividing cardiac output by body surface area, thus relating it to the individual patient. It is usually expressed in l/min/m^2.

Current service provision

Until 10 years ago PAH was managed mainly by supportive care alone. Since this time many patients have been enrolled in trials of new technologies that aim to be disease modifying rather than only tackling symptoms, and many of these drugs have been licensed for use in the UK. Thus, there is not a clear distinction between the current service provision and the technologies of this assessment. Given the uptake of the new technologies and their disease-modifying strategies they have become a routine part of clinical practice.

Information on what is commonly referred to as supportive care and the technologies covered by this assessment are given in separate sections below.

Supportive treatment

A variety of treatments have been used in the management of PAH prior to the advance of the five technologies under assessment. These include anticoagulation therapy, diuretics, oxygen, digoxin and calcium channel blockers. They are commonly referred to as conventional therapy or background therapy and are used in clinical practice in addition to the technologies under assessment. Each of the treatments is briefly described below.

Anticoagulation

The aim of treatment with anticoagulants is to reduce the risk of venous thromboembolism, the risk of which is increased by PAH.[16] Usually, a target of an international normalised ratio (INR) ranging between 2.0 and 3.0 in Europe (and 1.5–2.5 in North America) is assumed.[1]

The effectiveness of oral anticoagulants was originally demonstrated in retrospective single centre studies including only patients with IPAH and PAH related to anorexigens. Anticoagulation is also used in patients with other aetiologies of PAH, but all contraindications (such as a high risk of gastrointestinal bleeding in patients with CTD) have to be carefully considered. If there are no contraindications, patients treated with intravenous medication (e.g. epoprostenol; see Prostanoids, Epoprostenol) are also treated with anticoagulants, as they are at an increased risk of thrombosis associated with the use of a catheter.[1]

In recent PAH randomised controlled trials (RCTs) the use of anticoagulants was reported in 51–86% of patients.[1] Warfarin is frequently the anticoagulant used in the treatment of PAH and, as with its use in other diseases, patients require frequent monitoring to reduce serious adverse effects such as haemorrhage.

Diuretics

Diuretics are used to prevent or reduce fluid retention. The aim of using diuretics in patients with PAH is to treat oedema or fluid retention connected with right heart failure, such as ankle swelling or ascites.[16] There are several classes of diuretics, including thiazides, loop diuretics and potassium-sparing diuretics. In recent PAH RCTs 49–70% of patients were treated with diuretics.

Because of the lack of trials including specific classes of these drugs the choice of type and dose of medication are left to the decision of the physician. Monitoring of serum electrolytes and indices of renal function is advised in patients undergoing diuretic therapy.[1]

Examples of diuretics used in the treatment of PAH include furosemide, amiloride and spironolactone.

Oxygen

Oxygen is used in patients with hypoxaemia, an abnormal deficiency of oxygen in arterial blood.[16] Hypoxaemia at rest is usually mild in patients with PAH. Some patients experience improvement in PAH with low-flow supplemental oxygen. Although the effect has not been proven in controlled studies it is considered important to maintain an oxygen saturation greater than 90% in patients with PAH.[1]

The use of oxygen in patients suffering from PAH associated with some underlying conditions, such as cardiac shunts, can be controversial. A clinical trial[1] assessing the efficacy of nocturnal use of oxygen in patients with PAH associated with Eisenmenger syndrome found no effect of oxygen therapy on haematological variables, quality of life or survival.

The need for oxygen often decreases in patients treated with epoprostenol. Patients without targeted treatment require more oxygen therapy.

Digoxin

The progression of right heart failure often results in depression of myocardial contractility. This condition can be treated with inotropic agents, for example agents that affect the force of muscle contraction.

Digoxin is used in patients with refractory right heart failure in sinus rhythm.[1] Digoxin is available in tablet form or as an injection. An increase in cardiac output, as well as a reduction in circulating noradrenaline levels, can be obtained by short-term intravenous use of digoxin. There is no evidence indicating the long-term efficiency of this drug.[1] Digoxin may be prescribed for improvement of cardiac output; however, now it is considered useful in rare cases of atrial fibrillation or atrial flutter to slow the ventricular rate.[16] It was used in 18–53% of patients taking part in recent PAH RCTs.[1]

Calcium channel blockers

Calcium channel blockers are used in PAH patients with no right heart failure for reduction of PVR. No more than 10% of IPAH patients respond acutely to vasodilator therapy.[17] Treatment of paediatric IPAH with calcium channel blockers has also shown some favourable results. It is less clear if therapy in patients suffering from PAH associated with other conditions is effective.

Only patients responding substantially in the short term to this therapy are considered for treatment with calcium channel blockers alone.[1] They are identified by means of an acute vasodilator challenge using short-acting agents, such as intravenous prostacyclin (see Description of technology under assessment, Prostanoids), adenosine or inhaled nitric oxide during right heart catheterisation.[18] As a result of a retrospective analysis of 557 patients tested with intravenous epoprostenol and inhaled nitric oxide, response criteria have been accepted of a fall in mPAP of 10 mmHg to an absolute mPAP ≤ 40 mmHg with an unchanged or increased cardiac output.[2]

Nifedipine and diltiazem are the vasodilators most frequently used in clinical trials. There are also new-generation calcium channel blockers (e.g. amlodipine and felodopine). Limited reports on efficacy, tolerability and dosage are available.

The choice of a calcium channel blocker can be based on the patient's heart rate, with relative bradycardia indicating nifedipine and relative tachycardia favouring diltiazem. The effective daily doses of these drugs tend to be high, ranging from 120 to 240 mg for nifedipine and from 240 to 720 mg for diltiazem. The advised procedure is to start with lower doses and gradually increase them to the highest tolerated ones. Usually, systemic hypotension and lower limb peripheral oedema limit the dose increase. The side effects can at times be decreased by the use of digoxin and/or diuretics (see earlier sections on these treatments).[1] This therapy requires close monitoring as the positive effect is not always maintained over time.[19]

Description of technology under assessment

Five technologies are under assessment in this report. These are:

- epoprostenol sodium (Flolan®, GlaxoSmithKline), administered by continuous intravenous infusion (hereafter referred to as epoprostenol)

TABLE 4 *Technologies: licensed indications, pharmacology and route of administration*

		Licensed indication[a]			
Technology	**Pharmacology**	**Population**	**Functional class**	**Other**	**Route of administration**
Epoprostenol (Flolan®, GlaxoSmithKline)[20]	Prostacyclin (synthetic)	Primary pulmonary hypertension	III and IV[b]		Continuous intravenous infusion
Iloprost (Ventavis®, Schering Health Care)[21]	Prostacyclin (analogue)	Primary pulmonary hypertension	III[b]	To improve exercise capacity and symptoms	Inhaled via nebuliser
Bosentan (Tracleer®, Actelion Pharmaceuticals)[22]	Endothelin receptor antagonist (non-selective)	Pulmonary arterial hypertension	III[c]	To improve exercise capacity and symptoms	Oral
Sitaxentan (Thelin®, Encysive Pharmaceuticals)[23]	Endothelin receptor antagonist (selective)	Pulmonary arterial hypertension	III[d]	To improve exercise capacity	Oral
Sildenafil (Revatio®, Pfizer)[24]	Phosphodiesterase-5 inhibitor	Pulmonary arterial hypertension	III[d]	To improve exercise capacity	Oral

a As in August 2007 when this technology assessment was completed. The licensed indication may have been changed subsequently.
b New York Heart Association (NYHA) classification.
c Classification not stated.
d World Health Organization (WHO) classification.

- iloprost (Ventavis®, Schering Health Care), administered by inhalation through a nebuliser (hereafter referred to as iloprost or inhaled iloprost)
- bosentan (Tracleer®, Actelion Pharmaceuticals), administered orally (hereafter referred to as bosentan)
- sitaxentan, sitaxsentan (Thelin®, Encysive Pharmaceuticals), administered orally (hereafter referred to as sitaxentan)
- sildenafil (Revatio®, Pfizer), administered orally (hereafter referred to as sildenafil).

All have marketing authorisation in the UK/EU. All apart from epoprostenol have orphan disease medicinal products designation within the EU. These technologies can be grouped into three categories based on pharmacological mechanism of action: prostanoids, endothelin receptor antagonists and phosphodiesterase inhibitors. Further details on each technology is given in the following sections and a summary of the technologies, including licensed indication, pharmacological action and mode of delivery, is given in *Table 4*.

Prostanoids

Prostacyclin is mainly produced in the vascular endothelium. It is a powerful vasodilator of both the pulmonary circulation and the systemic circulation, inhibits platelet aggregation and inhibits smooth muscle growth. A relative deficiency of endogenous prostacyclin, as indicated by a deficiency of prostacyclin synthase expression in pulmonary arteries and of prostacyclin urinary metabolites, may be involved in the pathology of PAH.[1,18,19] Whether deficiency is causative or a consequence of PAH is unclear, but it has presented a justification for the use of prostacyclin to treat PAH patients. Prostacyclin is not very stable in solution at room temperature and is rapidly metabolised in the circulation. The prostanoids epoprostenol and iloprost (inhaled) are under assessment here. Other prostanoids [beraprost, treprostinil and iloprost (intravenous)] are not licensed in the UK and are thus not considered in this assessment report.

Epoprostenol

Epoprostenol is a synthetic sodium salt of prostacyclin. It is indicated for the intravenous treatment of PPH in NYHA FCIII and FCIV patients who do not respond adequately to conventional/background therapy.[20] For this indication epoprostenol is licensed in vial sizes of 1.5 mg. (1.5-mg vials along with 0.5-mg vials are also licensed for renal dialysis when the use of heparin is otherwise contraindicated or heparin use carries a high risk of causing or exacerbating

bleeding.[20,25]) Conventional/background therapy, although not explicitly defined, can be considered to be those treatments not classed as interventions in this assessment and as specified in the section on current service provision.

Epoprostenol is contraindicated in patients with known hypersensitivity to the drug, with congestive heart failure from severe left ventricular dysfunction and/or who develop pulmonary oedema during dose ranging.[20]

Epoprostenol has a short half-life in the circulation (3–5 minutes) and therefore is administered continuously via pump into a central venous catheter (Hickman line).[1] Furthermore, once in solution epoprostenol is only stable for 8 hours at room temperature, requiring it to be kept cool before infusion with ice packs. Given the route of delivery, continuous administration and limited stability the treatment is not without complications. Not all patients are suitable for epoprostenol treatment as a great deal of self- or carer-ability and commitment is required to prepare and administer the drug under sterile conditions and to maintain sterility of the permanent central venous catheter. Ongoing patient/carer education and training are vital and these are delivered regularly by a specialist nurse.

Treatment must be initiated as an inpatient under specialist care because of the intensive training of patients and/or their carers and the close monitoring and emergency backup required. Initiation of treatment is by short-term dosing to determine the patient-specific infusion rate (this process can also be undertaken using a peripheral rather than a central line). Initially the infusion rate is 1–2 ng/kg/min and this is increased until maximum benefit on haemodynamic parameters is achieved and/or dose-limiting pharmacological effects occur.

Patients well enough to return home do so after this period, which usually lasts 1–2 weeks. Not all patients can safely manage epoprostenol treatment without help from carers.

Patients require two serviceable pumps at home in case one fails. These, along with a regular supply of sterile and other consumables and epoprostenol, are usually delivered by home care services to the patient. Patients have access to telephone support from the specialist centre, usually immediate access to outpatient and inpatient care and district nursing services.

Over time the infusion rate is gradually increased by 1–2 ng/kg/min steps to assess the clinical response and, overall, gradual dose increases are to be expected in most patients to arrest a deterioration in symptoms.[20] Typical doses might be in the range of 15–50 ng/kg/min (higher upper doses have been used in the USA) depending on the length of time on treatment, the resistance of the disease to adequate control and the severity of any adverse effects.

Patients who deteriorate appreciably while on treatment and/or who are not fit/able to return home after initiation of treatment usually require full-time hospitalisation.

Once initiated, withdrawal of epoprostenol treatment is problematic because of rebound pulmonary hypertension and rapid clinical deterioration, which may result in death. For this reason, once initiated, epoprostenol treatment is considered to be lifelong by many.

Because of the difficulties associated with epoprostenol treatment it is a very considered decision by both the patient/carer and clinical team whether and when to initiate treatment. For this reason the other interventions outlined in the following sections will be considered or utilised initially in preference. However, epoprostenol is considered to be the last defence against deterioration of the disease. It is therefore added to treatment regimes when other treatments begin to fail. Thus, many patients will be receiving epoprostenol, usually in combination with an oral treatment (see Endothelin receptor antagonists, phosphodiesterase-5 inhibitors and Current usage of technologies in the NHS). Patients presenting with aggressive disease and/or in FCIV will receive epoprostenol.

The price of epoprostenol is approximately £130–390 per day (15–45 ng/kg/min per 70-kg patient; one to three vials per day; net price).[26] This price only includes the epoprostenol powder and diluent and not the pumps, consumables, delivery or any other costs associated with administration (insertion of Hickman line), monitoring, inpatient time and training. The price for some of these items is difficult to ascertain and/or contained in confidential service agreements.

Iloprost (inhaled)

Iloprost is a stable prostacyclin analogue that has been developed for intravenous, oral and inhaled administration. Only administration by inhalation is part of this assessment.

Inhaled iloprost has EU marketing authorisation for the treatment of PPH patients in NYHA FCIII to improve exercise capacity and symptoms.[21] Two vial sizes, 1 ml and 2 ml, are licensed.

The administration of iloprost by inhalation is an attractive idea as potentially it is selectively delivered to the pulmonary circulation. To ensure distribution to the alveoli a delivery system is required to produce small enough aerosol particles. Three types of delivery systems (nebulisers) are available: compressed air, ultrasonic and vibrating mesh nebulisers. The recommended dose is 2.5 µg or 5.0 µg of iloprost (as delivered at the mouthpiece of the nebuliser) per inhalation session according to individual need and tolerability. One vial is sufficient for each inhalation session. Each inhalation session takes 3–10 minutes depending on the dose, the nebuliser and the patient breathing pattern.[21] The serum half-life of iloprost is about 20–25 minutes and this short duration requires six to nine inhalation sessions per day.

Treatment is usually initiated under specialist care with the patient admitted to hospital for about 3 days for training, education and monitoring of self-delivery. Patients can return home once stabilised and trained. Patients receive two nebulisers (one as backup) and consumables are delivered regularly to their home. Nebulisers are replaced approximately every 2 years. Support from the specialist centre is readily available.

Length of treatment is patient specific and unless discontinued for other reasons will continue until the patient's condition deteriorates and epoprostenol treatment (see Epoprostenol) is accepted by the patient and initiated.

Inhaled iloprost is often seen as an additional treatment to the oral therapies in this assessment, bridging the gap for those patients in whom oral interventions do not adequately reduce progression of disease, but who are either not so severely affected that epoprostenol treatment is indicated or not suitable for epoprostenol treatment.

Iloprost is contraindicated in patients with known hypersensitivity to the drug, conditions in which activity on platelets might be undesirable (e.g. active peptic ulcers, intracranial bleeds, trauma), severe coronary disease events (e.g. severe artery disease, angina, recent myocardial infarction), recent cerebrovascular events (e.g. stroke), pulmonary hypertension due to veno-occlusive disease, valvular defects with clinically relevant myocardial function disorders unrelated to pulmonary hypertension, pregnancy and lactation. Furthermore, iloprost is not recommended in patients with unstable pulmonary hypertension, with advanced right heart failure.[21]

The cost of iloprost nebuliser solution is approximately £85–127 per day (one vial six to nine times per day; net price same for each vial size).[26] This price is for the solution only and does not include the nebulisers, consumables, service, delivery, inpatient time and training. The price for some of these items is difficult to ascertain and/or contained in confidential service agreements.

Endothelin receptor antagonists

Endothelin-1 (ET-1), which is produced primarily in vascular endothelial cells, is a potent vasoconstrictor and mitogen (promoter of cell proliferation) in smooth muscle. ET-1 expression and concentration in plasma and lung tissue are elevated in PAH.[1,19] It is unclear whether increases in ET-1 are a consequence or a cause of PAH. Irrespectively, the ET-1 system is a target for the treatment of PAH.

ET-1 action is mediated through two types of receptors: ET_A and ET_B. ET_A receptors are found in smooth muscle cells and ET_B receptors in endothelial cells and smooth muscle cells. ET-1 interaction with ET_A and ET_B receptors in smooth muscle cells promotes sustained vasoconstriction and proliferation of vascular smooth muscle cells.[1,19] ET-1 stimulation of ET_B receptors promotes ET-1 clearance and release of nitric oxide and prostacyclin. Blocking ET-1 interaction with ET_A and/or ET_B receptors therefore has a theoretical basis in the treatment of PAH and has led to the development of agents that bind to the receptors without eliciting a biological response, thus blocking binding of ET-1. Such agents are commonly referred to as receptor antagonists. Three endothelin receptor antagonists are available: bosentan and sitaxentan are covered by this assessment, whereas ambrisentan (Volibris/Letairis®) is not as it was not licensed in the UK when the technology assessment was carried out in 2007. Ambrisentan was approved in the USA for PAH in June 2007 and received marketing authorisation in the EU in April 2008.[27,28]

Bosentan

Bosentan is an orally administered dual ET_A and ET_B receptor antagonist. It has UK marketing authorisation for PAH to improve exercise capacity

and symptoms in patients in FCIII.[22] Two tablet sizes are available: 62.5 mg and 125 mg.

Treatment should be initiated and monitored under specialist care. Initially, dosing is 62.5 mg twice daily (morning and evening with or without food) for 4 weeks, increased thereafter to a maintenance dose of 125 mg twice daily. Doses for some patients may be increased to 250 mg twice daily but this is rare.

Patients are usually admitted to hospital as day cases under specialist care for the initiation of treatment. Some education is also given. Patients return home and drugs are usually delivered to them at regular intervals.

Length of treatment is patient specific. Limited or no response after 8–16 weeks of treatment or a deterioration of condition at any time requires re-evaluation of treatment. This usually entails either the addition of, or the replacement with, other treatments. Withdrawal of bosentan requires careful management.

Bosentan is metabolised by the liver and has been associated with a dose-dependant increase in the liver enzymes aspartate aminotransferase and alanine aminotransferase (more than eight times the upper limit of normal in some cases). Such elevation can be the marker of potentially serious liver injury. This is reflected in the recommended maintenance dose of 125 mg twice daily rather than 250 mg twice daily. This is not a unique feature of bosentan as it also occurs with sitaxentan. Regular monitoring of hepatic enzymes (usually monthly) is required for as long as the drug is taken.

Bosentan is not indicated in patients with a known hypersensitivity to the drug, those with hepatic impairment (including aminotransferase levels more than three times the upper limit of normal) and those taking ciclosporin A (amplifies the plasma concentration of bosentan by an unknown mechanism). Bosentan is contraindicated in pregnancy as it is assumed to be teratogenic and therefore women with childbearing potential should not receive bosentan unless using reliable contraception (bosentan may interact and lessen the effectiveness of hormonal contraception).

The cost of bosentan tablets is approximately £55 per day (2×62.5 or 2×125 mg as the net price is the same for each tablet size).[26] This price is for the drug only and does not include delivery, monitoring of liver function or inpatient time, etc.

Sitaxentan

Sitaxentan is an orally administered selective receptor antagonist for ET_A (but not ET_B). It has EU marketing authorisation for PAH to improve exercise capacity in FCIII.[23] One tablet size is available: 100mg.

Treatment should be initiated and monitored under specialist care. Dosing is 100 mg once a day with or without food. Patients are usually admitted to hospital as a day case under specialist care for the initiation of treatment. Some education is also given. Patients return home and drugs are usually delivered to them at regular intervals.

Length of treatment is patient specific. Limited response after 24 weeks of treatment or a deterioration of condition at any time requires re-evaluation of treatment.[23] This usually entails either the addition of, or the replacement with, other treatments. Withdrawal of treatment requires careful management.

As with bosentan, sitaxentan is associated with effects on liver enzymes and these require regular monitoring, with subsequent treatment adjustment if elevated more than three times the upper limit of normal.[23]

Contraindications are similar to those of bosentan. There is significant drug interaction between sitaxentan and warfarin. Reducing the dose of warfarin upon starting sitaxentan and regular monitoring of the INR is required to reduce the risk of bleeding.

The cost of sitaxentan is approximately £55 per day (1×100 mg; net price).[26] This price is for the drug only and does not include delivery, monitoring of liver function or inpatient time, etc.

Phosphodiesterase-5 inhibitors

PAH is associated with a defect in the production of nitric oxide.[1,18,19] Nitric oxide is an endogenous pulmonary arterial vasodilator that acts by relaxing vascular smooth muscle through its stimulation of increased production of intracellular cyclic guanosine monophosphate (cGMP). Thus, dilation through this mechanism is reduced in PAH. cGMP is a short-lived molecule because of its rapid degradation by phosphodiesterases. Phosphodiesterase-5 is strongly expressed in the lung and its expression and activity are elevated in chronic pulmonary hypertension.[19] Thus, inhibitors of phospodiesterase-5 will decrease cGMP

degradation, enhancing nitric oxide-dependant cGMP-mediated pulmonary vasodilation.[1,18,19]

Sildenafil

Sildenafil is an orally administered specific inhibitor of phosphodiesterase-5. It has UK/EU marketing authorisation for PAH to improve exercise capacity in patients in FCIII.[24] It is available as 20-mg tablets.

Treatment should be initiated and monitored under specialist care. Dosing is 20 mg three times per day (6–8 hours apart) with or without food.[24]

Patients are usually admitted to hospital as a day case under specialist care for the initiation of treatment. Some education is also given. Patients return home and drugs are usually delivered to them at regular intervals.

Length of treatment is patient specific. Deterioration of condition at any time requires a re-evaluation of treatment.[24] This usually entails either the addition of, or the replacement with, other treatments. Withdrawal of treatment requires careful management.

Contraindications for sildenafil include hypersensitivity to the drug; use with nitric oxide-producing treatment or nitrates is not recommended as sildenafil potentiates the hypotensive effects of these agents. It is also contraindicated in patients with severe hepatic impairment, recent history of stroke or myocardial infarction, and severe hypotension at initiation. Furthermore it is contraindicated in some specific eye conditions.[24]

The cost of sildenafil is approximately £12.45 per day (20 mg×3; net price).[26] This price is for the drug only and does not include delivery, inpatient time and training, etc.

Current guideline for use in the NHS

Since 2001, patients in the UK with PAH have been referred to and managed at specialist centres. There are seven centres in England designated by the Department of Health through the National Commissioning Group (NCG) (formerly known as the National Specialist Commissioning Advisory Group or NSCAG).[29] There is one centre in Scotland designated by the National Service Division of NHS Scotland. There are no centres in Wales and Northern Ireland and patients are seen at English centres. The centres are:

- London: Hammersmith Hospital, Royal Free Hospital, Royal Brompton Hospital, Great Ormond Street Hospital (Children)
- Newcastle-upon-Tyne: Freeman Hospital
- Papworth/Cambridge: Papworth Hospital
- Sheffield: Royal Hallamshire Hospital
- Scotland: Western Infirmary Glasgow.

The cost of the service at the English centres is not funded through NSCAG but by the NHS, except for the designated children's centre.[29]

Treatment guidelines

In 2001, the British Cardiac Society sought for the first time to gain a consensus on the treatment of pulmonary hypertension.[10] The resulting recommendations set out criteria for the use of disease-targeting therapies, such as the technologies in this assessment, primarily based on cardiac catheterisation. Given the findings of many trials published more recently in which patients were enrolled based on NYHA/WHO FC and the granting of marketing authorisation for new technologies, the recommendations are considered by many to be out of date.[30] An update to the recommendations, including new treatment algorithms, has been published.[31]

Guidelines published by the European Society of Cardiology (ESC) in 2004[1] are considered the most current with regard to practice in the UK at the time of writing (August 2007). Guidelines have also been produced by the American College of Chest Physicians. Both organisations are believed to be updating their guidelines for 2008.[30]

The ESC guidelines cover all aspects of the diagnosis, monitoring and treatment of PAH. They contain an evidence-based algorithm for the treatment of PAH FCIII and FCIV. This algorithm is reproduced in *Figure 2* along with a complete description.

Current usage of technologies in the NHS

All five technologies are currently being utilised within the NHS. Perhaps the best information on uptake comes from the submission from the Royal College of Physicians[30] for this appraisal, which contains year-on-year utilisation of the technologies from 2004 to 2007 collated by the National Pulmonary Hypertension Service of the UK and Ireland. The data are available for all pulmonary hypertension patients and thus the census is likely to cover a wider population than just PAH

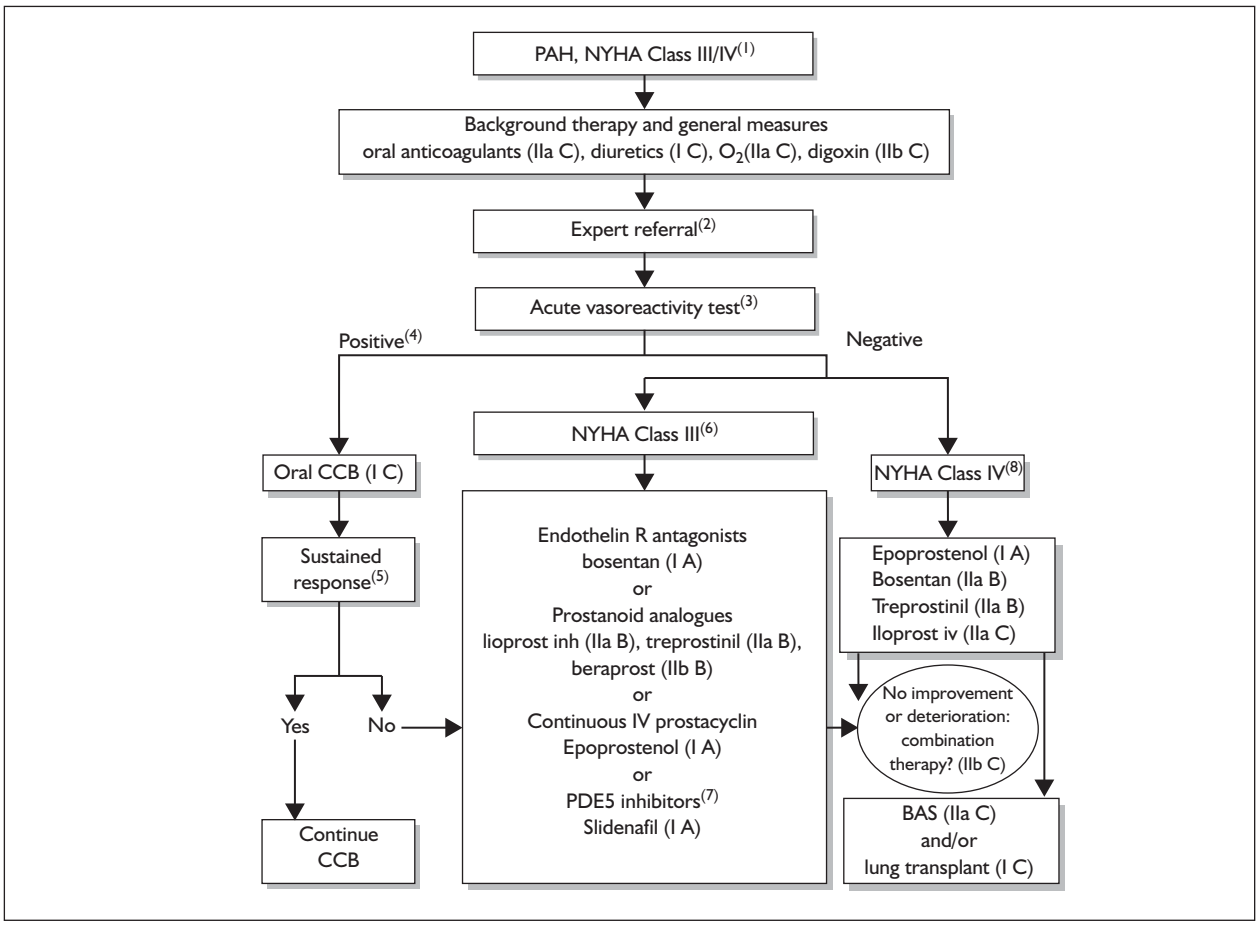

FIGURE 2 *European Society of Cardiology (ESC) evidence-based treatment algorithm. (1) The algorithm is restricted to patients in NYHA functional class III or IV because they represent the largest population included in controlled clinical trials. For NYHA functional class I or II very few data are available. In addition, the different treatments have been evaluated mainly in sporadic idiopathic pulmonary hypertension (IPAH) and in patients with PAH associated with scleroderma or anorexigen use. Extrapolation of these recommendations to other PAH subgroups should be carried out with caution. (2) Because of the complexity of the acute vasoreactivity tests, and of the treatment options available, it is strongly recommended that consideration be given to referral of patients with PAH to specialised centres. (3) Acute vasoreactivity tests should be performed in all patients with PAH even if the greater incidence of a positive response is achieved in patients with IPAH and PAH associated with anorexigen use. (4) A positive acute response to vasodilators is defined as a fall in mean pulmonary artery pressure of at least 10 mmHg to ≤ 40 mmHg with an increase or unchanged cardiac output during acute challenge with inhaled nitric oxide, intravenous (i.v.) epoprostenol or i.v. adenosine. (5) Sustained response to calcium channel blockers (CCB) is defined as patients being in NYHA class I or II with near-normal haemodynamics after several months of treatment. (6) In patients in NYHA functional class III first-line therapy may include oral endothelin receptor antagonists, chronic i.v. epoprostenol or prostanoid analogues. (7) At the time of writing sildenafil is not approved for PAH by any regulatory agency. (8) Most experts consider that NYHA functional Class IV patients in an unstable condition should be treated with iv epoprostenol (survival improvement, worldwide experience and rapidity of action). A, B, C grading according to definitions in Tables 4 and 5 of the ESC guidelines. BAS, balloon atrial septostomy; inh, inhaled; PDE, phosphodiesterase; R, receptor. Reproduced from Galiè* et al. *Guidelines on diagnosis and treatment of pulmonary arterial hypertension*. European Heart Journal *(2004;**25**:2243–78) by kind permission of the European Society of Cardiology.*[1]

patients. The number of patients with pulmonary hypertension who received disease-targeted therapy in the UK designated centres (in both clinical practice and clinical trials) on 31 March was 638 in 2004, 912 in 2005, 1242 in 2006 and 1499 in 2007.[31] It has been requested that further data from this utilisation survey remains academic-in-confidence. A small number of patients may not be seen at the Pulmonary Hypertension Service and therefore will be missing from the census.

[Academic-in-confidence information has been removed]. The 2007 census contains data from [Academic-in-confidence information has been removed] UK designated centres [Academic-in-confidence information has been removed]. This data is reproduced in Appendix 1 (*Tables 64–67*) and outlined as follows and summarised in *Table 5*. There are currently about [Academic-in-confidence information has been removed] UK patients attending the Pulmonary Hypertension Service. Of these just under [Academic-in-confidence

TABLE 5 *Current service utilisation: National Pulmonary Hypertension Service census 31 March 2007*

Name of therapy	English patients[a]
Monotherapy	
Epoprostenol (i.v.)	[Academic-in-confidence information has been removed]
Treprostinil (s.c.)	[Academic-in-confidence information has been removed]
Treprostinil (i.v.)	[Academic-in-confidence information has been removed]
Iloprost (i.v.)	[Academic-in-confidence information has been removed]
Iloprost (nebulised)	[Academic-in-confidence information has been removed]
Bosentan	[Academic-in-confidence information has been removed]
Sitaxentan	[Academic-in-confidence information has been removed]
Sildenafil	[Academic-in-confidence information has been removed]
Trial drug[b]	[Academic-in-confidence information has been removed]
Monotherapy total	[Academic-in-confidence information has been removed]
Dual therapy	
Bosentan and sildenafil	[Academic-in-confidence information has been removed]
Sitaxentan and sildenafil	[Academic-in-confidence information has been removed]
Bosentan + epoprostenol (i.v.)	[Academic-in-confidence information has been removed]
Bosentan + iloprost (i.v. or nebulised)	[Academic-in-confidence information has been removed]
Bosentan + treprostinil (s.c. or i.v.)	[Academic-in-confidence information has been removed]
Sildenafil + iloprost (i.v. or nebulised)	[Academic-in-confidence information has been removed]
Sildenafil + treprostinil (s.c. or i.v.)	[Academic-in-confidence information has been removed]
Sildenafil + epoprostenol (i.v.)	[Academic-in-confidence information has been removed]
Trial drug[b]	[Academic-in-confidence information has been removed]
Dual therapy total	[Academic-in-confidence information has been removed]
Triple therapy	
Bosentan + sildenafil + epoprostenol (i.v.)	[Academic-in-confidence information has been removed]
Bosentan + sildenafil + iloprost (i.v. or nebulised)	[Academic-in-confidence information has been removed]
Bosentan + sildenafil + treprostinil (s.c. or i.v.)	[Academic-in-confidence information has been removed]
Treprostinil (s.c.) + bosentan + sildenafil + iloprost (nebulised)	[Academic-in-confidence information has been removed]
Triple therapy total	[Academic-in-confidence information has been removed]

i.v., intravenous; s.c., subcutaneous.
a [Academic-in-confidence information has been removed].
b Not specified.

information has been removed] are children. Of the adult patients nearly [Academic-in-confidence information has been removed] are in Scotland. The remaining [Academic-in-confidence information has been removed] patients are seen in England (there are no Welsh or Northern Irish Pulmonary Hypertension Service centres).

In England, over [Academic-in-confidence information has been removed]. A small number of patients are on unspecified trial drugs (see *Table 5*). [Academic-in-confidence information has been removed].

Chapter 2

Definition of the decision problem

Decision problem

According to the final scope issued by the National Institute for Health and Clinical Excellence (NICE) for this technology appraisal the decision problems were:

- Whether epoprostenol, iloprost, bosentan, sitaxentan and sildenafil, when used within their licensed indications, are clinically effective and cost-effective compared with supportive treatments (see Chapter 1, Supportive treatment) in adults with PAH for whom calcium channel blockers are inappropriate or no longer effective.
- Whether the interventions being considered are clinically more effective, or more cost-effective, in patients with certain subpopulations of PAH according to the Venice 2003 clinical classification (see Chapter 1, Classification).
- Whether significant differences in clinical and cost-effectiveness exist between the interventions being considered (either used alone or in combination) when compared with each other and/or intravenous iloprost.

It was clear that this assessment report would be able to address only some of the issues surrounding these decision problems for the following reasons:

1. Although the Venice 2003 clinical classification provides a significantly improved framework for the diagnosis and management of PAH, patients with PAH represent diverse populations that vary greatly in aetiology, disease progression and prognosis. Cases being grouped under each of the Venice subcategories can still be heterogeneous in terms of severity, the choice and response to treatment and prognosis. For example, within the Venice subcategory 1.3.1, scleroderma has distinct features that may warrant it being considered separately from other forms of CTD (see Chapter 1, Clinical classification).
2. The five interventions being considered in this technology appraisal have different routes of administration, demands on patients' self-management, speeds of action, adverse effect profiles and contraindications. The selection of treatment is to some extent dependent on the nature of the underlying condition, the clinical circumstances and patient ability and acceptance. As such the choice of treatment and appropriate comparators is dependent on all of these factors.
3. PAH is a rare condition. The number of patients included in clinical studies is relatively small. There was unlikely to be sufficient data to allow meaningful comparison between many of the subpopulations of PAH and between different treatments (or combinations of treatments).
4. The resources available to undertake this assessment report were comparable to those for other assessment reports and therefore not limitless.
5. Bearing these in mind the assessment group planned to undertake a systematic review of RCTs and a review of manufacturer submissions to establish the underlying evidence base that is available to answer the above decision problems and to highlight issues that are unlikely to be addressed because of the paucity of evidence. Then a model-based economic evaluation was to be carried out to address refined and focused decision problem(s) that take into account the availability of evidence, the appropriateness of combining different populations of PAH in terms of underlying cause (e.g. whether the model can include all PAH populations or the modelling can be reasonably carried out only for a specific population according to the evidence) and disease severity (e.g. it may be necessary to model patients in FCIII and FCIV separately), and the most appropriate place in the treatment pathway for each of the interventions being considered (e.g. oral treatments would not be considered as alternative, competing interventions against intravenous epoprostenol for patients in NYHA/WHO FCIV).

Population and relevant subgroups

The population considered is adults with PAH (category 1 of the Venice 2003 clinical classification) in NYHA/WHO FCIII (and also

FCIV for epoprostenol) for whom calcium channel blockers are inappropriate or no longer effective.

Potentially relevant subgroups include:

- subcategories of PAH (e.g. IPAH) under category 1 of the Venice 2003 clinical classification
- NYHA/WHO functional classes.

Subcategories are best perceived as different patient populations that share similar clinical manifestations of PAH rather than as 'subgroups' of a well-characterised disease. Given the likely volume of available evidence and the resources available for this technology assessment, the key specific subgroup to be examined was patients with IPAH in FCIII.

Definition of the interventions

For patients in FCIII, interventions being considered are:

- epoprostenol (Flolan®, GlaxoSmithKline), administered by continuous intravenous infusion
- iloprost (Ventavis®, Schering Health Care), administered by inhalation through a nebuliser, 2.5–5.0 µg as delivered at the mouthpiece per inhalation session
- bosentan (Tracleer®, Actelion Pharmaceuticals), administered orally, 62.5–250 mg twice daily
- sitaxentan (Thelin®, Encysive Pharmaceuticals), administered orally, 100 mg once daily
- sildenafil (Revatio®, Pfizer), administered orally, 20 mg three times daily.

For patients in FCIV:

- epoprostenol administered by continuous intravenous infusion was the only intervention considered.

Relevant comparators

- Supportive treatments – these include digoxin, diuretics, anticoagulants and oxygen (see Chapter 1, Supportive treatment).
- Placebo or no treatment – although the above supportive treatments are used for preventing/treating conditions and symptoms associated with PAH, the goals and mechanisms of these treatments are generally different from those of the interventions being considered. As these supportive treatments usually start earlier in the treatment pathway and are usually continued when introducing the interventions, studies in which the interventions were compared with placebo or no treatment are clinically relevant provided that supportive treatments were continued in all study arms.
- The interventions being considered, either used alone or in combination, were to be compared with each other if evidence was available from RCTs.
- Intravenous iloprost was considered as a comparator if evidence was available from RCTs.

Outcomes

The key outcomes to be examined for the technology assessment include changes in survival and quality of life with treatment; change in FC; time to clinical deterioration (including switch of drug therapy and lung transplantation); serious adverse events (SAEs); and incremental cost-effectiveness ratios (ICERs) for the interventions compared with supportive treatments.

Place of the intervention in the treatment pathway(s)

Based on the final scope the interventions being considered were to be used when conventional supportive treatments and calcium channel blockers either are inappropriate or have failed to control symptoms and maintain functional capacity.

For this technology assessment, only the first use of listed interventions was considered. Use of any of the interventions after failure of another listed intervention was not considered in the economic evaluation section, but was described in the clinical effectiveness section for information only (when evidence was available from RCTs). One exception to this was for epoprostenol as second-line treatment for patients progressing to FCIV as many such patients would have received other listed interventions first.

Key issues

Potentially problematic factors

- Trials including patients with mixed functional classes. Given that none of the interventions were licensed for FCII and only one of them (epoprostenol) was licensed for FCIV the main focus of the technology assessment was on patients in FCIII. Nevertheless, existing trials have included patients of various functional classes (e.g. FCII–IV)(see Chapter 1, Functional

classification). Data for the specific subgroup of patients in FCIII were believed in many cases to be unlikely to be readily available and therefore were to be requested from the sponsors/investigators of the trials.
- Trials including patients of mixed clinical classification of PAH. Existing trials may include types of PAH of a very different nature. Separate data for specific patient clinical classifications (see Chapter 1, Clinical classification) may not be available and therefore were to be requested from the sponsors/investigators of the trials.
- Insufficiency of data for subgroup analysis. As described already, the volume of existing evidence may not be sufficient for the exploration of treatment effects in subcategories of PAH or PAH associated with specific conditions even if the data were (made) available.
- Lack of long-term survival data from RCTs. Survival is one of the key outcomes that affect the cost-effectiveness of the interventions. The short duration of the trials was likely to restrict the availability of survival data from well-controlled studies. Economic modelling based on comparisons involving historical control subjects or data from non-randomised studies was inevitable. Prediction of survival had been based on patients' risk factors and/or surrogate outcomes such as haemodynamic assessment in many of the studies.
- Rapid and continuing development of treatment algorithms and patient pathways. Different treatment guidelines have been drawn up by various organisations and are being updated rapidly. For example, we are aware that the guidelines issued by the ESC are being updated and new guidelines are expected to be issued in 2009. It was unlikely that there would be sufficient evidence to deal with the issues around the sequencing of the technologies and, as stated already [see Place of the intervention in the treatment pathway(s)], only the first use of the technologies was considered, except for epoprostenol for which second-line use for patients in FCIV was considered.
- Co-morbidity and functional capacity can affect treatment choice, for example bosentan and sitaxentan cannot be considered in patients with moderate to severe hepatic impairment; epoprostenol cannot be considered in outpatients who are unable and/or unwilling to have this treatment administered by themselves or a carer.
- Request for data from manufacturers/sponsors. Because of the low prevalence of PAH it was likely that there would be a discrepancy between the patient groups included in clinical trials and the patient groups for whom the interventions are licensed. Furthermore it was unlikely that published trial data would be available purely for the licensed populations (clinical and functional classification) and on the licensed dose of the interventions. Such data for published and unpublished studies were to be requested from individual trial sponsors and therefore the assessment report was somewhat reliant on the availability of such data.

Areas that are considered outside the scope of the appraisal

The assessment group was aware of the emerging evidence that suggests a potential benefit of early treatment in patients with PAH who have mild symptoms and mild functional limitation. However, this group of patients was excluded from the final scope as none of the interventions being considered were licensed for PAH patients of FCII.

Drugs and preparations that were not licensed for treating PAH in the UK in 2007, such as treprostinil (Remodulin®, United Therapeutics), Beraprost® (United Therapeutics), ambrisentan (Volibris®/Letaris®, GlaxoSmithKline) and iloprost intravenous infusion (Ilomedin(e)®, Schering Health Care), were not considered as an intervention, even though they may be being used in clinical practice. However, intravenous iloprost was considered as a comparator when evidence permitted according to the final scope of the appraisal.

The assessment concentrated on the treatment of adults and, therefore, the treatment of children was not considered specifically.

Overall aims and objectives of assessment

The aims of this technology assessment were :

- to assess whether epoprostenol, iloprost, bosentan, sitaxentan and sildenafil (alone or in combination) are clinically effective and cost-effective when used within their licensed indications for the treatment of adults with PAH for whom calcium channel blockers are inappropriate or no longer effective compared

with supportive treatment (and/or intravenous iloprost)
- to assess, as far as available clinical data from RCTs would allow, whether epoprostenol, iloprost, bosentan, sitaxentan and sildenafil (alone or in combination) are clinically effective and cost-effective when used within their licensed indications for the treatment of adults with IPAH for whom calcium channel blockers are inappropriate or no longer effective compared with supportive treatment (and/or intravenous iloprost)
- if head-to-head RCTs exist, to assess whether one technology is significantly more or less clinically effective and cost-effective than another (alone or in combination) when used within their licensed indications for the treatment of adults with PAH for whom calcium channel blockers are inappropriate or no longer effective.

These aims were to be achieved by:

- a systematic review of RCTs that investigated the effectiveness of the technologies in PAH; variations in effectiveness between the drugs and/or between different PAH populations were to be explored if evidence from RCTs permitted
- a systematic review of published studies on the costs and cost-effectiveness of the technologies in PAH
- a review of the dossiers submitted to NICE by the manufacturers of the technologies
- a focused, model-based economic evaluation of the cost-effectiveness of the technologies from the perspective of the UK NHS.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

Search strategy

The following resources were searched for relevant primary studies:

- Bibliographic databases: Cochrane Library (CENTRAL) 2007 Issue 1, MEDLINE (Ovid) 1950 to February 2007, MEDLINE In-Process & Other Non-Indexed Citations (Ovid) and EMBASE (Ovid) 1980 to February 2007. Searches used index and text words that encompassed the condition (pulmonary arterial hypertension) and the interventions [epoprostenol, iloprost, bosentan, sitaxentan (and sitaxsentan) and sildenafil]. When the databases allowed, a methodological 'filter' was applied to identify trials.
- Citations of relevant studies were examined.
- Further information was sought from clinical experts.
- Research registers of ongoing trials including the National Research Register 2007 Issue 1, Current Controlled Trials and ClinicalTrials.gov.
- Manufacturer submissions.

Searches were not limited by date and neither were there language restrictions. Full search strategies can be found in Appendix 2.1.

Search results were entered into an electronic bibliographic database (REFERENCE MANAGER version 11; Thomson ISI ResearchSoft) and duplicate entries were removed.

Study selection

One reviewer screened all titles and abstracts for relevance and a subset of approximately half were checked by a second reviewer for quality assurance purposes. Full papers of potentially relevant studies were obtained and assessed for inclusion by two reviewers independently. Disagreements were resolved by consensus or referral to a third reviewer when necessary.

Studies that met all of the following criteria were included in the clinical effectiveness review:

- Study design – an RCT or article including data from one or more RCTs [e.g. systematic reviews or additional analyses of data from RCT(s)] in which the duration of the RCT(s) was greater than 1 week.
- Intervention(s) – any of epoprostenol (intravenous), iloprost (inhaled), bosentan (oral), sitaxentan (oral), sildenafil (oral).
- Comparator(s) – any treatment(s) other than different doses, formulations or methods of administration of the intervention itself. These could be placebo, conventional supportive treatments, other interventions listed above, other treatments not currently licensed in the UK (see Chapter 2, Areas that are considered outside the scope of the appraisal) or any combination of these.
- Population – adult patients diagnosed with PAH (even if not all of the patients enrolled had PAH or were adults).
- Outcomes – any.

A list of excluded studies and the reason for exclusion were recorded.

Included systematic reviews were not themselves systematically reviewed, but were utilised to identify further RCTs.

Data extraction strategy

Data extraction for published papers was performed independently by two reviewers into a specific proforma. Disagreements were resolved by consensus or by referral to a third reviewer when necessary. Additional data from manufacturer submissions, unpublished manuscripts and clinical study reports were extracted by only one reviewer because of time constraints.

Data were extracted on study design, patient characteristics, method of data analysis and results.

Critical appraisal strategy

The quality of each of the included studies was assessed by one reviewer and checked by another. Disagreements were resolved by consensus and a third reviewer was available to resolve any disagreements. The criteria on which studies were assessed were:

- Randomisation – whether allocation was truly random. Randomisation using computer or random number tables was considered adequate whereas the use of alternation, case record numbers or dates of birth and day of the week was considered inadequate. Strata for randomisation (if used) were recorded for information.
- Allocation concealment – whether allocation concealment was adequate. Any of the following methods was considered adequate: centralised (e.g. allocation by a central office unaware of subject characteristics) or pharmacy-controlled randomisation; prenumbered or coded identical containers that are administered serially to participants; on-site computer system combined with allocations kept in a locked unreadable computer file that can be accessed only after the characteristics of an enrolled participant have been entered; sequentially numbered, sealed, opaque envelopes.
- Blinding – use of blinding and who was blinded.
- Intention-to-treat (ITT) analysis – whether ITT analysis was used. During data extraction it became apparent that trials may have used ITT analysis for some of the outcomes but not others. Use of ITT analysis for each of the main outcomes (survival analysis, clinical worsening, change in FC, 6MWD, haemodynamic measures and quality of life measures) was therefore checked in detail for each trial by one reviewer.
- Follow-up – proportion (%) of patients completing the trial in each study arm.

The information from quality assessment was tabulated and utilised in a narrative assessment of the studies.

Methods of data synthesis

Outcomes of interest

Selected outcomes of interest were specified in the review protocol, based upon the final scope issued by NICE for this technology appraisal. They were:

- survival
- time to clinical deterioration (including switch of drug therapy and lung transplantation)
- health-related quality of life
- exercise capacity (6MWT)
- symptomatic improvement
- frequency and duration of hospitalisation and outpatient/GP visits
- SAEs
- adverse events that are considered as being clinically relevant or having a potential impact on tolerability
- withdrawal for any reason
- withdrawal because of lack of efficacy
- withdrawal because of adverse events
- haemodynamic assessment, e.g. cardiac index, RAP, pulmonary arterial oxygen saturation, PAP and PVR.

Of these, sufficient data were available from the included trials and meta-analyses were carried out for the following outcomes:

- dichotomous outcomes: death, clinical worsening (as defined in individual trials), symptomatic improvement (change in functional class), SAEs and withdrawal for any reason
- continuous outcomes: exercise capacity (6MWT), haemodynamic assessment including mPAP, RAP, PVR and cardiac index.

When data were available, narrative summaries were also provided in this review for time-to-event analyses of survival and clinical deterioration, and for other outcomes related to symptomatic relief (such as dyspnoea or fatigue) and health-related quality of life.

Individual adverse events were not meta-analysed as adverse event profiles varied between the interventions being assessed, and data on the severity or seriousness of specific adverse events were usually not provided. Withdrawal because of lack of efficacy and withdrawal because of adverse events were not separately analysed as it became apparent during data extraction that lack of efficacy of treatment in PAH naturally leads to adverse events associated with disease worsening. It was therefore not possible to attribute withdrawal to either lack of efficacy or adverse events in many cases and withdrawal for any reason would be a more appropriate outcome covering both. None of the included RCTs reported the frequency and duration of hospitalisation and outpatient/GP visits and pulmonary arterial oxygen saturation.

Handling of data and presentation of results

For dichotomous outcomes, results are presented as RRs. For continuous outcomes, results are presented as weighted mean differences (WMD).

Relative risks for 'FC improved or maintained' were initially calculated to provide more stable estimates as the proportion of patients with FC either improved or deteriorated was expected to be small. However, it was felt that 'FC improved' alone was also clinically important and thus RRs for this outcome were also calculated and presented. In addition, when data specifically for FCIII patients were available from the RCTs, odd ratios were compiled for 'FC improved' and 'FC worsened' at 12 weeks to inform the independent economic assessment (see Chapter 4).

For outcomes with continuous data the values of mean change from baseline (i.e. mean value measured at the end of the trial minus the mean value measured at baseline) were used in meta-analysis. When possible the standard deviation (SD) was taken directly from the reported results or derived from the standard error of the mean (SEM) or CIs. For the 6MWD data of Barst *et al.*,[11] SDs for mean change from baseline were imputed using the SDs of baseline values and SDs of post-treatment values assuming an intercorrelation coefficient of 0.5.[32] For the 6MWD data of Badesch *et al.*,[33] for which only the SD for the post-treatment value was available, it was used as the SD for the mean change from baseline.

Approaches for meta-analysis

Meta-analyses were carried out using REVIEW MANAGER version 4.2. Separate analyses were performed for each of the interventions being considered for the outcomes specified above. The primary analysis included data for licensed doses only (where appropriate) for patients with PAH (all subcategories in category 1 of the Venice 2003 clinical classification excluding the subcategory 1.5, persistent pulmonary hypertension of the newborn) in NYHA/WHO FCIII (and FCIV for epoprostenol) using the latest follow-up data available from the randomised controlled period of each trial. A random-effects model was used given the heterogeneous populations within PAH. Comparisons were made separately for:

- each of the interventions versus placebo/nothing with ongoing supportive treatments
- each of the interventions versus placebo/nothing with another ongoing intervention and ongoing supportive treatment (trials were available for iloprost versus placebo/nothing with ongoing bosentan and supportive treatment; and sildenafil versus placebo with ongoing epoprostenol and supportive treatment)
- comparison of the interventions against each other (trials were available for sitaxentan versus bosentan and sildenafil versus bosentan)
- comparison between different combinations of interventions (one trial was available for epoprostenol plus bosentan versus epoprostenol).

No indirect comparisons or mixed treatment comparisons were planned or performed.

Given the expected discrepancy between the scope of this technology appraisal (specific types of PAH, FC and dose for each of the drugs within their licensed indication) and the heterogeneous trial evidence actually available for each drug, several sensitivity analyses taking into account the population mix in terms of FC and pulmonary hypertension categories, intervention doses, trial design and data status, as well as subgroup analyses for IPAH and PAH associated with connective tissue disease (CTD-APAH), were planned. The primary analysis (analysis A) and other planned analyses (analyses B–H) are listed in *Table 6*. Whether each of the listed analyses was actually carried out depended on the availability of data, and this is stated in an analyses checklist within each of the specific comparisons. The aims of these analyses were to ensure that available evidence that was directly applicable to this technology appraisal (or the lack of such evidence) was highlighted, while allowing other potentially relevant evidence to also be considered.

Assessment of heterogeneity

Statistical heterogeneity between studies was assessed with the chi-squared test and I^2. The I^2 is a measure of inconsistency in studies' results in meta-analysis.[34] It describes the percentage of the total variation across studies that is due to heterogeneity rather than to chance (sampling error), and lies between 0% (no observed heterogeneity) and 100% (significant heterogeneity). An I^2 of 25%, 50% and 75% would indicate low, moderate and high heterogeneity respectively. When there was evidence of statistical heterogeneity ($p \leq 0.10$ for chi-squared test for heterogeneity or $I^2 \geq 50\%$), the values of I^2 were shown besides the pooled estimates within the results tables and the heterogeneity was discussed in the text. I^2 was reported for all of the pooled estimates quoted in the texts, irrespective of its value.

TABLE 6 *Planned analyses*

Planned analysis		Population/doses/data to be included
A	Primary analysis	All PAH, FCIII,[a] licensed dose(s)
B	Sensitivity analysis – mixed FC	All PAH, all FC, licensed dose(s)
C	Sensitivity analysis – mixed pulmonary hypertension	All pulmonary hypertension including categories 1–5 of the Venice 2003 classification, all FC, licensed dose(s)
D	Sensitivity analysis – including above licensed dose(s)	All PAH, all FC, licensed dose(s) and above licensed dose(s)
E	Sensitivity analysis – excluding data designated as confidential	All PAH, all FC, licensed dose(s), excluding commercial-in-confidence and academic-in-confidence data
F	Sensitivity analysis – excluding open-label trial(s)	All PAH, all FC, licensed dose(s), excluding open-label trials
G	Subgroup analysis – IPAH	IPAH, FCIII (or all FC), licensed dose(s)
H	Subgroup analysis – CTD-APAH	CTD-APAH, FCIII (or all FC), licensed dose(s)

CTD-APAH, PAH associated with connective tissue disease; FC, functional class; IPAH, idiopathic; PAH, pulmonary arterial hypertension.
a Plus FCIV for epoprostenol.

Assessment of publication bias

All manufacturers were requested to provide a list of all company-sponsored RCTs that were relevant to this appraisal. Requests were also made for reports of unpublished trials and data that are potentially available but not reported in published papers. Given that the lists of RCTs were provided by all of the companies and the number of trials for each of the technologies was small, publication bias was not formally assessed.

Ongoing studies

Ongoing studies (RCTs/open-label studies) were identified as already described in the search strategy. These were not included in the systematic review, but were tabulated separately for information.

Long-term follow-up studies

A systematic review of follow-up studies of the long-term use of the technologies was not undertaken. However, long-term studies were identified from scrutiny of the manufacturer submissions in order to inform the economic assessment. Information in these studies was tabulated.

Results

Overall quantity of research available

The searches resulted in the identification of 1354 articles after duplicates had been removed. Screening of the titles and abstracts of these articles indicated that 1307 were not directly relevant to the clinical effectiveness section of this report. Inclusion criteria were applied to the remaining 47 articles. Of these 16 were excluded for not meeting one or more of the criteria. Details of these studies can be found in Appendix 3.

Of the 31 articles meeting the criteria, 23 were papers documenting 16 RCTs, and eight were reports of systematic reviews. The systematic reviews were only utilised to identify further RCTs. A list of these systematic reviews can be found in Appendix 4. One additional published RCT[35] was identified from the systematic reviews. A further three unpublished RCTs[36–38] were identified through screening of the five manufacturer submissions for this assessment. All of these met the inclusion criteria. This resulted in 20 RCTs being included in the review. *Figure 3* documents the selection process.

There were RCTs on all of the five technologies for this assessment. The distribution of the RCTs across the technologies and the respective comparisons undertaken in them are shown in *Table 7*. Most RCTs compared one technology plus supportive care against placebo and/or supportive care. There were few head-to-head comparisons of the technologies and few RCTs comparing a single technology with combination technologies. There were no RCTs comparing any of the technologies with unlicensed drugs for PAH [e.g. treprostinil, iloprost (intravenous), beraprost, ambrisentan].

The assessment of effectiveness of the technologies is reported in the following six sections, one for each of the technologies and one on head-to-head comparisons. When RCTs assessed a combination

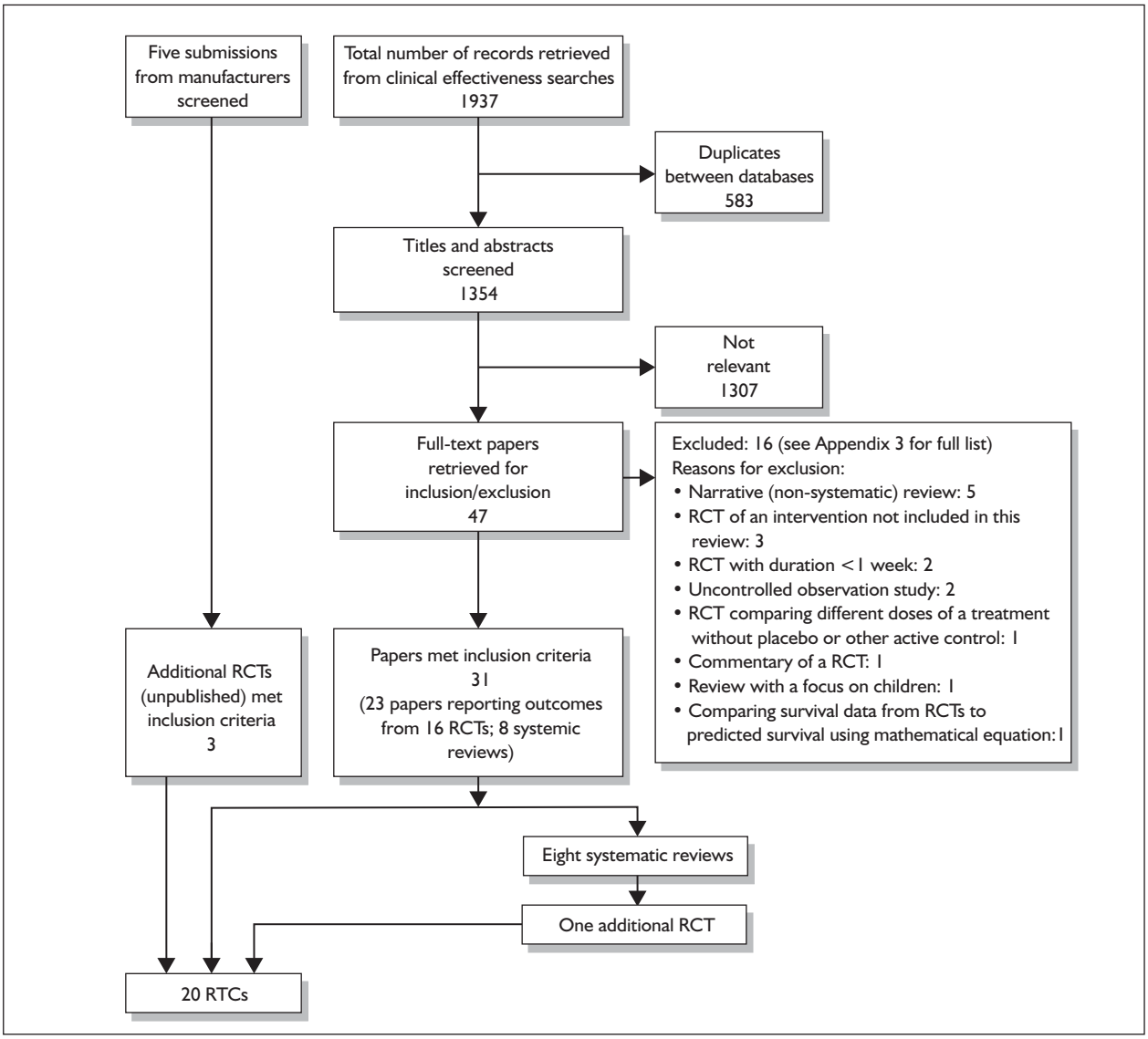

FIGURE 3 *Flow chart of clinical effectiveness study selection.*

of the technologies this is addressed as a subsection of the main technology under assessment.

Epoprostenol

Quantity and quality of included studies

Three RCTs[11,33,39,40] compared epoprostenol (added to supportive treatment) with supportive treatment. [An additional study (BREATHE-2; Bosetan Randomised Trial of Endothelin Antagonist Therapy)[56] that compared the initiation of bosentan–epoprostenol combination with epoprostenol alone will be described in the bosentan section and a further study (PACES-1)[36] that compared sildenafil with placebo in patients who were stable on epoprostenol treatment will be described in the sildenafil section.] In addition to the main publications associated with these trials, further data not included in these publications were available from the Cochrane review by Paramothayan and colleagues.[60] The clinical study report for one of the RCTs[11] was made available to the assessment group by GlaxoSmithKline.

The characteristics of the three trials are summarised in *Table 8*. All were industry-sponsored multicentre studies conducted in the USA. The number of patients randomised ranged from 23[39] to 111[33] and study duration was between 8[39] and 12[11,33] weeks. Rubin *et al.*[39] and Barst *et al.*[11] recruited exclusively patients with PPH, whereas Badesch *et al.*[33] recruited exclusively PAH patients with a scleroderma spectrum of disease. All three trials included patients with mixed FC, with 65–78% of patients in FCIII and 17–26% of patients in FCIV at baseline. The mean/median 6MWD at

TABLE 7 *Distribution of comparisons undertaken in the RCTs*

	Epoprostenol	**Iloprost**	**Bosentan**	**Sitaxentan**	**Sildenafil**	**Bosentan + epoprostenol**	**Iloprost + (ongoing) bosentan**	**Sildenafil + (ongoing) epoprostenol**
Placebo/ existing treatment	*n* = 3; Rubin 1990,[39] Barst 1996,[11,40] Badesch 2000[33]	*n* = 2; Olschewski 2002 (AIR),[41,42] unpublished (AIR-2)[36]	*n* = 4; Channick 2001,[15,43,44] Rubin 2002 (BREATHE-1),[44–46] Galiè 2006 (BREATHE-5),[47] Barst 2006 (STRIDE-2)[48]	*n* = 3; Barst 2004 (STRIDE-1),[49–51] Barst 2006 (STRIDE-2),[48] Barst 2007 (STRIDE-4)[37,52]	*n* = 4; Galiè 2005 (SUPER-1),[53] Bharani 2003,[35] Sastry 2004,[54] Singh 2006[55]	*n* = 0	*n* = 0	*n* = 0
Epoprostenol[a]	n/a	*n* = 0	*n* = 0	*n* = 0	*n* = 0	*n* = 1; Humbert 2004 (BREATHE-2)[56]	*n* = 0	*n* = 1; unpublished (PACES-1)[38]
Iloprost	n/a	n/a	*n* = 0	*n* = 0	*n* = 0	*n* = 0	*n* = 0	*n* = 0
Bosentan[b]	n/a	n/a	n/a	*n* = 1; Barst 2006 (STRIDE-2)[48]	*n* = 1; Wilkins 2005 (SERAPH)[57]	*n* = 0	*n* = 2; Hoeper 2006 (COMBI),[58] McLaughlin 2006 (STEP)[59]	*n* = 0
Sitaxentan	n/a	n/a	n/a	n/a	*n* = 0	*n* = 0	*n* = 0	*n* = 0
Sildenafil	n/a	n/a	n/a	n/a	n/a	*n* = 0	*n* = 0	*n* = 0

n/a, not applicable.
a Newly initiated for BREATHE-2, ongoing for PACES-1.
b Newly initiated for STRIDE-2 and SERAPH, ongoing for COMBI and STEP.

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TABLE 8 *Characteristics of included epoprostenol trials*

Trial name/key paper; location/ centres	Duration; design; number of patients randomised	Intervention[a]	Comparator[a]	Type of PAH	Functional class	Age (years), mean (SD); % female	Baseline exercise capacity and haemodynamic measures, mean (SD)[b]
Rubin *et al.*, 1990;[39] USA, four centres	8 weeks; open-label, parallel; $n = 23$	Epoprostenol (i.v. infusion) individualised dose ($n = 11$)	None ($n = 12$)	PPH (100%)	II (9%), III (65%), IV (26%)	36 (14); 70%	6MWD ($n = 19$): 227 (NR); cardiac index: NR; mPAP: 61.3 (NR); PVR: NR; RAP: NR; SvO_2: NR
Barst *et al.*, 1996;[11] USA, multicentre	12 weeks; open-label, parallel; $n = 81$	Epoprostenol (i.v. infusion) individualised dose ($n = 41$)	None ($n = 40$)	PPH (100%)	III (74%), IV (26%)	40 (15); 73%	6MWD: 294 (126); cardiac index: 2.1 (0.8); mPAP: 60 (13); PVR: 1280 (560);[c] RAP: 12 (7); SvO_2: 61 (13)
Badesch *et al.*, 2000;[33] USA, 17 centres	12 weeks, open-label, parallel; $n = 111$	Epoprostenol (i.v. infusion) individualised dose ($n = 56$)	None ($n = 55$)	Scleroderma spectrum of disease (100%)	II (5%), III (78%), IV (17%)	55 (12); 86%	6MWD: 272/240;[d] cardiac index: 2.0 (0.7); mPAP: 50 (10); PVR: 1016 (504);[c] RAP: 12 (5); SvO_2: 58.1 (10.4)

6MWD, 6-minute walk distance; mPAP, mean pulmonary arterial pressure; NR, not reported; PAH, pulmonary arterial hypertension; PPH, primary pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SvO_2, mixed venous oxygen saturation.

a With ongoing conventional therapy unless otherwise specified.

b Units are: 6MWD, metres; cardiac index, l/min/m^2; mPAP, mmHg; PVR, dyn s/cm^5; RAP, mmHg; SvO_2, %.

c Converted from mmHg/l/min (Wood units).

d Median value for intervention/comparator arms; mean values were not reported.

baseline was less than 300 metres in all three trials. The primary end point was change in 6MWD for Barst *et al*.[11] and Badesch *et al*.,[33] and was not stated for Rubin *et al*.[39]

Quality assessment of these trials is summarised in *Table 9*. All of the trials were open-label studies as a double-blind, placebo-controlled design was not considered possible because of the known incidence of sepsis caused by central venous catheters and the unique or highly predictable symptoms during long-term epoprostenol treatment.[11] However, assessors for the 6MWT were blinded in Barst *et al*.[11] and Badesch *et al*.[33] With the exception of survival and 6MWD in Barst *et al*.[11] and 6MWD in Badesch *et al*.,[33] ITT analysis was not used. Treatment withdrawal/loss to follow-up was not clearly reported in Rubin *et al*.[39] and Badesch *et al*.[33]

Epoprostenol (added to supportive treatment) versus supportive treatment

Planned meta-analyses for this comparison and those actually carried out are summarised in *Table 10*.

As outcome data stratified by FC were available neither from published papers nor from the clinical study report it was not possible to perform the planned primary analyses [analysis for PAH, by FC (FCIII and FCIV), treated with licensed doses]. Furthermore, some other planned analyses were also not possible or not required. The reasons for these are also given in *Table 10*.

All of the findings presented in this section are on analyses that could be performed and these are associated with patient populations of mixed FC (III and IV). The results of meta-analyses (or of individual trials when only one trial provided the data) are listed in *Table 11*. Results for individual outcomes are summarised in the following subsections.

Survival

A total of 21 deaths (five for epoprostenol, 16 for supportive treatment) were reported in the three trials.[11,33,39] A significant decrease in the risk of death was reported in Barst *et al*.,[11] in which eight deaths occurred in the control group versus none in the epoprostenol group (RR = 0.06, 95% CI 0.00–0.96). The pooled RR favours epoprostenol although it does not reach statistical significance (RR = 0.37, 95% CI 0.09–1.57, $I^2 = 39\%$).

Time to clinical worsening

This outcome was not reported in any of the epoprostenol trials.

Functional class

The proportion of patients who had their FC unchanged/worsened was not reported in Rubin *et al*.[39] or Badesch *et al*.[33]

Results from Barst *et al*.[11] showed a non-significant RR of 1.22 (95% CI 0.96–1.55) for having FC improved or maintained (the planned dichotomous outcome for FC) for the epoprostenol group compared with the control group.

A significantly higher proportion of patients in the epoprostenol group had their FC improved compared with those in the control group in all three trials[11,33,39] (pooled RR = 10.58, 95% CI 3.07–36.50, $I^2 = 25\%$).

Exercise capacity

The mean changes from baseline for the 6MWD for the three trials[11,33,39] are shown in *Figure 4*. Improvements were seen in all three trials and the pooled result for the WMD was an increase of 81 metres (95% CI 45–117, $I^2 = 25\%$) for epoprostenol groups compared with control groups.

Quality of life

This outcome was reported only in Barst *et al*.[11] Patients who died during the trial (0/41 in the epoprostenol group and 8/40 in the control group) were excluded from the analysis. A significant improvement for the epoprostenol group compared with the control group was observed for all four parts of the Chronic Heart Failure Questionnaire (dyspnoea, fatigue, emotional function and mastery) and for two (emotional reaction and sleep), but not four (energy, pain, physical mobility and social isolation) of the six parts of the Nottingham Health Profile.

Haemodynamic measures

The pooled results shown in *Table 11* demonstrate that epoprostenol significantly reduced mPAP, RAP and PVR and increased the cardiac index compared with supportive treatment. The results were consistent across the trials with little heterogeneity between them.

Other effectiveness measures

Both Barst *et al*.[11] and Badesch *et al*.[33] reported a significant improvement in the dyspnoea–fatigue

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TABLE 9 *Quality assessment of included epoprostenol trials*

Study; duration	Truly random allocation (strata for randomisation)	Adequate allocation concealment	Blinding	Use of ITT analysis[a] (n included in analysis/*N* randomised)	% of patients completing the trial	Comments
Rubin *et al.*, 1990;[39] 8 weeks	Yes (FC, pre-existing drug therapy)	Yes	Open-label	Survival analysis: N/A; clinical worsening: N/A; functional class: no (19/23); 6MWD: no (19–21/23); haemodynamics: no (19–21/23); quality of life: N/A	Not reported	Patients who died during the trial ($n = 1$ for epoprostenol; $n = 3$ for control) were excluded from analysis. Additional data were available from Paramothayan 2005[60] (Cochrane review)
Barst *et al.*, 1996;[11] 12 weeks	Yes (FC, study centre, baseline vasodilator use)	Unclear	Open-label (assessor for 6MWT and quality of life blinded)	Survival analysis: yes; clinical worsening: N/A; functional class: no (71/81); 6MWD: yes; haemodynamics; no (44–68/81); quality of life: no (73/81)	Control: 75% (30/40); epoprostenol: 93% (38/41)	
Badesch *et al.*, 2000;[33] 12 weeks	Yes (vasodilator use and exercise capacity at baseline)	Yes	Open-label (assessor for 6MWT blinded)	Survival analysis: unclear; clinical worsening: N/A; functional class; unclear; 6MWD: yes; haemodynamics: unclear; quality of life: N/A	Not reported	

6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; FC, functional class; ITT, intention to treat; N/A, data not available.
a Defined as an analysis that includes all randomised patients (or all randomised patients who received at least one dose of study medication) according to the treatment group to which they were assigned, irrespective of actual treatment received or early withdrawal of treatment. N/A, data not available (outcome not measured in the trial or unclear if it was measured; analysis for the outcome not performed or unclear if it was performed). When analysis for the outcome was performed but the number of patients included was not reported, this was noted as 'unclear'. When ITT analysis was not used the number of patients included in the analysis (or a range of numbers when more than one outcome was analysed/more than one analysis was performed with various numbers of patients used) over the number that should have been used in an ITT analysis is shown.

TABLE 10 *Analysis checklist – epoprostenol added to supportive treatment versus supportive treatment alone*

Planned analyses	Population/doses/data to be included	Analysis carried out	Comments and source of data
A1. Primary analysis	All PAH, FCIII, licensed doses	No	All trials included patients with mixed FC but data stratified by FC were not available
A2. Primary analysis	All PAH, FCIV, licensed doses	No	All trials included patients with mixed FC but data stratified by FC were not available
B. Sensitivity analysis – mixed FC	All PAH, all FC, licensed doses	Yes	Data from all three trials[11,33,39] were included
C. Sensitivity analysis – mixed pulmonary hypertension	All pulmonary hypertension including categories 1–5 of the Venice 2003 classification, all FC, licensed doses	No	None of the epoprostenol trials included pulmonary hypertension other than PAH
D. Sensitivity analysis – including above licensed dose	All PAH, all FC, licensed doses and above licensed doses	No	The dose for epoprostenol was individualised and no maximum dose was specified in its license
E. Sensitivity analysis – excluding data designated as confidential	All PAH, all FC, licensed doses, excluding commercial-in-confidence and academic-in-confidence data	No	The amount of data classified as confidential was small and unlikely to have a significant impact on the results
F. Sensitivity analysis – excluding open-label trials	All PAH, all FC, licensed doses, excluding open-label trials	No	Not applicable – all of the epoprostenol trials were open label
G. Subgroup analysis – IPAH	IPAH (PPH), mixed FC, licensed doses	Yes	Data from Rubin *et al.*[39] and Barst *et al.*[11] were included. This analysis matches most closely with epoprostenol's licensed indication (FCIII and FCIV, PPH), although two patients from Rubin *et al.*[39] were in FCII at baseline
H. Subgroup analysis – CTD-APAH	CTD-APAH, mixed FC, licensed doses	Yes	Data from Badesch *et al.*[33] were included

CTD-APAH, PAH associated with connective tissue disease; FC, functional class; IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension; PPH, primary pulmonary hypertension.

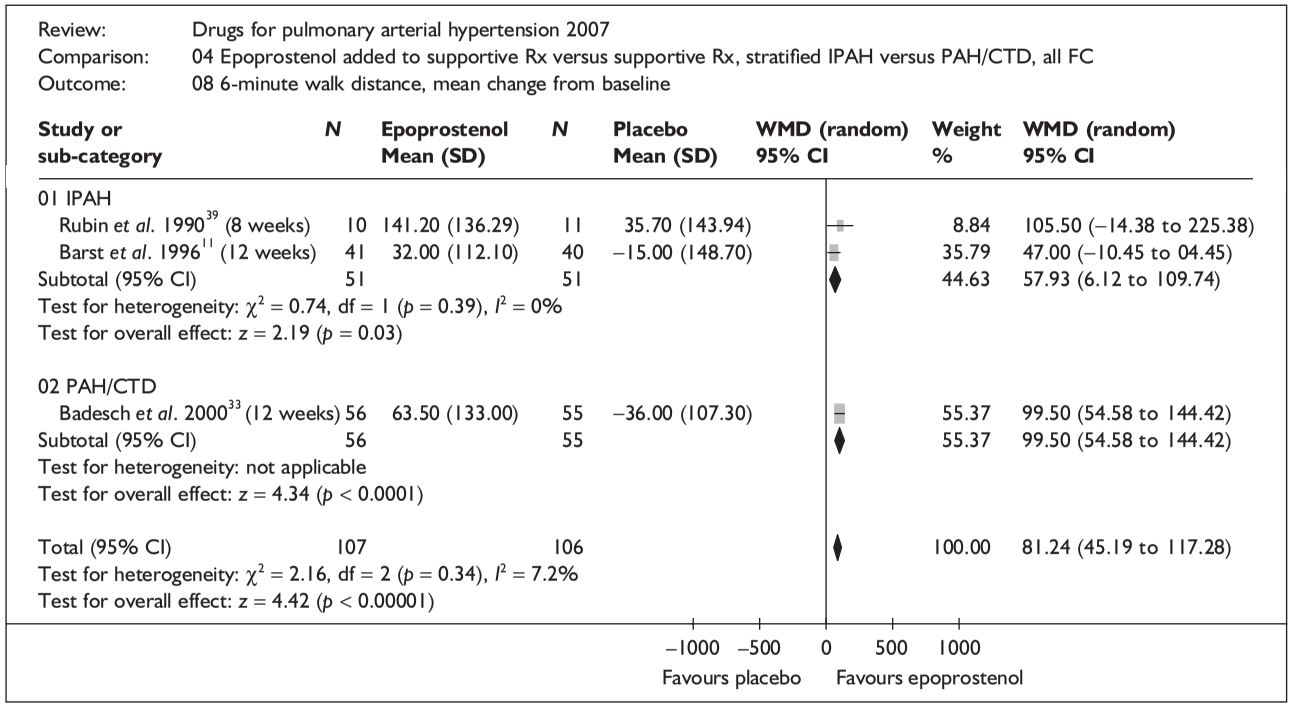

FIGURE 4 *Forest plot: epoprostenol added to supportive treatment versus supportive treatment alone – change in 6-minute walk distance. Note: The standard deviations for Barst* et al.[11] *and Badesch* et al.[33] *were not reported and were imputed using the methods described in the section on handling of data and presentation of results. CI, confidence interval; CTD, connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; SD, standard deviation; WMD, weighted mean difference.*

TABLE 11 *Meta-analysis: epoprostenol added to supportive treatment versus supportive treatment alone*

	Analysis (see Table 10)			
	A1/A2: Primary analyses	**B: Sensitivity analysis – mixed FC**	**G: Subgroup analysis – IPAH**	**H: Subgroup analysis – CTD-APAH**
PAH population	All PAH subcategories	All PAH subcategories	IPAH only	CTD-APAH only
Functional class (FC)	A1: FCIII; A2: FCIV	All FC (II–IV)	All FC (II–IV)	All FC (II–IV)
Doses	Licensed doses	Licensed doses	Licensed doses	Licensed doses
Total no. eligible for analysis	162[11,33,39]	215[11,33,39]	104[11,39]	111[33]
No. included in analysis	0 (none of the trials reported data stratified by FC)	85–215 (data from all three trials were included)	65–104 (data from Rubin *et al.*[39] and Barst *et al.*[11] were included)	≤ 111 (data from Badesch *et al.*[33] were included)

Outcomes	**Statistics**	***n***	**Effect size (95% CI)**	***n***	**Effect size (95% CI)**	***n***	**Effect size (95% CI)**	***n***	**Effect size (95% CI)**
Efficacy									
Death	RR	0	Data not available	215[11,33,39]	0.37 (0.09–1.57)	104[11,39]	0.18 (0.03–1.18)	111[33]	0.79 (0.22–2.77)
Clinical worsening	RR	0	Data not available	0	Data not available	0	Data not available	0	Data not available
FC improved	RR	0	Data not available	215[11,33,39]	**10.58 (3.07–36.50)**[a]	104[11,39]	**7.45 (2.55–21.77)**[a]	111[33]	**42.25 (2.62–680.61)**[a]
FC maintained or improved	RR	0	Data not available	81[11]	1.22 (0.96–1.55)[b]	81[11]	1.22 (0.96–1.55)[a]	0	Data not available
Withdrawal for any reason	RR	0	Data not available	81[11]	**0.29 (0.09–0.99)**[a]	81[11]	**0.29 (0.09–0.99)**[a]	0	Data not available
6-minute walk distance (metres)[c]	WMD	0	Data not available	213[11,33,39]	**81 (45–117)**[a]	102[11,39]	**58 (6–110)**[a]	111[33]	**100 (55–144)**[a]

Outcomes	Statistics	*n*	Effect size (95% CI)	*n*	Effect size (95% CI)	*n*	Effect size (95% CI)	*n*	Effect size (95% CI)
Haemodynamics									
Mean pulmonary arterial pressure (mPAP) (mmHg)[c]	WMD	0	Data not available	200[11,33,39]	**–6.3 (–8.7 to –3.9)[a]**	89[11,39]	**–6.8 (–10.6 to –3.0)[a]**	111[33d]	**–6.0 (–9.0 to –2.9)[a]**
Right atrial pressure (RAP) (mmHg)[c]	WMD	0	Data not available	176[11,33]	**–2.4 (–4.1 to –0.7)[a]**	65[11]	–2.3 (–5.1 to 0.5)	111[33d]	**–2.5 (–4.6 to –0.4)[a]**
Pulmonary vascular resistance (PVR) (dyn s/cm^5)[d]	WMD	0	Data not available	176[11,33,39]	**–427 (–548 to –306)[a]**	65[11,39]	**–401 (–613 to –189)[a]**	111[33d]	**–440 (–588 to –292)[a]**
Cardiac index (l/min/m^2)[e]	WMD	0	Data not available	179[11,33]	**0.6 (0.4–0.8)[a]**	68[11]	0.6 (0.2–0.9)	111[33d]	**0.6 (0.4–0.8)[a]**
Safety									
Serious adverse events	RR	0	Data not available	0	Data not available	0	Data not available	0	Data not available

CI, confidence interval; CTD-APAH, PAH associated with connective tissue disease; FC, functional class; IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension; RR, relative risk; WMD, weighted mean difference.

a Statistically significant result.

b Intention to treat analysis in which patients who died or who had lung transplantation in Barst *et al.*[11] ($n = 1$ for epoprostenol group and $n = 10$ for control group) were assumed to have their functional class worsened. Original data reported in Barst *et al.*[11] excluded these patients.

c Mean change from baseline; positive value favours epoprostenol.

d Mean change from baseline; negative value favours epoprostenol.

e The number of patients contributing to the data was not stated in Badesch *et al.*[33] The number of patients randomised was used in the analysis.

rating for the epoprostenol group compared with the control group. A significant improvement in the Borg dyspnoea index in favour of epoprostenol was also observed in Badesch *et al*.[33]

Serious adverse events and other adverse events

SAEs were not described separately from other adverse events in the three trials and the total number of SAEs was not reported. However, serious complications due to the delivery system including catheter-related sepsis, pneumothorax and paradoxical embolism were observed in the trials.[11,33,39] Common adverse events occurred more frequently in patients receiving epoprostenol including jaw pain, diarrhoea, nausea, flushing and headache.

Subgroup analysis – PAH subcategories

As the existing epoprostenol RCTs included either patients with PPH only or patients with scleroderma only, no within-trial comparisons between PAH subcategories can be made. Little heterogeneity was observed between the pooled results of the two trials in patients with PPH[11,39] and the results of the trial in patients with scleroderma.[33]

Summary and discussion

- Three open-label RCTs[11,33,39] comparing epoprostenol (added to supportive treatment) with supportive treatment alone were identified. The duration of the studies ranged from 8 to 12 weeks.
- Except for Barst *et al*.,[11] in which allocation concealment was not clear, methods of randomisation and allocation concealment were adequate in the trials. The reporting of treatment withdrawal and SAEs was poor. ITT analysis was not used for many of the outcomes reported. The potential bias, however, is likely to be in favour of control groups as most patients who were excluded from analyses were those who died or withdrew from the trials because of deterioration, and this occurred more frequently in the control groups.
- The trials included predominantly FCIII and FCIV patients, who were likely to be the sickest of any PAH trial participants judging from a mean 6MWD of less than 300 metres at baseline and other haemodynamic measures.
- Data stratified by FC were not available from published literature and were not provided by the manufacturer. Results were summarised based on patient populations with mixed FC.
- Compared with supportive treatment alone, epoprostenol significantly improved exercise capacity (6MWD) and haemodynamic measures (mPAP, RAP, PVR, cardiac index), and increased the proportion of patients with improved FC during 8–12 weeks of treatment in patients with PPH (licensed indication) and scleroderma spectrum of disease (unlicensed indication). Significant improvements in survival, PAH-associated symptoms (dyspnoea) and certain domains of quality of life measures were also observed in individual trials.
- No significant differences were observed in any of the outcomes examined in this review between the trials in patients with PPH[11,39] and the trial in patients with scleroderma.[33]

Iloprost

Quantity and quality of included studies

Two RCTs [AIR (Aerosolized Iloprost Randomised study),[41] AIR-2[36]] compared iloprost (added to supportive treatment) with supportive treatment. The AIR-2 study[36] was identified through industry submission and Schering Health Care provided the assessment group with an unpublished manuscript. The study had not been published at the completion of this report and data from the manuscript are considered academic-in-confidence. Two further RCTs [COMBI (Combination Therapy of Bosetan and Aerosolized Iloprost in Idiopathic Pulmonary Arterial Hypertension),[58] STEP (*S*afety and Pilot Efficacy *T*rial in Combination with Bosetan for *E*valuation in *P*AH)[59]] compared iloprost (added to ongoing bosentan therapy and supportive treatment) with ongoing bosentan therapy and supportive treatment.

The characteristics of these four trials are summarised in *Table 12*. All were industry-sponsored multicentre studies (COMBI[58] was investigator-initiated, but was supported by the manufacturer[58]). The AIR study[41] was a multinational study conducted in Europe and was the pivotal trial for iloprost. The AIR-2[36] and COMBI[58] trials were conducted in Germany and the STEP study[59] was conducted in the USA. The number of patients randomised ranged from 40[58] to 203[41] and the duration of study was 12 weeks for all four trials.

Both the AIR and the AIR-2 studies were carried out in mixed populations including IPAH and other PAH within category 1 of the Venice classification, as well as other pulmonary

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TABLE 12 *Characteristics of included iloprost trials*

Trial name/key paper (protocol number); location/ centres	Duration; design; number of patients randomised	Intervention[a]	Comparator[a]	Type of PAH	Functional class	Age (years), mean (SD, range); % female	Baseline exercise capacity and haemodynamic measures, mean (SD)[b]
AIR/Olschewski *et al.*, 2002[41] (A02997); Europe, 37 centres	12 weeks; double-blind, parallel; $n = 203$	Iloprost (inhalation) 2.5 or 5.0 μg six or nine times daily[c] ($n = 101$)	Placebo (inhalation) ($n = 102$)	PPH (50%),[d] collagen vascular disease (17%), appetite suppressant (4%), non-PAH[e] (28%)	III (59%), IV (41%)	52 (13, 20–70); 68%	6MWD: 323 (95); cardiac index: NR; mPAP: 53 (13); PVR ($n = 187$): 1035 (446); RAP: NR; SvO_2 ($n = 169$): 60.5 (7.9)
AIR-2/Olschewski *et al.*,[36] (A02237); Germany, multicentre	12 weeks, open-label, parallel; $n = 63$	Iloprost (inhalation) 24 μg daily divided into six or nine doses[f] ($n = 30$)	None ($n = 33$)	PPH (63%), [Academic-in-confidence information has been removed][g]	II (33%), III (48%), IV (19%)	46 (12, 24–78); 70%	6MWD: [Academic-in-confidence information has been removed]; cardiac index: NR; mPAP: 56 (14); PVR: [Academic-in-confidence information has been removed]; RAP: NR; SvO_2: [Academic-in-confidence information has been removed]
COMBI/Hoeper *et al.*, 2006;[58] Germany, multicentre	12 weeks, open-label, parallel; $n = 40$	Iloprost (inhalation) 5 μg six times daily + ongoing bosentan (oral) 125 mg b.d. ($n = 19$)	Ongoing bosentan (oral) 125 mg b.d. ($n = 21$)	IPAH (100%)	III (100%)	52 (NR); 78%	6MWD: 306 (77); cardiac index: 2.1 (0.6); mPAP: 57 (16); PVR: 1056 (536);[h] RAP: 9 (5); SvO_2: 62 (9)
STEP/McLaughlin *et al.*, 2006;[59] USA, multicentre	12 weeks, double-blind, parallel; $n = 67$	Iloprost (inhalation) 5 μg six to nine times daily + ongoing bosentan (oral) 125 mg b.d. ($n = 34$)	Placebo + ongoing bosentan (oral) 125 mg b.d. ($n = 33$)	IPAH (55%), associated PAH including scleroderma, other connective tissue diseases, repaired congenital heart disease, HIV infection and anorexigen use (45%)	II (1.5%), III (94%), IV (4.5%)	50 (14, 10–77); 79%	6MWD: 335 (67); cardiac index: NR; mPAP ($n = 57$): 52 (12); PVR: 799 (381); RAP: NR; SvO_2: 63.8 (7.7)

6MWD, 6-minute walk distance; b.d., twice daily; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; NR, not reported; PAH, pulmonary arterial hypertension; PPH, primary pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SD, standard deviation; SvO_2, mixed venous oxygen saturation.

a With ongoing supportive treatment unless otherwise specified.

b Units are: 6MWD, metres; cardiac index, l/min/m2; mPAP, mmHg; PVR, dyn s/cm^5; RAP, mmHg; SvO_2, %.

c Individualised total daily dose of 15–45 μg depending on how well the patient tolerated the treatment.

d 53% according to manufacturer submission and Ghofrani.[42]

e Chronic thromboembolic pulmonary hypertension.

f [Academic-in-confidence information has been removed].

g [Academic-in-confidence information has been removed].

h Converted from mmHg/l/min (Wood units).

hypertension (mainly chronic thrombolic, Venice category 4). The COMBI study recruited exclusively IPAH patients and the STEP study included mixed PAH populations (all within Venice category 1). The trials were also different in the mix of patients in terms of baseline FC: the AIR study had mixed FCIII and FCIV patients, whereas the AIR-2 study also included patients in FCII. The COMBI study recruited exclusively patients in FCIII. The vast majority of patients in the STEP trial were also in FCIII at baseline. Mean 6MWD at baseline was lowest in the COMBI study (306 metres)[58] and was highest [Academic-in-confidence information has been removed].

With regard to end points, the AIR study[41] used a composite end point of 'at least a 10% increase in 6MWD *and* improvement in FC without deterioration' as the primary outcome. Change in 6MWD was the primary outcome for the COMBI study,[58] whereas the AIR-2[36] and the STEP[59] trials did not clearly state their primary end points.

Quality assessment of these trials is summarised in *Table 13*. The AIR and the STEP studies were double-blind, placebo-controlled trials, whereas the AIR-2 and the COMBI trials were open-label studies. Methods of randomisation and allocation concealment were adequate except in the COMBI study in which the method of randomisation was unclear. Neither of the open-label studies[36,58] mentioned blinding of outcome assessors. Only the COMBI study used ITT analysis across all of the outcomes examined. The AIR study used ITT analysis for its primary composite end point, clinical worsening and 6MWD, but not for changes in FC and other measures. ITT analysis was not used in the AIR-2 and the STEP trials. As more patients from the iloprost arms than from the control arms were excluded from the analysis in these two studies there was a potential bias in favour of iloprost (if excluded patients had poorer outcomes) in these studies.

The results of the AIR and AIR-2 studies, and of the COMBI and STEP studies are described separately in the following sections given the different nature of the comparisons between the trials. Because of the relatively short half-life of iloprost (hence short acute effect) and the intermittent nature of drug inhalation (as opposed to continuous infusion in the case of epoprostenol), studies of iloprost frequently measure treatment effect both before and after iloprost inhalation, which corresponds to the expected trough and peak drug concentration/effect. The post-inhalation measures (which represent acute effects) are used in the analysis in this review, although relevant findings from preinhalation measures (which represent chronic effects) are also discussed.

Iloprost added to supportive treatment versus supportive treatment alone

This comparison was investigated in the AIR and AIR-2 studies. Planned meta-analyses for the comparison and those actually carried out are summarised in *Table 14*. Because both trials included non-PAH patients, and outcome data excluding these patients and stratified by FC were not available, it was not possible to perform the planned primary analysis (all PAH, FCIII). However, various sensitivity analyses and limited subgroup analysis were carried out to summarise the available evidence, which may help inform the technology appraisal. The results of meta-analyses (or of individual trials when only one trial provided the data) are listed in *Table 15*. Results for individual outcomes are summarised in the following subsections. As there was a paucity of results that were directly applicable to iloprost's licensed indication (PPH, FCIII), findings presented here were mainly based on the overall results of the AIR and AIR-2 studies, which included patients with mixed pulmonary hypertension and FC.

Survival

A total of nine deaths (three for iloprost and six for supportive treatment) were reported in the AIR[41] and AIR-2[36] studies. The numbers are too small to draw any firm conclusions.

Time to clinical worsening

No time-to-event analysis of this outcome was reported.

Deterioration was defined as two or more of the following in the AIR study:[41] refractory systolic arterial hypotension (blood pressure < 85 mmHg); worsening right ventricular failure (e.g. as indicated by the development of refractory oedema or ascites); rapidly progressing cardiogenic, hepatic or renal failure; a decrease of at least 30% in the 6MWD; and a decline in measures of haemodynamic function, such as central venous pressure and mixed venous oxygen saturation. Fewer patients in the iloprost arm (5/101) died or deteriorated compared with the control arm (12/102), but this did not reach statistical significance (RR = 0.42, 95% CI 0.15–1.15). This outcome was not reported in the AIR-2 study.[36]

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TABLE 13 *Quality assessment of included iloprost trials*

Study; duration	Truly random allocation (strata for randomisation)	Adequate allocation concealment	Blinding	Use of ITT analysis[a] (n included in analysis/N randomised)	% of patients completing the trial	Comments
AIR/Olschewski *et al.*, 2002;[41] 12 weeks	Yes (FCIII or FCIV; PPH or non-PPH)	Yes	Double-blind	Survival analysis: N/A; clinical worsening: yes; functional class: no (184/203); 6MWD: yes; haemodynamic: unclear; quality of life: no (177/203)	Placebo: 86% (88/102); iloprost: 96% (97/101)	
AIR-2/Olschewski *et al.*;[36] 12 weeks	Yes (PPH or non-PPH; use of calcium channel blocker; baseline 6MWD)	Yes	Open-label	Survival analysis: N/A; clinical worsening: N/A; functional class: no (54/63); 6MWD: no (49/63); haemodynamic: no (43–50/63); quality of life: no (49/63)	Control: 79% (26/33); iloprost: 73% (22/30)	
COMBI/Hoeper *et al.*, 2006;[58] 12 weeks	Unclear	Yes	Open-label	Survival analysis: no death; clinical worsening: yes; functional class: yes; 6MWD: yes; haemodynamic: N/A; quality of life: yes	Control: 100% (21/21); iloprost: 100% (19/19)	
STEP/McLaughlin *et al.*, 2006;[59] 12 weeks	Yes	Yes	Double-blind	Survival analysis: no death; clinical worsening: no (65/67); functional class: no (64/67); 6MWD: no (65/67); haemodynamic: no (57/67); quality of life: N/A	Placebo: 85% (28/33); iloprost: 88% (30/34)	Two patients in the iloprost group had no post-baseline data (reason not stated) and were excluded from efficacy analysis

6MWD, 6-minute walk distance; FC, functional class; ITT, intention to treat; N/A, data not available; PPH, primary pulmonary hypertension.

a Defined as an analysis that includes all randomised patients (or all randomised patients who received at least one dose of study medication) according to the treatment group to which they were assigned, irrespective of actual treatment received or early withdrawal of treatment. N/A, data not available (outcome not measured in the trial or unclear if it was measured; analysis for the outcome not performed or unclear if it was performed). When analysis for the outcome was performed but the number of patients included was not reported, this was noted as 'unclear'. When ITT analysis was not used the number of patients included in the analysis (or a range of numbers when more than one outcome was analysed/more than one analysis was performed with various numbers of patients used) over the number that should have been used in an ITT analysis is shown.

TABLE 14 *Analysis checklist – iloprost added to supportive treatment versus supportive treatment alone*

Planned analyses	Population/doses/data to be included	Analysis carried out	Comments and source of data
A. Primary analysis	All PAH, FC III, licensed doses	No	Both the AIR[41] and AIR-2[36] studies included non-PAH patients (categories 2–5 of the Venice 2003 classification). Data separating out these patients and stratified by FC were not available
B. Sensitivity analysis – mixed FC	All PAH, all FC, licensed doses (only IPAH actually available/included)	Yes	Both the AIR[41] and AIR-2[36] studies included non-PAH patients (categories 2–5 of the Venice 2003 classification). Separate data including only PAH patients (all those in category 1) were not available; however, limited data specifically for IPAH patients were available form the AIR study[41]
C. Sensitivity analysis – mixed pulmonary hypertension	All pulmonary hypertension including categories 1–5 of the Venice 2003 classification, all FC, licensed doses	Yes	This analysis allows the inclusion of all participants from both the AIR[41] and AIR-2[36] studies
D. Sensitivity analysis – including above licensed doses	All PAH, all FC, licensed doses and above licensed doses	No	The doses for iloprost were individualised and doses used in the trials were in line with its license
E. Sensitivity analysis – excluding data designated as confidential	All pulmonary hypertension, all FC, licensed dose(s), excluding commercial-in-confidence and academic-in-confidence data	Yes	Data designated as academic-in-confidence from the AIR-2 study[36] were excluded. This analysis was, however, not separately described as the results were identical to those in analysis F (excluding open-label trial)
F. Sensitivity analysis – excluding open-label trial(s)	All pulmonary hypertension including categories 1–5 of the Venice 2003 classification, all FC, licensed doses, excluding open-label trial(s)	Yes	This analysis included data only from the AIR study[41] and excluded data from the AIR-2 study,[36] which was an open-label trial. This analysis also serves as a sensitivity analysis of excluding confidential information as most data from the AIR-2 study were academic-in-confidence
G. Subgroup analysis – IPAH	IPAH (PPH), FCIII, licensed doses	Yes	This analysis matches iloprost's licensed indication. Data were available only for the outcome of change in FC from the AIR[41] and AIR-2[36] studies
H. Subgroup analysis – CTD-APAH	CTD-APAH, FCIII, licensed dose(s)	No	No data available

CTD-APAH, PAH associated with connective tissue disease; FC, functional class; PAH, pulmonary arterial hypertension; IPAH, idiopathic PAH.

Functional class

Both the AIR[41] and AIR-2[36] trials failed to report this outcome according to the ITT principle. In the AIR trial[41] patients who did not complete the study were excluded ($n = 14$ for placebo and $n = 5$ for iloprost). In the AIR-2 trial[36] [Academic-in-confidence information has been removed]. In both studies the proportion of patients (non-ITT population) who maintained or improved FC was not significantly different between the iloprost and control arms, although there was a trend approaching statistical significance in favour of iloprost in the AIR study[41] (RR = 1.07, 95% CI 0.97–1.18), which was also observed in the subgroup of patients with PPH in FCIII (RR = 1.22, 95% CI 0.98–1.51). The proportion of patients who had their FC improved was significantly higher for iloprost-treated patients according to the pooled estimate of the two trials[36,41] (RR = 1.98, 95% CI 1.13–3.48, $I^2 = 0$).

Exercise capacity

The mean changes from baseline for the 6MWD for the two trials[36,41] are shown in *Figure 5*. The post-inhalation measurement from AIR-2 was not available, hence results from the two trials were not pooled. In addition, the analysis in the AIR-2 study [Academic-in-confidence information has been removed], hence the data shown for this study needs to be interpreted with great caution. A significant improvement in 6MWD of 36 metres (95% CI 12–60) was seen for the iloprost group compared with the placebo group in the post-inhalation measurement of the AIR study (mixed

FIGURE 5 *Forest plot: iloprost added to supportive treatment versus supportive treatment – change in 6-minute walk distance. Note that the data shown were measured post inhalation for the AIR study (top) and preinhalation for the AIR-2 study (bottom). [Academic-in-confidence information has been removed].*

pulmonary hypertension and FC).[41] On the contrary, [Academic-in-confidence information has been removed].[36] No data specifically for PPH, FCIII were available.

Quality of life

Both trials[36,41] reported improvement in the EuroQol visual analogue scale (VAS; 0–100) for the iloprost group compared with the control group (WMD = [Academic-in-confidence information has been removed], $I^2 = 0\%$, non-ITT). An improvement of 0.09 in the EuroQol health state score in the iloprost group compared with no change in the placebo group was also reported in the AIR study[41] but the difference was not statistically significant ($p = 0.11$ by analysis of covariance). None of the other measures (12-item Medical Outcomes Study Short-Form General Health Survey) of the quality of life were significantly different between treatment groups in this study. No data specifically for PPH, FCIII were available.

Haemodynamic measures

The results of the post-inhalation measures from the AIR study,[41] shown in *Table 15*, demonstrated that iloprost significantly reduced mPAP, RAP and PVR compared with supportive treatment although it is unclear if ITT analysis was used. Preinhalation values measured before the first morning dose of iloprost were largely unchanged from baseline in the iloprost group and were either unchanged or worsened in the placebo group. For mPAP and RAP the differences in preinhalation values between groups were not significantly different, but for PVR the difference was significantly in favour of iloprost (–105 dyn s/cm^5, 95% CI –191 to –19).

[Academic-in-confidence information has been removed].

No data specifically for PPH, FCIII were available.

Other effectiveness measures

The AIR study[41] reported a significant improvement in the Mahler dyspnoea index transition score for the iloprost group compared with the placebo group.

Serious adverse events and other adverse events

There was no significant difference in the risk of SAEs between the iloprost and control groups in the two trials (pooled RR = 1.16, 95% CI 0.77–1.75, $I^2 = 0\%$). Significantly more syncope classified as a SAE was reported in the iloprost group than in the placebo group (5 versus 0). Common adverse events that occurred more frequently in the iloprost group included flushing, jaw pain, increased cough and headache.[41]

Subgroup analysis – PAH subcategories

No randomised comparison between iloprost and supportive treatment in PAH subcategories other than those in the PPH population mentioned above was identified.

Summary and discussion

- Two RCTs (AIR,[41] which was double-blind, and AIR-2,[36] which was open-label) comparing iloprost (added to supportive treatment) with supportive treatment alone were identified. The duration of study was 12 weeks for both trials.
- The trials appeared to be well conducted, although whether [Academic-in-confidence information has been removed]. ITT was not used for the change in FC measure in the AIR study, and [Academic-in-confidence information has been removed].[36] The potential bias was likely to be in favour of the control group in the AIR study [Academic-in-confidence information has been removed]. Despite this the AIR study demonstrated favourable outcomes for iloprost treatment [Academic-in-confidence information has been removed]. The results from the AIR-2 study needed to be interpreted with great caution, particularly because of the potential bias in the exclusion of patients from analysis and the weakness of open-label study.
- The trials included populations of mixed pulmonary hypertension, including non-PAH (chronic thromboembolic pulmonary hypertension), and mixed FC. Patients had a mean 6MWD of 323 metres and [Academic-in-confidence information has been removed] at baseline in the AIR[41] and AIR-2[36] studies respectively. Only 34% of the patients in the AIR study and 30% in the AIR-2 study had PPH in FCIII at baseline (licensed indication for iloprost).
- Few data for patients with PAH only (category 1 of the Venice classification) stratified by FC were available from published literature and manufacturer submissions.

TABLE 15 *Meta-analysis results: iloprost added to supportive treatment versus supportive treatment alone*

		Analysis (see analysis checklist)							
		B. Sensitivity analysis – mixed FC		**C. Sensitivity analysis – mixed pulmonary hypertension**		**F. Sensitivity analysis – excluding open-label study**		**G. Subgroup analysis**	
PAH population		All PAH subcategories (only IPAH actually included)		All pulmonary hypertension (Venice categories 1–5)		All pulmonary hypertension (Venice categories 1–5)		IPAH only	
Functional class (FC)		All FC (II–IV)		All FC (II–IV)		All FC (II–IV)		FCIII	
Doses		Licensed doses		Licensed doses		Licensed doses		Licensed doses	
Total no. eligible for analysis		[Academic-in-confidence information has been removed][36,41]		266[36,41]		203[41]		89[36,41]	
No. included in analysis		101–108 (only data for IPAH from the AIR study[41] were available and were included)		187–266 (data from both the AIR[41] and AIR-2[36] studies were included)		187–203 (only data from the AIR[41] were included)		70 (subgroup data were available only from the AIR study[41] for changes in FC)	
Outcomes	**Statistics**	***n***	**Effect size (95% CI)**	***n***	**Effect size (95% CI)**	***n***	**Effect size (95% CI)**	***n***	**Effect size (95% CI)**
Efficacy									
Death	RR	108[41]	0.52 (0.05 to 5.55)	266[36,41]	0.58 (0.14 to 2.46)	203[41]	0.25 (0.03 to 2.22)	0	Data not available
Clinical worsening	RR	0	Data not available	203[41]	0.42 (0.15 to 1.15)	203[41]	0.42 (0.15 to 1.15)	0	Data not available
FC improved	RR	101[41]	**3.19 (1.11 to 9.11)**[a]	252[36,41]	1.98 (1.13 to 3.48)	189[41]	1.82 (0.99 to 3.35)	70[41]	3.71 (0.83 to 16.61)
FC maintained or improved	RR	101[41]	1.12 (0.97 to 1.29)[c]	[Academic-in-confidence information has been removed][36,41]	1.05 (0.96 to 1.15)	189[41]	1.07 (0.97 to 1.18)	70[41]	1.22 (0.98 to 1.51)
Withdrawal for any reason	RR	108[41]	0.30 (0.06 to 1.36)	266[36,41]	0.62 (0.14 to 2.70); I^2 78%	203[41]	**0.29 (0.10 to 0.85)**[a]	0	Data not available
6-minute walk distance (metres)[b]	WMD	0	Data not available	203[41]	**36 (12 to 60)**[a]	203[41]	**36 (12 to 60)**[a]	0	Data not available

Outcomes	Statistics	*n*	Effect size (95% CI)	*n*	Effect size (95% CI)	*n*	Effect size (95% CI)	*n*	Effect size (95% CI)
Haemodynamics									
Mean pulmonary arterial pressure (mPAP) (mmHg)[c]	WMD	0	Data not available	201[41d]	**–4.4 (–6.7 to –2.1)[a]**	201[41d]	**–4.4 (–6.7 to –2.1)[a]**	0	Data not available
Right atrial pressure (RAP)[c] (mmHg)	WMD	0	Data not available	203[41d]	**–2.2 (–3.5 to –0.9)[a]**	203[41d]	**–2.2 (–3.5 to –0.9)[a]**	0	Data not available
Pulmonary vascular resistance (PVR) (dyn s/cm^5)[c]	WMD	0	Data not available	187[41d]	**–335 (–421 to –249)[a]**	187[41d]	**–335 (–421 to –249)[a]**	0	Data not available
Cardiac index[b] (l/min/m^2)	WMD	0	Data not available	0	Data not available	0	Data not available	0	Data not available
Safety									
Serious adverse events	RR	0	Data not available	266[36,41]	1.16 (0.77 to 1.75)	203[41c]	1.13 (0.71 to 1.80)	0	Data not available

CI, confidence interval; IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension; RR, relative risk; WMD, weighted mean difference.

a Statistically significant result.

b Mean change from baseline; positive value favours iloprost.

c Mean change from baseline; negative value favours iloprost

d The number of patients contributing to the data was not stated in the AIR study. The number of patients providing baseline data (or the number of patients randomised if this was also not available) was used in the analysis.

Results were summarised mainly based on patient populations with mixed pulmonary hypertension and FC.

- Given the cautions with respect to the AIR-2 study already highlighted, the following results were mainly based on findings from a single trial, the AIR study.[41] Compared with supportive treatment alone, iloprost significantly improved exercise capacity (6MWD) and haemodynamic outcomes (mPAP, RAP and PVR) when measured post inhalation, and increased the proportion of patients with improved FC during 12 weeks of treatment in a patient population of mixed pulmonary hypertension and FC. Significant improvements in a PAH-associated symptom (dyspnoea) and in the EuroQol VAS were also observed. The paucity of data prevents any inference specific to PPH, FCIII being made.
- Outcomes measured immediately after inhalation demonstrate acute effects of inhaled iloprost. Whether these represent overall treatment effects is debatable, as outcomes measured preinhalation showed much smaller effects (within the duration of the trials).
- No randomised comparison between iloprost and supportive treatment in PAH subcategories other than the PPH population was identified.

Iloprost added to ongoing bosentan and supportive treatment versus ongoing bosentan and supportive treatment

This comparison was investigated in the COMBI[58] and STEP[59] studies. Planned meta-analyses for this comparison and those actually carried out are summarised in *Table 16*. Because all patients in the COMBI study and the vast majority of patients in the STEP study were in FCIII at baseline, both

TABLE 16 *Analysis checklist – iloprost added to ongoing bosentan and supportive treatment versus ongoing bosentan and supportive treatment*

Planned analyses	Population/doses/data to be included	Analysis carried out	Comments and source of data
A. Primary analysis	All PAH, FCIII, licensed doses	Yes	Both the COMBI[58] and STEP[59] studies were included. Note that, although the STEP study[59] included patients with mixed FC, the vast majority (94%, 63/67) of the patients were in FCIII at baseline and thus this study was included in this analysis
B. Sensitivity analysis – mixed FC	All PAH, all FC, licensed doses	No	See above. Only a minority of patients were not in FCIII at baseline and the impact on the results is expected to be very small
C. Sensitivity analysis – mixed pulmonary hypertension	All pulmonary hypertension including categories 1–5 of the Venice 2003 classification, all FC, licensed doses	No	Neither of the two trials included patients outside category 1 of the Venice 2003 classification
D. Sensitivity analysis – including above licensed doses	All PAH, all FC, licensed doses and above licensed doses	No	The doses for iloprost were individualised and doses used in the trials were in line with its license
E. Sensitivity analysis – excluding open-label trials	All PAH, all FC, licensed doses, excluding open-label trials	Yes	This analysis excluded data from the COMBI study,[58] which was open-label, and included only data from the STEP study[59]
F. Sensitivity analysis – excluding data designated as confidential	All PAH, all FC, licensed doses, excluding commercial-in-confidence and academic-in-confidence data	No	All available data were from published literature
G. Subgroup analysis – IPAH	IPAH (PPH), all FC licensed doses	Yes	All data from the COMBI study[58] and IPAH subgroup data from the STEP study[59] were included. This analysis matches closely with iloprost's licensed indication (PPH, FCIII), as the vast majority of the participants in these two trials were in FCIII
H. Subgroup analysis – CTD-APAH	CTD-APAH, FCIII, licensed dose(s)	No	Data were not available

CTD-APAH, PAH associated with connective tissue disease; FC, functional class; IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension; PPH, primary pulmonary hypertension.

studies were included in the primary analysis (all PAH, FCIII) and no sensitivity analysis including mixed FC was performed. The results of meta-analyses (or of individual trials when only one trial provided the data) are listed in *Table 17*. Results for individual outcomes are summarised in the following subsections.

Survival
No deaths occurred in the two studies.[58,59]

Time to clinical worsening
The pooled RR indicated a trend in favour of iloprost, but this did not reach statistical significance (RR = 0.39, 95% CI 0.04–3.45) and showed moderate heterogeneity between the studies ($I^2 = 53\%$). Sensitivity analyses excluding the open-label RCT (COMBI) increased the effect size but this was also not a statistically significant finding (see *Table 17*, analyses A and E) (the STEP trial used the log rank test for time to clinical worsening and reported a statistically significant finding in favour of iloprost; as individual patient data were not available for this assessment this measure could not be used for the pooled or sensitivity analysis).

Functional class
Changes in FC were reported as a continuous outcome in the COMBI study.[58] No significant difference between treatment groups was found. The STEP study[59] provided sufficient data for calculating RRs and the results are shown in *Table 17*. The proportion of patients who had their FC improved or maintained was not significantly different between the iloprost and placebo groups. Significantly more patients in the iloprost group than in the placebo group had their FC improved (11/31 versus 2/33, RR = 5.85, 95% CI 1.41–24.34); however, three patients randomised to the iloprost group (and none randomised to the placebo group) were excluded from the analysis.

Exercise capacity
The mean changes from baseline for the 6MWD (post inhalation) for the two trials are shown in *Figure 6*. The mean 6WMD for the iloprost group compared with the placebo/control group increased by 26 metres in the STEP trial,[59] but decreased by 10 metres in the COMBI trial.[58] Neither difference was statistically significant. The difference between treatment groups was smaller (18 metres) when 6MWD was measured preinhalation in the STEP trial.[59]

Quality of life
This outcome was reported only in the COMBI study.[58] No significant difference in the EuroQoL questionnaire (0–100 scale) was observed between the treatment groups (+7 for the iloprost group versus –3 for the control group, $p = 0.14$).

Haemodynamic measures
Haemodynamic outcomes were measured in the STEP study,[59] but not in the COMBI study.[58] Results (post inhalation) from the STEP study (see *Table 17*) showed that iloprost significantly reduced mPAP and PVR compared with placebo. When measured preinhalation the between-group differences were in the same direction but were smaller and not statistically significant.

Other effectiveness measures
The change in Borg dyspnoea index from baseline was not significantly different between treatment groups (–0.5 for iloprost versus no change for placebo, $p = 0.16$) in the STEP study.[59]

Serious adverse events and other adverse events
SAEs were not described separately from other adverse events in the COMBI study.[58] One patient in the iloprost arm stopped treatment because of intractable coughing.[58] Similar numbers of patients experienced at least one SAE in the two treatment groups in the STEP study[59] (5/35 for iloprost versus 7/32 for placebo). The SAEs included worsening PAH requiring hospitalisation and right heart failure in the placebo group, and headache and rectal bleeding in the iloprost group. Common adverse events that occurred more frequently in patients receiving iloprost included jaw pain, headache and flushing.[59]

Subgroup analysis – PAH subcategories
The proportions of patients having their FC improved were similar between the subgroups of IPAH patients (6/16 in the iloprost group versus 1/20 in the placebo group) and patients with other PAH (iloprost 5/16 versus placebo 1/13) in the STEP trial[59] (test for heterogeneity: $\chi^2 = 0.18$, df = 1, $p = 0.67$). The improvement in 6MWD was also similar between these two subgroups (25 metres for IPAH versus 30 metres for other PAH).

Summary and discussion
- Two RCTs, one double-blind (STEP[59]) and one open-label (COMBI[58]), compared inhaled iloprost with placebo/control with ongoing bosentan and supportive treatment. The duration of both trials was 12 weeks.

TABLE 17 *Meta-analysis results: iloprost added to ongoing bosentan and supportive treatment versus ongoing bosentan and supportive treatment*

		Analysis (see analysis checklist)					
		A. Primary analyses		**E. Sensitivity analysis – excluding open-label trial**		**G. Subgroup analysis – IPAH**	
PAH population		All PAH subcategories		All PAH subcategories		IPAH only	
Functional class (FC)		FCIII		All FC (data mainly on FCIII)		All FC (data mainly on FCIII)	
Doses		Licensed doses		Licensed doses		Licensed doses	
Total no. eligible for analysis		107[58,59]		67 (only data from the STEP trial[59] were included)		77[58,59]	
No. included in analysis		0–107		0–67		0–77 (all data available from COMBI[58] were included; STEP trial[59] provided IPAH data only for the outcome of 'FC improved')	
Outcomes	**Statistics**	***n***	**Effect size (95% CI)**	***n***	**Effect size (95% CI)**	***n***	**Effect size (95% CI)**
Efficacy							
Death	RR	107[58,59]	Not estimable (no death)	67[59]	Not estimable (no death)	77[58,59]	Not estimable (no death)
Clinical worsening	RR	105[58,59]	0.39 (0.04 to 3.45), $I^2 = 53\%$	65[59]	0.09 (0.01 to 1.63)	40[58]	0.83 (0.21 to 3.24)
FC improved	RR	64[59]	**5.85 (1.41 to 24.34)[a]**	64[59]	**5.85 (1.41 to 24.34)[a]**	36[59]	7.50 (1.00 to 56.11)
FC maintained or improved	RR	64[59]	1.03 (0.95 to 1.12)	64[59]	1.03 (0.95 to 1.12)	0	No data available
Withdrawal for any reason	RR	107[58,59]	0.94 (0.30 to 2.94)	67[59]	0.78 (0.23 to 2.64)	40[58]	3.30 (0.14 to 76.46)

Outcomes	Statistics	*n*	Effect size (95% CI)	*n*	Effect size (95% CI)	*n*	Effect size (95% CI)
6-minute walk distance (metres)[b]	WMD	105[58,59]	13 (–21 to 47)	65[59]	26 (–3 to 55)	40[58]	–10 (–56 to 36)
Haemodynamics							
Mean pulmonary arterial pressure (mPAP) (mmHg)[c]	WMD	57[59]	**–8.0 (–11.4 to –4.6)[a]**	57[59]	**–8.0 (–11.4 to –4.6)[a]**	0	No data available
Right atrial pressure (RAP) (mmHg)[c]	WMD	0	No data available	0	No data available	0	No data available
Pulmonary vascular resistance (PVR) (dyn s/cm^5)[c]	WMD	57[59]	**–245 (–373 to –117)[a]**	57[59]	**–245 (–373 to –117)[a]**	0	No data available
Cardiac index[b] (l/min/m^2)	WMD	0	No data available	0	No data available	0	No data available
Safety							
Serious adverse events	RR	67[59]	0.65 (0.23 to 1.85)	67[59]	0.65 (0.23 to 1.85)	0	No data available

CI, confidence interval; FC, functional class; IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension; RR, relative risk; WMD, weighted mean difference.
a Statistically significant result.
b Mean change from baseline; positive value favours iloprost.
c Mean change from baseline; negative value favours iloprost

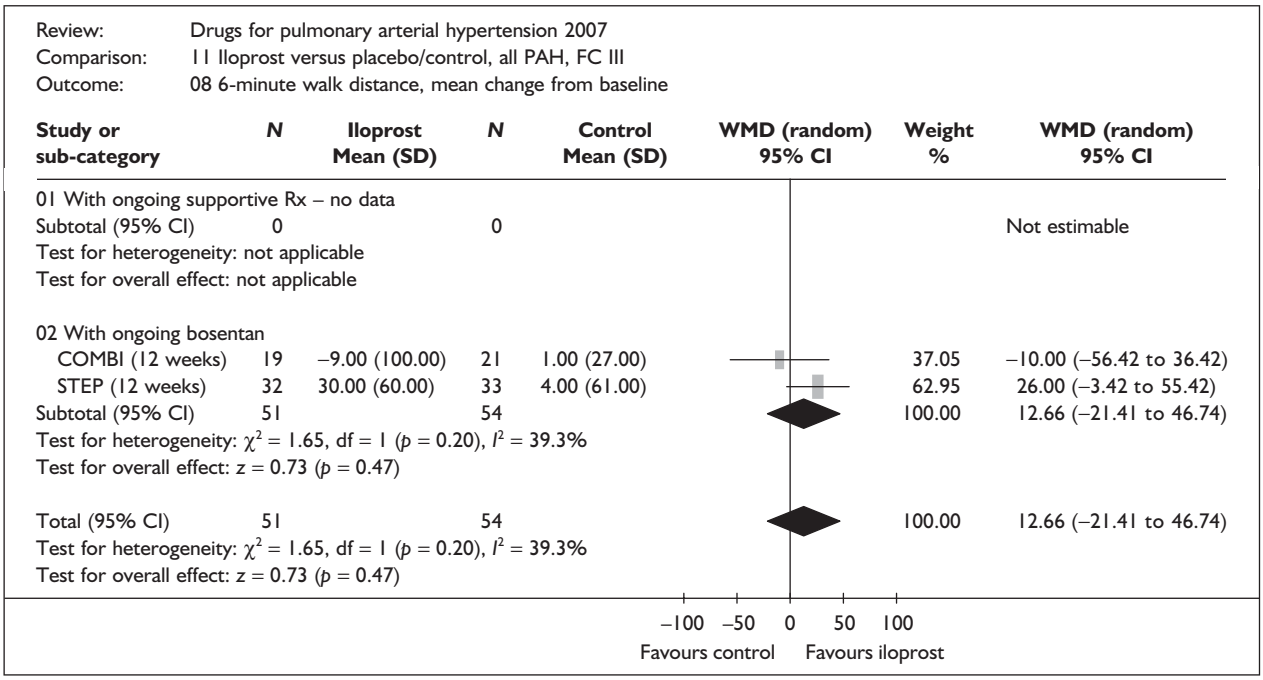

FIGURE 6 *Iloprost added to ongoing bosentan and supportive treatment versus ongoing bosentan and supportive treatment – change in 6-minute walk distance. CI, confidence interval; FC, functional class; PAH, pulmonary arterial hypertension; SD, standard deviation; WMD, weighted mean difference.*

- The method of randomisation and SAEs were not clearly reported in the COMBI study.[58] The methodology and outcomes were well reported in the STEP study.[59] ITT analysis was used in the COMBI study,[58] but not in the STEP study.[59] The potential bias in the latter may be in favour of the iloprost group.
- The trials included predominantly FCIII patients. The COMBI trial recruited exclusively patients with IPAH,[58] whereas the STEP trial included patients with IPAH (55%) as well as PAH of various causes. The mean 6MWD at baseline was 306 metres for the COMBI study and 335 for the STEP study.
- In the COMBI study no significant differences between the iloprost group and the control group were observed for any of the outcome measures examined.[58] By contrast, the STEP study showed a significant reduction in the risk of clinical worsening and an increased likelihood of FC improvement for iloprost-treated patients compared with placebo-treated patients (with ongoing bosentan and supportive treatment), and also a significant improvement in post-inhalation haemodynamic measures (mPAP and PVR).[59] The changes in 6MWD between treatment groups were not statistically significant in either trial.
- The differences between treatment groups were generally smaller and not statistically significant for measures taken preinhalation. This is consistent with results from the AIR study (iloprost versus placebo with ongoing supportive treatment).[41]
- Compared with the COMBI study the STEP study had the advantage of being a multicentre, double-blind trial and having a slightly larger sample size. However, the failure to use ITT analysis in the STEP study was a potential threat to the credibility of its results. Patients included in the COMBI study appeared to have more severe disease than those in the STEP study according to the mean 6MWD at baseline. It is not clear whether the inconsistent results between the two studies can be attributed to any of these factors.
- No significant differences in the improvements in 6MWD and FC were observed in the STEP study between patients with IPAH and those with PAH of other causes.[59]

Bosentan

Quantity and quality of included studies

Bosentan was investigated in six of the included RCTs. Four of these [Channick *et al.*,[15,43] BREATHE-1,[45,46] BREATHE-5[47] and STRIDE (*S*itaxsentan *t*o *R*elieve *I*mpaire*d* *E*xercise study)-2[48]] allowed the comparison between bosentan and placebo with ongoing background therapy. Another trial (BREATHE-2[56]) compared the combination of epoprostenol plus bosentan

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TABLE 18 *Characteristics of included bosentan trials*

Trial name/key paper (protocol number); location/ centres	Duration; design; number of patients randomised	Intervention[a]	Comparator[a]	Type of PAH	Functional class	Age (years), mean (SD, range); % female	Baseline exercise capacity and haemodynamic measures,[b] mean (SD)
Bosentan vs placebo							
Channick *et al.*, 2001 (AC-052–351);[43] USA and France, six centres	12 weeks; double-blind, parallel; *n* = 32	Bosentan (oral) 125 mg b.d.[c] (*n* = 21)	Placebo (*n* = 11)	PPH (84%), scleroderma (16%)	III (100%)	51 (13); 88%	6MWD: 358 (85); cardiac index (n=30): 2.4 (0.8); mPAP (n=30): 55 (12); PVR (n=29): 912 (427); RAP (n=29): 9.8 (5.1); SvO_2: NR
BREATHE-1/ Rubin *et al.*, 2002;[45] international, 27 centres	16 weeks;[d] double-blind, parallel; *n* = 213	Bosentan (oral) 125 mg b.d.[c] (*n* = 74), 250 mg b.d.[c] (*n* = 70)	Placebo (*n* = 69)	PPH (70%), CTD (30%)	III (92%), IV (8%)	48 (16); 79%	6MWD: 334 (75); cardiac index (n=208): 2.4 (0.8); mPAP: 54 (16); PVR (n=200): 970 (628); RAP (n=210): 9.5 (5.7); SvO_2: NR
BREATHE-5/ Galiè *et al.*, 2006;[47] international, 15 centres	16 weeks; double-blind, parallel; *n* = 54	Bosentan (oral) 125 mg b.d.[c] (*n* = 37)	Placebo (*n* = 17)	Eisenmenger syndrome (100%)	III (100%)	39 (11); 61%	6MWD: 343 (78); cardiac index: NR; mPAP: 76 (17); PVR: 3250 (1352); RAP: 5.8 (3.5); SvO_2: NR
STRIDE-2/Barst *et al.*, 2006[48] (FPH02); international, 55 centres	18 weeks; double-blind (open-label for bosentan), parallel; *n* = 247	Bosentan (oral) 125 mg b.d.[c] (*n* = 60); sitaxentan (oral) 50 mg o.d. (*n* = 62), 100 mg o.d. (*n* = 61)	Placebo (*n* = 62)	IPAH (59%), CTD (30%), congenital heart disease (11%)	II (37%), III (59%), IV (4%)	54 (15); 78%	6MWD: 337 (80); cardiac index: 2.4 (0.8); mPAP: 48 (14); PVR: 880 (560);[e] RAP: NR; SvO_2: NR
Bosentan + epoprostenol vs epoprostenol							
BREATHE-2/ Humbert *et al.*, 2004;[56] USA and Europe, seven centres	16 weeks; double-blind, parallel; *n* = 33	Bosentan (oral) 125 mg b.d.[c] + epoprostenol (i.v. infusion) started with 2 ng/kg/min and increased to 12–16 ng/kg/min between weeks 14 and 16 (*n* = 22)	Placebo + epoprostenol (i.v. infusion) started with 2 ng/kg/min and increased to 12–16 ng/kg/min between weeks 14 and 16 (*n* = 11)	PPH (82%), CTD (18%)	III (76%), IV (24%)	46 (18, 15–69); 70%	6MWD: NR; cardiac index: 1.7 (0.5); mPAP: 60 (16); PVR: 1483 (537); RAP: 11.9 (5.9); SvO_2: NR

6MWD, 6-minute walk distance; b.d., twice daily; CTD, PAH associated with connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; NR, not reported; o.d., once daily; PAH, pulmonary arterial hypertension; PPH, primary pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SD, standard deviation; SvO_2, mixed venous oxygen saturation.

a With ongoing supportive treatment unless otherwise specified.

b Units are: 6MWD, metres; cardiac index, l/min/m^2; mPAP, mmHg; PVR, dyn s/cm^5; RAP, mmHg; SvO_2, %.

c 62.5 mg twice daily for the first 4 weeks.

d Patients who were randomised within the first 2 months of the study (*n* = 48) were treated and followed up for a further 12 weeks.

e Converted from mmHg/litre/min (Wood units).

with epoprostenol alone. The characteristics of these five studies are summarised in *Table 18*.

Bosentan was compared with sitaxentan in STRIDE-2[48] and with sildenafil in a further study by Wilkins and colleagues.[57] These direct comparisons will be described separately.

All of the five studies shown in *Table 18* were industry-sponsored international studies (STRIDE-2 was sponsored by the manufacturer of sitaxentan). The number of patients randomised (excluding the sitaxentan arms in STRIDE-2) ranged from 32[43] to 213[45] and the duration of study was 12 weeks,[43] 18 weeks[48] or 16 weeks.[45,47,56] The bosentan dose of 125 mg twice daily was used in all of the trials. In addition, BREATHE-1 also included the dose of 250 mg twice daily. In line with bosentan's license, an initiation dose of 62.5 mg twice daily for the first 4 weeks was used before patients were uptitrated to the targeted doses in all trials.

The patient populations varied between trials in terms of PAH subcategories and FC. With the exception of BREATHE-5,[47] which recruited exclusively patients with Eisenmenger syndrome, all of the trials included a mixed population of IPAH (59–84% within each trial) and CTD-APAH (16–30% within each trial). STRIDE-2 also included 11% of patients with CHD. The submission to NICE by Actelion indicates that patients with PAH associated with CHD (postsurgically corrected) were enrolled in BREATHE-1, although this was not stated in the published papers.[45,46] The Actelion submission also states that:

> … as the post-surgical CHD patient numbers were small and since they are believed by clinicians to act like IPAH patients, the CHD patients were grouped with the IPAH patients for all analyses. Within this submission, the CHD group is never separated out from the IPAH sub-group, but is implicitly included.

Two[43,47] of the five trials recruited exclusively patients in FCIII. Most of the patients in the other three studies were also in FCIII. STRIDE-2[48] and BREATHE-1[45] included a small proportion of patients in FCIV (4% and 8% respectively), whereas nearly one-quarter of patients in BREATHE-2[56] were in FCIV at baseline. STRIDE-2[48] also included a significant proportion of patients in FCII at baseline (37%). Baseline 6MWD was not reported in BREATHE-2 and was fairly similar for the other four trials (range 334–358 metres) despite the differences in FC mix. The primary outcome measure was change in 6MWD for Channick *et al*.,[43] BREATHE-1[45] and STRIDE-2;[48] change in total pulmonary resistance (determined by right heart catheterisation) for BREATHE-2;[56] and change in systemic pulse oximetry for BREATHE-5.[47]

Quality assessment of the five trials is summarised in *Table 19*. The method of randomisation was adequate in Channick *et al*.,[43] BREATHE-5[47] and STRIDE-2[48] and was not clearly described in the published papers for BREATHE-1[45,46] and BREATHE-2.[56] Allocation concealment was also adequate in BREATHE-5[47] and STRIDE-2[48] and was not clearly described in the other three trials. All of the five trials were double-blind studies, except that the bosentan arm in the STRIDE-2 trial was open-label (the only open-label arm in the trial). The investigators stated that this was because 'bosentan was only available commercially on a named-patient basis and blinded drug supplies were not available'. Nevertheless, the assessors for 6MWT, FC assessments and Borg dyspnoea scores were blinded. ITT analysis was used in all trials for most outcomes, but not for haemodynamic measures. The proportion of patients completing each study was slightly lower in the placebo group than in the bosentan group, except for the BREATHE-2 study in which a slightly lower proportion of patients treated with bosentan (plus epoprostenol) completed the trial compared with those treated with placebo (plus epoprostenol).

Given the different nature of the comparisons between the trials, the results of Channick *et al*.[43] and the BREATHE-1,[45] BREATHE-5[47] and STRIDE-2 (bosentan versus placebo only)[48] studies will be described separately from the results of the BREATHE-2 study.

Bosentan added to supportive treatment versus supportive treatment alone

This comparison was investigated in Channick *et al*.,[43] BREATHE-1,[45] BREATHE-5[47] and STRIDE-2.[48] Planned meta-analyses for the comparison and those actually carried out are summarised in *Table 20*. As no data stratified by FC were available from BREATHE-1 (the largest among the bosentan trials) and the only stratified data available from STRIDE-2 were for change in FC, the planned primary analysis (all PAH, FCIII) included data only from Channick *et al*.[43] and BREATHE-5[47] for most outcomes. If the stratified data were available, 195 out of 213 patients in BREATHE-1 and 72 out of 122 patients in STRIDE-2 receiving either bosentan or placebo would have also been included in this analysis. However, sensitivity analyses including populations

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TABLE 19 *Quality assessment of included bosentan trials*

Study; duration	Truly random allocation (strata for randomisation)	Adequate allocation concealment	Blinding	Use of ITT analysis[a] (*n* included in analysis/*N* randomised)	% of patients completing the trial	Comments
Bosentan vs placebo						
Channick *et al.*, 2001;[43] 12 weeks	Yes	Unclear	Double-blind	Survival analysis: no death; clinical worsening: yes; functional class: yes; 6MWD: yes; haemodynamic: no (29–30/32); quality of life: N/A	Placebo: 82% (9/11); bosentan: 100% (21/21)	
BREATHE-1/ Rubin *et al.*, 2002;[45] 16 weeks	Unclear	Unclear	Double-blind	Survival analysis: N/A; clinical worsening: yes; functional class: yes; 6MWD: yes; haemodynamic: N/A; quality of life: N/A	Not reported	
BREATHE-5/ Galiè *et al.*, 2006;[47] 16 weeks	Yes	Yes	Double-blind	Survival analysis: no death; clinical worsening: N/A; functional class: yes; 6MWD: yes; haemodynamic: no (unclear[b]); quality of life: N/A	Placebo: 88% (15/17); bosentan: 95% (35/37)	
STRIDE-2/Barst *et al.*, 2006;[48] 18 weeks	Yes	Yes	Double-blind for placebo (and sitaxentan); open-label for bosentan	Survival analysis: N/A; clinical worsening: yes; functional class: no (120/122); 6MWD: no (120/122); haemodynamic: N/A; quality of life: N/A	Placebo: 82% (51/62); bosentan: 87% (52/60)	Seven randomised patients (two did not receive treatment, five did not have a valid post-baseline 6MWT) were excluded from efficacy analyses
Bosentan + epoprostenol vs epoprostenol						
BREATHE-2/ Humbert *et al.*, 2004;[56] 16 weeks	Unclear	Unclear	Double-blind	Survival analysis: N/A; clinical worsening: yes; functional class: yes; 6MWD: no (29/33); haemodynamic: yes except PVR; quality of life: N/A	Epoprostenol: 91% (10/11); epoprostenol + bosentan: 82% (18/22)	

6MWD, 6-minute walk distance; ITT, intention to treat; N/A, data not available; PVR, pulmonary vascular resistance.

a Defined as an analysis that includes all randomised patients (or all randomised patients who received at least one dose of study medication) according to the treatment group to which they were assigned, irrespective of actual treatment received or early withdrawal of treatment. N/A, data not available (outcome not measured in the trial or unclear if it was measured; analysis for the outcome not performed or unclear if it was performed). When analysis for the outcome was performed but the number of patients included was not reported, this was noted as 'unclear'. When ITT analysis was not used, the number of patients included in the analysis (or a range of numbers when more than one outcome was analysed/more than one analysis was performed with various numbers of patients used) over the number that should have been used in an ITT analysis is shown.

b Stated 'the number of patients per treatment group varied slightly for each parameter because of missing assessments'.

TABLE 20 *Analysis checklist – bosentan added to supportive treatment versus supportive treatment alone*

Planned analysis	Population/doses/data to be included	Analysis carried out	Comments and source of data
A. Primary analysis	All PAH, FCIII, licensed dose(s)	Yes	Data from Channick *et al.*[43] ($n = 32$) and BREATHE-5[47] ($n = 54$) were included. STRIDE-2[48] only provided data (commercial-in-confidence) for change in FC. BREATHE-1[45] was not included as data stratified by FC were not available
B. Sensitivity analysis – mixed FC	All PAH, all FC, licensed dose(s)	Yes	Data from Channick *et al.*[43] ($n = 32$), BREATHE-1[45] ($n = 213$), BREATHE-5[47] ($n = 54$) and STRIDE-2[48] ($n = 122$) were included
C. Sensitivity analysis – mixed pulmonary hypertension	All pulmonary hypertension including categories 1–5 of the Venice 2003 classification, all FC, licensed dose(s)	No	None of the bosentan trials included pulmonary hypertension other than PAH
D. Sensitivity analysis – including above licensed dose	All PAH, all FC, licensed doses and above licensed dose	No	None of the bosentan trials used above licensed doses
E. Sensitivity analysis – excluding data designated as confidential	All PAH, all FC, licensed dose(s), excluding commercial-in-confidence and academic-in-confidence data	No	No confidential data were provided
F. Sensitivity analysis – excluding open-label trial	All PAH, all FC, licensed dose(s), excluding open-label trial (STRIDE-2)	Yes	Data from Channick *et al.*[43] ($n = 32$), BREATHE-1[45] ($n = 213$) and BREATHE-5[47] ($n = 54$) were included. STRIDE-2[48] was excluded as the bosentan arm was open-label
G. Subgroup analysis – IPAH	IPAH, all FC, licensed dose	No	Stratified data were not available
H. Subgroup analysis – CTD-APAH	CTD-APAH, all FC, licensed dose(s)	Yes	Subgroup analyses reported by Denton and colleagues[44] were included. See texts for detail

CTD-APAH, PAH associated with connective tissue disease; FC, functional class; IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension.

of mixed FC from these two trials were carried out. The results of meta-analyses (or of individual trials when only one trial provided the data) are listed in *Table 21*. Results for individual outcomes are summarised in the following subsections. Given the relatively small number of patients included in the primary analysis, results presented are mainly drawn from data of mixed FC. Findings specifically for FCIII are stated separately when appropriate.

When data from BREATHE-1[45] were included, the results from the two bosentan arms (125 mg twice daily and 250 mg twice daily) in the trial were combined unless otherwise specified. When STRIDE-2[48] is mentioned in this section it is only referred to with regard to data from the placebo and bosentan arms.

Survival

A total of five deaths (one from the bosentan groups, four from the placebo groups) were reported in the four trials.[43,45,47,48] An additional three deaths from the bosentan group (250 mg twice daily) occurred within 4 weeks after withdrawal from or completion of the BREATHE-1 trial. The number is too small to draw any firm conclusions.

Time to clinical worsening

Clinical worsening was not reported in BREATHE-5[47] and was defined differently in Channick *et al.*[43] (right ventricular heart failure or aggravated pulmonary hypertension), BREATHE-1[45] (death, lung transplantation, hospitalisation for pulmonary hypertension, lack of clinical improvement or worsening leading to discontinuation, need for epoprostenol therapy, or atrial septostomy) and STRIDE-2[48] (hospitalisation for PAH, death, transplantation, atrial septostomy, initiation of new chronic PAH treatment, or combined WHO FC deterioration and ≥ 15% decrease in 6MWD from baseline). Time-to-event

analysis was carried out in all three trials, although hazard ratios were not reported. Two of these reported a significant increase in time to clinical worsening for the bosentan group(s) compared with the placebo groups ($p = 0.033$ in Channick *et al.*;[43] $p = 0.01$ for both doses of bosentan in BREATHE-1[45]). No difference in time to clinical worsening between the bosentan group (open-label) and the placebo group was found in the STRIDE-2 study ($p = 0.80$). *Table 21* shows that, when analysed as a binary outcome, the pooled RR of clinical worsening for the Channick *et al.*[43] and BREATHE-1[45] trials significantly favours bosentan (analysis F: RR = 0.28, 95% CI 0.13–0.60, $I^2 = 0\%$). Inclusion of data from STRIDE-2 introduced substantial statistical heterogeneity and the pooled result was no longer statistically significant (analysis B: RR = 0.43, 95% CI 0.15–1.24, $I^2 = 62\%$).

Functional class

Table 21 shows that the proportion of patients who maintained or improved FC was not significantly different between the bosentan and placebo groups. BREATHE-1[45] could not be included in the analysis as it only reported the proportion of patients whose FC was improved but did not report the proportion of patients whose FC was unchanged or worsened. The pooled result including data from all four trials[43,45,47,48] for having FC improved significantly favours bosentan (mixed FC, RR = 1.51, 95% CI 1.05–2.15, $I^2 = 0\%$). The pooled result from three trials[43,47,48] specifically for FCIII (excluding BREATHE-1, data not available) also favours bosentan, but just fails to reach statistical significance (RR = 2.08, 95% CI 0.97–4.46, $I^2 = 0\%$).

Exercise capacity

The mean changes from baseline for the 6MWD for the four trials[43,45,47,48] (mixed FC) are shown in *Figure 7*. A significant increase in 6MWD for the bosentan groups compared with the placebo groups was observed in all trials, including those by Channick *et al.*[43] and BREATHE-5,[47] which recruited only patients in FCIII. The pooled result from these two studies (analysis A, *Table 21*) was 59 metres in favour of bosentan (95% CI 20–99, $I^2 = 0\%$).

Quality of life

No trial reported quality of life outcomes.

Haemodynamic measures

As post-treatment haemodynamic outcomes were measured only in Channick *et al.*[43] and BREATHE-5,[47] which recruited exclusively patients in FCIII, the results shown in *Table 21* for haemodynamic outcomes were identical for analyses A, B and F. Compared with placebo, bosentan significantly reduced mPAP and PVR and increased the cardiac index. A significant difference in the change of RAP between the bosentan and placebo groups was observed in Channick *et al.*[43] (–6.2 mmHg, 95% CI –9.6 to –2.8), but not in BREATHE-5 (–0.1, 95% CI –2.1 to 1.9). In Channick *et al.* the RAP reduced by 1.3 mmHg in the bosentan group, whereas it increased by 4.9 mmHg in the placebo group. RAP increased slightly in both the bosentan and placebo groups (0.3 and 0.4 mmHg respectively) in BREATHE-5.

Other effectiveness measures

A significant decrease (improvement) in the Borg dyspnoea index for the bosentan groups compared with the placebo group was observed in BREATHE-1[45] (mean difference –0.6, 95% CI –1.2 to –0.1) and Channick *et al.*[43] (–1.6, 95% CI –3.1 to 0.0); however, no significant difference between the bosentan and placebo groups was observed in STRIDE-2.[48]

Serious adverse events and other adverse events

The total number of patients who experienced at least one SAE was not reported in Channick *et al.*[43] and BREATHE-1.[45] The pooled result (mixed FC) for BREATHE-5 and STRIDE-2 showed a significant decreased risk for bosentan-treated patients compared with placebo-treated patients (RR = 0.45, 95% CI 0.23–0.89, $I^2 = 0\%$). Common adverse events that occurred more frequently in the bosentan group include abnormal liver function,[45] peripheral oedema and palpitation.[47]

Subgroup analysis – PAH subcategories

Denton and colleagues[44] reported post hoc analyses of data from two of the bosentan trials[43,45] for the subgroup of PAH patients with CTD. Data from the two trials were pooled together before analyses were carried out and thus initial randomisation was not preserved; however, the number of patients with CTD-APAH in Channick *et al.* would have been too small to be analysed separately ($n = 5$ for the bosentan group and $n = 1$ for the placebo group).

The baseline characteristics for the CTD-APAH patients ($n = 66$) indicated that patients treated with bosentan may have had more severe disease than those treated with placebo (6MWD 312 metres versus 361 metres, $p = 0.01$). The change in 6MWD from baseline was +19.5 metres in patients treated with bosentan and –3 metres in patients treated with placebo. The difference between groups was

TABLE 21 *Meta-analysis results: bosentan added to supportive treatment versus supportive treatment alone*

		Analysis (see analysis checklist)							
		A. Primary analysis		**B. Sensitivity analysis – mixed FC**		**F. Sensitivity analysis – excluding open-label trial**		**H. Subgroup analysis – CTD-APAH**	
PAH population		All PAH subcategories		All PAH subcategories		All PAH subcategories		CTD-APAH only	
Functional class (FC)		FCIII		All FC		All FC		All FC	
Doses		Licensed dose (125–250 mg twice daily)		Licensed dose (125–250 mg twice daily)		Licensed dose (125–250 mg twice daily)		Licensed dose (125–250 mg twice daily)	
Total no. eligible for analysis		353[43,45,47,48]		421[43,45,47,48]		299[43,45,47] (data from STRIDE-2[48] were excluded)		66[43,45]	
No. included in analysis		29–156 (data stratified by FC were not available from BREATHE-1[45])		29–421		29–299		0–66	
Outcomes	**Statistics**	***n***	**Effect size (95% CI)**	***n***	**Effect size (95% CI)**	***n***	**Effect size (95% CI)**	***n***	**Effect size (95% CI)**
Efficacy									
Death	RR	86[43,47]	Not estimated (no death)	421[43,45,47,48]	0.23 (0.03 to 1.47)	299[43,45,47]	0.24 (0.02 to 2.60)	0	Data not available
Clinical worsening	RR	32[43]	0.08 (0.00 to 1.39)	367[43,45,48]	0.43 (0.15 to 1.24), I^2 62%	245[43,45]	**0.28 (0.13 to 0.60)**[a]	0	Data not available
FC improved	RR	156[43,47,48]	2.08 (0.97 to 4.46)	419[43,45,47,48]	**1.51 (1.05 to 2.15)**[a]	299[43,45,47]	1.80 (0.93 to 3.47)	0	Data not available
FC maintained or improved	RR	156[43,47,48]	1.05 (0.96 to 1.15)	206[43,47,48]	1.06 (0.97 to 1.15)	86[43,47]	1.09 (0.91 to 1.30)	0	Data not available
Withdrawal for any reason	RR	86[43,47]	0.30 (0.06 to 1.48)	208[43,47,48]	0.62 (0.29 to 1.29)	86[43,47]	0.30 (0.06 to 1.48)	0	Data not available

Outcomes	Statistics	*n*	Effect size (95% CI)	*n*	Effect size (95% CI)	*n*	Effect size (95% CI)	*n*	Effect size (95% CI)
6-minute walk distance (metres)[b]	WMD	86[43,47]	**59 (20 to 99)[a]**	421[43,45,47,48]	**41 (24 to 58)[a]**	299[43,45,47]	**49 (27 to 70)[a]**	66[43,45]	22 (–32 to 76)
Haemodynamics									
Mean pulmonary arterial pressure (mPAP) (mmHg)[c]	WMD	84[43,47]	**–5.9 (–9.3 to –2.5)[a]**	84[43,47]	**–5.9 (–9.3 to –2.5)[a]**	84[43,47]	**–5.9 (–9.3 to –2.5)[a]**	0	Data not available
Right atrial pressure (RAP) (mmHg)[c]	WMD	83[43,47]	–3.0 (–9.0 to 3.0), I^2 89%	83[43,47]	–3.0 (–9.0 to 3.0), I^2 89%	83[43,47]	–3.0 (–9.0 to 3.0), I^2 89%	0	Data not available
Pulmonary vascular resistance (PVR) (dyn s/cm^5)[c]	WMD	29[43]	**–414 (–596 to –232)[a]**	29[43]	**–414 (–596 to –232)[a]**	29[43]	**–414 (–596 to –232)[a]**	0	Data not available
Cardiac index (l/min/m^2)[b]	WMD	30[43]	**1.0 (0.7 to 1.3)[a]**	30[43]	**1.0 (0.7 to 1.3)[a]**	30[43]	**1.0 (0.7 to 1.3)[a]**	0	Data not available
Safety									
Serious adverse events	RR	54[47]	0.77 (0.21 to 2.84)	177[47,48]	**0.45 (0.23 to 0.89)[a]**	54[47]	0.77 (0.21 to 2.84)	0	Data not available

CI, confidence interval; CTD-APAH, PAH associated with connective tissue disease; PAH, pulmonary arterial hypertension; RR, relative risk; WMD, weighted mean difference.
a Statistically significant result.
b Mean change from baseline; positive value favours bosentan.
c Mean change from baseline; negative value favours bosentan

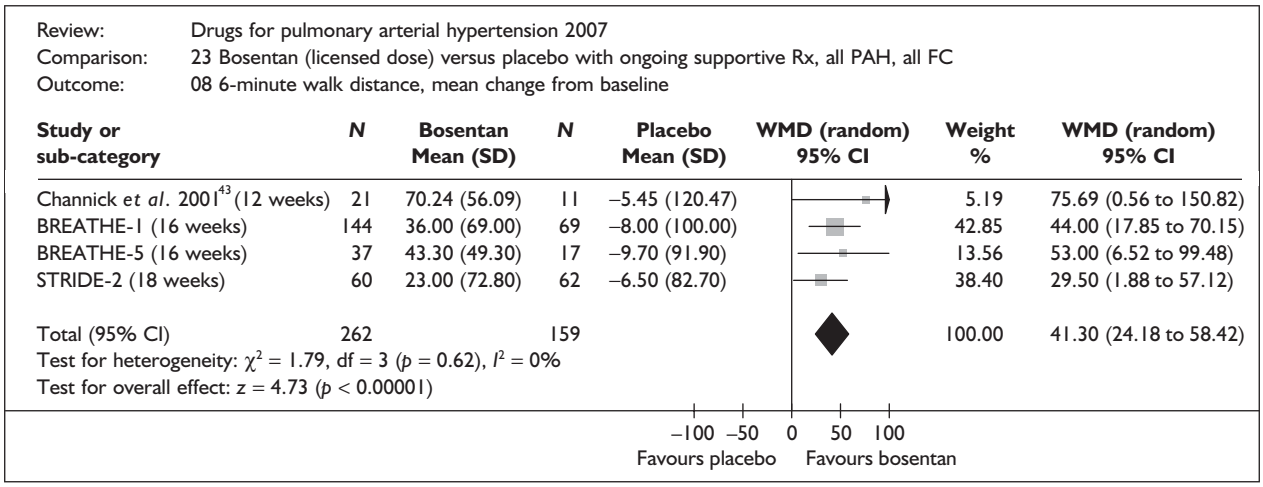

FIGURE 7 *Forest plot: bosentan added to supportive treatment versus supportive treatment – change in 6-minute walk distance. CI, confidence interval; SD, standard deviation; WMD, weighted mean difference.*

not statistically significant (22.5 metres, 95% CI –32 to 76). The Kaplan–Meier estimates of the percentage of patients not experiencing clinical worsening also showed a non-significant trend in favour of bosentan compared with placebo: 95.4% versus 90.9% at 12 weeks, and 90.3% versus 86.4% at 16 weeks. Dizziness, lower limb oedema and fatigue occurred more frequently in bosentan-treated patients.

Subgroup analysis within the BREATHE-1 trial[45] showed no significant difference between PPH (51 metres) and PAH associated with scleroderma (43 metres) in the change of 6MWD from baseline for bosentan-treated groups compared with the placebo group. Nevertheless, the treatment effect was mainly associated with increased 6MWD in PPH (+46 for bosentan group versus –5 for placebo group), but was related to the prevention of worsening in PAH associated with scleroderma (+3 for bosentan group versus –40 for placebo group).

The results from BREATHE-5,[47] which recruited exclusively patients with PAH associated with Eisenmenger syndrome, were similar to those of the other bosentan trials. No heterogeneity attributed to this trial was observed in the outcomes examined in this review, with the exception of right atrial pressure. A significant treatment effect was found in Channick *et al.*,[43] but not in BREATHE-5[47] (see Haemodynamic measures subsection).

Summary and discussion

- Four RCTs comparing bosentan (added to supportive treatment) with supportive treatment alone were identified. Three of them (Channick *et al.*[43], BREATHE-1[45] and BREATHE-5[47]) were double-blind studies, whereas the bosentan arm in the STRIDE-2 trial[48] was open-label. The duration of study ranged from 12 to 18 weeks.
- Methods of randomisation and allocation concealment were not clearly described in some bosentan trials.[43,45,47] ITT analysis was used in most trials except for STRIDE-2. The potential bias from non-ITT analysis was expected to be small in STRIDE-2 as the number excluded from analysis in each treatment group was very small; however, the interpretation of results from this study for outcomes not blindly assessed (such as clinical worsening, treatment withdrawal and adverse events) requires greater caution because of its open-label design.
- There was heterogeneity with regard to the populations enrolled in the trials. For example, BREATHE-5 enrolled exclusively those with Eisenmenger syndrome, whereas the other trials enrolled mixed IPAH and CTD-APAH populations. The mean 6MWD at baseline ranged from 334 metres to 358 metres.
- Few data stratified by FC were available from the two larger trials with mixed FC (BREATHE-1 and STRIDE-2), although two smaller trials (Channick *et al.* and BREATHE-5) provided some data specific to FCIII.
- Compared with supportive treatment alone, bosentan added to supportive treatment has demonstrated significant improvements in exercise capacity (6MWD) and haemodynamic outcomes (mPAP, PVR and cardiac index), both in PAH populations with mixed FC and specifically in FCIII. A significant increase in time to clinical worsening, improvements in FC and a PAH symptom (dyspnoea), and a decreased risk of SAEs were also observed

among bosentan-treated patients compared with placebo-treated patients in PAH populations with mixed FC.
- Subgroup analysis of CTD-APAH patients in Channick *et al*.[43] and BREATHE-1[45] showed similar results to those of the whole trial population (mixed IPAH and CTD-APAH).

Bosentan plus epoprostenol versus epoprostenol

This comparison was investigated in the BREATHE-2 trial.[56] This trial was the only study included in this review that genuinely compared the initiation of a drug combination with a single drug (rather than comparing the addition of a drug to placebo with another ongoing drug). The characteristics and quality assessment of the study are shown in *Tables 18* and *19* respectively. Methods of randomisation and allocation concealment were not clearly reported, and ITT analysis was not used for 6MWD (patients who were unable to or who did not perform the assessment were excluded from the analysis). Although the majority of patients included in this study were in FCIII at baseline, nearly one-quarter of the patients (8/33) were in FCIV. As data stratified by FC were only available for FC improvement, results described in this section were mainly based on patients with mixed FC. Given that the findings were from a single trial with a relatively small sample size ($n = 33$), only a narrative summary of the study findings will be provided.

Findings

Two patients died during this 16-week study (one of acute cardiopulmonary failure, the other of anaemia and pneumonia with rapidly progressing right heart failure). A third patient died after being withdrawn from the study for worsening PAH. All three patients received the epoprostenol/bosentan combination; however, the number was too small to make any firm conclusions. Worsening pulmonary hypertension was reported as an adverse event in two patients in the epoprostenol group and one patient in the combination group. These figures obviously do not include deaths and thus are not comparable to the composite outcome of clinical worsening reported in other studies.

No significant difference was observed between the treatment groups in the proportion of patients who had their FC improved (13/22 for the combination group and 5/11 for the epoprostenol group; RR = 1.30, 95% CI 0.62–2.71). Results specifically for patients in FCIII at baseline showed little difference (9/17 for the combination group and 4/8 for the epoprostenol group; RR = 1.06, 95% CI 0.46–2.42). The proportion of patients with FC unchanged or worsened was not reported. Improvement in 6MWD and the dyspnoea–fatigue rating was similar between treatment groups (median increase 68 metres versus 74 metres, median improvement 0 versus 1.0 unit, for the combination group and epoprostenol group respectively). No quality of life data were reported. Improvement in haemodynamic outcomes from baseline was observed in both treatment groups and was generally larger (in terms of percentage improvement) in the combination group than in the epoprostenol group. None of the differences between groups, however, was statistically significant.

The proportion of patients who experienced at least one SAE in each treatment group was not reported. Common adverse events that occurred in higher proportions of patients in the combination group included leg oedema and diarrhoea. Four patients (out of 22) in the combination group versus one patient (out of 11) in the epoprostenol group withdrew from the study (RR = 2.00, 95% CI 0.25–15.82).

Summary and discussion

- One double-blind, placebo-controlled trial (BREATHE-1[56]) compared the initiation of epoprostenol plus bosentan with epoprostenol alone in mixed PAH populations (IPAH and CTD-APAH) with mixed FC (III and IV).
- Methods of randomisation and allocation concealment were not clearly described in the published paper for this trial,[56] and ITT analysis was not used for 6MWD.
- No significant differences between the group treated with the epoprostenol/bosentan combination and the group treated with epoprostenol were observed for any of the outcomes assessed in the trial.

Sitaxentan

Quantity and quality of included studies

Sitaxentan was investigated in three of the included RCTs. All three of the trials (STRIDE-1,[49] STRIDE-2,[48] STRIDE-4[37]) compared sitaxentan with placebo in patients with ongoing supportive treatment. The STRIDE-2 trial[48] also included an open-label bosentan arm. The bosentan–placebo comparison from this trial has already been described; the bosentan–sitaxentan comparison is described later in this chapter [see Direct (head-to-head) comparisons]. This section focuses on the comparison of sitaxentan added to supportive treatment versus supportive treatment alone. The

TABLE 22 *Characteristics of included sitaxentan trials*

Trial name/key paper (protocol number); location/centres	Duration; design; number of patients randomised	Intervention[a]	Comparator[a]	Type of PAH	Functional class	Age (years), mean (SD, range); % female	Baseline exercise capacity and haemodynamic measures,[b] mean (SD)
STRIDE-1/Barst *et al.*, 2004[49] (FPH01); USA and Canada, 23 centres	12 weeks; double-blind, parallel; *n* = 178	Sitaxentan (oral) 100 mg o.d. (*n* = 55), 300 mg o.d. (*n* = 63)	Placebo (*n* = 60)	IPAH (53%), CTD (24%), congenital S–P shunts (24%)	II (33%), III (66%), IV (1%)	46 (13, 17–74); 79%	6MWD: 398 (110); cardiac index: 2.4 (0.8); mPAP: 54 (15); PVR: 958 (560); RAP: 8 (5); SvO_2: NR
STRIDE-2/Barst *et al.*, 2006[48] (FPH02); international, 55 centres	18 weeks; double-blind (open-label for bosentan), parallel; *n* = 247	Bosentan (oral) 125 mg b.d.[c] (*n* = 60); sitaxentan (oral) 50 mg o.d. (*n* = 62), 100 mg o.d. (*n* = 61)	Placebo (*n* = 62)	IPAH (59%), CTD (30%), congenital heart disease (11%)	II (37%), III (59%), IV (4%)	54 (15); 78%	6MWD: 337 (80); cardiac index: 2.4 (0.8); mPAP: 48 (14); PVR: 880 (560);[g] RAP: NR; SvO_2: NR
STRIDE-4/Barst, 2007[37] (FPH04); Latin America, Poland, Spain	18 weeks; double-blind, parallel; *n* = 98	Sitaxentan (oral) 50 mg o.d. (*n* = 32), 100 mg o.d. (*n* = 32)	Placebo (*n* = 34)	IPAH (68%), CTD (15%), congenital heart disease (16%)	II (61%), III (38%), IV (1%)	41 (14); 84%	6MWD: 345 (80); cardiac index: NR; mPAP: 61 (18); PVR: 1148 (752); RAP: NR; SvO_2: NR

6MWD, 6-minute walk distance; b.d., twice daily; CTD, PAH associated with connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; NR, not reported; o.d., once daily; PAH, pulmonary arterial hypertension; PPH, primary pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SD, standard deviation; S–P, systemic-to-pulmonary; SvO_2, mixed venous oxygen saturation.

a With ongoing conventional therapy unless otherwise specified.

b Units are: 6MWD, metres; cardiac index, l/min/m^2; mPAP, mmHg; PVR, dyn s/cm^5; RAP, mmHg; SvO_2, %.

c 62.5 mg twice daily for the first 4 weeks.

characteristics of the three studies are summarised in *Table 22*. The STRIDE-2 trial[48] has been listed in relevant tables in the section on bosentan, but is also listed in this section for the convenience of readers.

All three studies[37,48,49] were industry-sponsored multicentre trials that randomised between 98 and 247 patients. The STRIDE-1 study was conducted in North America. The STRIDE-2 study was an international study and the STRIDE-4 trial was conducted mainly in South America, but also in Spain and Poland. The clinical study reports (commercial-in-confidence) for all three trials were made available to the assessment group by Encysive. The study duration was 12 weeks for STRIDE-1[49] and 18 weeks for STRIDE-2[48] and STRIDE-4.[37] The licensed dose (100 mg once daily) for sitaxentan was investigated in all three trials. In addition, STRIDE-1[49] included an above licensed dose of 300 mg once daily (included only in the relevant sensitivity analysis in this review) and STRIDE-2[48] and STRIDE-4[37] included a sublicensed dose of 50 mg once daily (not considered in this review).

All three trials recruited mixed PAH populations of IPAH (ranging from 53% in STRIDE-1 to 68% in STRIDE-4), CTD-APAH (15–30% within each trial) and CHD (11–24% within each trial). The majority of patients in STRIDE-1 and STRIDE-2 were in FCIII at baseline (66% and 59% respectively), whereas in STRIDE-4 only 38% were in FCIII at baseline (the majority being in FCII: 61%). The primary end point was per cent of predicted peak oxygen uptake (VO_2) in STRIDE-1 and change in 6MWD in STRIDE-2 and STRIDE-4.

Quality assessment of the three trials is summarised in *Table 23* (only information relevant to the placebo and sitaxentan arms is listed). Methods of randomisation and allocation concealment were adequate in all three trials.[37,48,49] ITT analysis was used for most of the outcomes in STRIDE-1[49] and STRIDE-4.[37] STRIDE-2[48] excluded a small number of patients ([Academic-in-confidence information has been removed]) without a valid post-baseline 6MWT.

Sitaxentan (added to supportive treatment) versus supportive treatment

This comparison was investigated in all three trials.[37,48,49] Planned analyses and those actually carried out are summarised in *Table 24*. Results of the meta-analysis are listed in *Table 25* according to planned comparisons. Results for individual outcomes are described in the following subsections. As all three trials included patients with mixed FC, and data stratified by FC were available only for the outcome of change in FC, the findings presented in this section are mainly based on meta-analysis results of mixed PAH populations. Findings specifically for FCIII are stated separately when appropriate.

Survival

A total of three deaths were reported in the three trials, one in STRIDE-1 (sitaxentan 300-mg arm)[49] and two in STRIDE-2 (both in placebo arm).[48] The number is too small to draw any conclusions.

Time to clinical worsening

Clinical worsening was defined as death, epoprostenol use, atrial septostomy or transplantation in STRIDE-1.[49] A broader definition was used in STRIDE-2[48] and STRIDE-4,[37] which included hospitalisation for PAH, death, transplantation, atrial septostomy, initiation of new chronic PAH treatment, or combined WHO FC deterioration and ≥ 15% decrease in 6MWD from baseline. Time-to-event analysis for individual trials did not identify a statistically significant difference between any doses of sitaxentan and placebo. However, clinical worsening occurred more frequently in the placebo arm than in the sitaxentan arms across all three trials, and the pooled RR (mixed FC) for experiencing one or more clinical worsening events was significantly in favour of sitaxentan at the licensed dose (100 mg once daily) compared with placebo (RR = 0.33, 95% CI 0.12–0.87, $I^2 = 0\%$). Inclusion of the above licensed dose had little impact on the estimate.

Functional class

Table 25 shows that the proportion of patients who maintained or improved FC was significantly higher among patients treated with sitaxentan (licensed dose) than among those treated with placebo (RR = 1.10, 95% CI 1.04–1.16, $I^2 = 0\%$). The proportion of patients having FC improved was also significantly higher among sitaxentan (licensed dose)-treated patients than among placebo-treated patients (RR = 1.74, 95% CI 1.12–2.70, $I^2 = 0\%$). Inclusion of the above licensed dose had little impact on the estimates. The results specifically for FCIII patients for both outcomes were in the same direction, but did not reach statistical significance (see analysis A, *Table 25*).

Exercise capacity

The mean changes from baseline for 6MWD for the three trials[37,48,49] are shown in *Figure 8*. Sitaxentan at the licensed dose significantly increased the 6MWD compared with placebo (32 metres, 95% CI

TABLE 23 *Quality assessment of included sitaxentan trials*

Study; duration	Truly random allocation (strata for randomisation)	Adequate allocation concealment	Blinding	Use of ITT analysis[a] (*n* included in analysis/*N* randomised)	% of patients completing the trial	Comments
STRIDE-1/Barst *et al.*, 2004;[49] 12 weeks	Yes (centre)	Yes	Double-blind	Survival analysis: N/A; clinical worsening: yes; functional class: yes; 6MWD: yes; haemodynamic: yes; quality of life: no (176–177/178)	Placebo: 92% (55/60); sitaxentan 100 mg o.d.: 100% (55/55), sitaxentan 300 mg o.d.: 89% (56/63)	
STRIDE-2/Barst *et al.*, 2006;[48] 18 weeks	Yes	Yes	Double-blind for sitaxentan and placebo; open-label for bosentan	Survival analysis: N/A; clinical worsening: yes; functional class: no [Academic-in-confidence information has been removed];[b] 6MWD: no [Academic-in-confidence information has been removed];[b] haemodynamic: not measured; quality of life: not measured	Placebo: 82% (51/62); sitaxentan 50 mg o.d.: 87% (54/62), sitaxentan 100 mg o.d.: 93% (57/61)	Patients who did not have a valid post-baseline 6MWT were excluded from efficacy analysis
STRIDE-4/Barst, 2007;[37] 18 weeks	Yes (baseline 6MWD)	Yes	Double-blind	Survival analysis: no death; clinical worsening: yes; functional class: yes; 6MWD: yes; haemodynamic: not measured; quality of life: not measured	Placebo: 88% (30/34); sitaxentan 50 mg o.d.: 88% (28/32), sitaxentan 100 mg o.d.: 91% (29/32)	

6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; ITT, intention to treat; N/A, data not available; o.d., once daily.

a Defined as an analysis that includes all randomised patients (or all randomised patients who received at least one dose of study medication) according to the treatment group to which they were assigned, irrespective of actual treatment received or early withdrawal of treatment. N/A, data not available (outcome not measured in the trial or unclear if it was measured; analysis for the outcome not performed or unclear if it was performed). When analysis for the outcome was performed but the number of patients included was not reported, this was noted as 'unclear'. When ITT analysis was not used, the number of patients included in the analysis (or a range of numbers when more than one outcome was analysed/more than one analysis was performed with various numbers of patients used) over the number that should have been used in an ITT analysis is shown.

b Numbers refer to placebo and sitaxentan 100-mg arms only.

TABLE 24 *Analysis checklist – sitaxentan added to supportive treatment versus supportive treatment alone*

Planned analysis	Population/doses/data to be included	Analysis carried out	Comments and source of data
A. Primary analysis	All PAH, FCIII, licensed dose	Yes	Data stratified by FC were available only for the outcome of change in FC from STRIDE-2[48] and STRIDE-4[37]
B. Sensitivity analysis – mixed FC	All PAH, all FC, licensed dose	Yes	Data from STRIDE-1,[49] STRIDE-2[48] and STRIDE-4[37] were included
C. Sensitivity analysis – mixed pulmonary hypertension	All pulmonary hypertension including categories 1–5 of the Venice 2003 classification, all FC, licensed dose(s)	No	None of the sitaxentan trials included patients outside category 1 of the Venice 2003 classification
D. Sensitivity analysis – including above licensed dose	All PAH, all FC, licensed dose and above licensed dose	Yes	Data from the sitaxentan 300-mg arm were combined with data from the 100-mg arm and included in this analysis
E. Sensitivity analysis – excluding data designated as confidential	All PAH, all FC, licensed dose(s), excluding commercial-in-confidence and academic-in-confidence data	Yes	Confidential data that were included in analysis B were excluded from this analysis
F. Sensitivity analysis – excluding open-label trial	All PAH, all FC, licensed dose(s), excluding open-label trial	No	Not applicable (only bosentan arm in STRIDE-2[48] was open-label)
G. Subgroup analysis – IPAH	IPAH, all FC, licensed dose and above	No	Only limited data were available from STRIDE-1,[61] described in the text
H. Subgroup analysis – CTD-APAH	CTD-APAH, all FC, licensed dose and above	No	Only limited data were available from STRIDE-1,[61] described in the text

CTD-APAH, PAH associated with connective tissue disease; FC, functional class; IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension.

18–47, $I^2 = 0\%$) in patients with mixed FC. Data specifically for FCIII patients were not available.

Quality of life

Quality of life outcomes were measured only in the STRIDE-1 study[49] using the Short-Form 36 (SF-36). No significant differences between treatment groups were found.

Haemodynamic measures

Haemodynamic outcomes were measured only in the STRIDE-1 study.[49] The results, summarised in *Table 25*, show that sitaxentan at its licensed dose significantly reduced mPAP (–3.0 mmHg, 95% CI –5.9 to –0.1) and PVR (–270 dyn s/cm^5, 95% CI –402 to –138) and improved the cardiac index (0.3, 95% CI 0.1–0.5) compared with placebo in patients with mixed FC. Inclusion of the above licensed dose appeared to slightly increase the treatment effects (except PVR), and the reduction in RAP also reached statistical significance.

Other effectiveness measures

The Borg dyspnoea index was measured in STRIDE-2[48] and STRIDE-4.[37] There was no significant difference between the sitaxentan groups and the placebo groups.

Serious adverse events and other adverse events

Significantly fewer patients treated with sitaxentan (licensed dose) experienced one or more SAEs than those treated with placebo in the STRIDE-2 study (8/61 versus 19/62).[48] The pooled RR of the three trials was not statistically significant (mixed FC, RR = 0.55, 95% CI 0.27–1.12, $I^2 = 31\%$). The above licensed dose (300 mg once daily) appears to be associated with increased liver toxicity.[49] Common adverse events that occurred more frequently in the sitaxentan groups included: headache, peripheral oedema, nasal congestion and increased INR and/or prothrombin time prolonged (interaction with warfarin).[48,49]

Subgroup analysis – PAH subcategories

Results for the subgroup of patients with connective tissue disease (CTD-APAH) within the STRIDE-1 study were reported by Girgis and colleagues.[61] Data from the sitaxentan 100-mg and 300-mg arms were combined in this post hoc analysis.

TABLE 25 *Meta-analysis results: sitaxentan added to supportive treatment versus supportive treatment alone*

		Analysis (see analysis checklist)							
		A. Primary analysis		**B. Sensitivity analysis – mixed FC**		**D. Sensitivity analysis – including above licensed doses**		**E. Sensitivity analysis – excluding data designated as confidential**	
PAH population		All PAH subcategories		All PAH subcategories		All PAH subcategories		All PAH subcategories	
Functional class (FC)		FCIII		All FC		All FC		All FC	
Doses		Licensed dose (100 mg once daily)		Licensed dose (100 mg once daily)		Licensed dose and above (100 mg, 300 mg once daily)		Licensed dose (100 mg once daily)	
Total no. eligible for analysis		172[37,48,49]		304[37,48,49]		367[37,48,49]		304[37,48,49]	
No. included in analysis		95 (data stratified by FC were not available from STRIDE-1[49])		66–304 (haemodynamic outcomes were measured only in STRIDE-1[49])		178–367 (haemodynamic outcomes were measured only in STRIDE-1[49])		115–304 (confidential data from clinical trial reports were excluded)	
Outcomes	**Statistics**	***n***	**Effect size (95% CI)**	***n***	**Effect size (95% CI)**	***n***	**Effect size (95% CI)**	***n***	**Effect size (95% CI)**
Efficacy									
Death	RR	0	Data not available	304[37,48,49]	0.20 (0.01 to 4.15)	367[37,48,49]	0.53 (0.06 to 4.73)	304[37,48,49]	0.20 (0.01 to 4.15)
Clinical worsening	RR	0	Data not available	304[37,48,49]	**0.33 (0.12 to 0.87)[a]**	367[37,48,49]	**0.32 (0.12 to 0.81)[a]**	304[37,48,49]	**0.33 (0.12 to 0.87)[a]**
FC improved	RR	95[37,48]	1.53 (0.74 to 3.17)	302[37,48,49]	**1.74 (1.12 to 2.70)[a]**	365[37,48,49]	**1.76 (1.15 to 2.70)[a]**	302[37,48,49]	**1.74 (1.12 to 2.70)[a]**
FC maintained or improved	RR	95[37,48]	1.11 (1.00 to 1.23)	302[37,48,49]	**1.10 (1.04 to 1.16)[a]**	365[37,48,49]	**1.09 (1.03 to 1.15)[a]**	302[37,48,49]	**1.10 (1.04 to 1.16)[a]**

Outcomes	Statistics	*n*	Effect size (95% CI)	*n*	Effect size (95% CI)	*n*	Effect size (95% CI)	*n*	Effect size (95% CI)
Withdrawal for any reason	RR	0	Data not available	304[37,48,49]	**0.43 (0.19 to 0.98)[a]**	367[37,48,49]	0.57 (0.29 to 1.12)	238[48,49]	**0.31 (0.11 to 0.87)[a]**
6-minute walk distance (metres)[b]	WMD	0	Data not available	302[37,48,49]	**32 (18 to 47)[a]**	365[37,48,49]	**32 (18 to 46)[a]**	302[37,48,49]	**32 (18 to 47)[a]**
Haemodynamics									
Mean pulmonary arterial pressure (mPAP) (mmHg)[c]	WMD	0	Data not available	115[49]	**–3.0 (–5.9 to –0.1)[a]**	178[49]	**–4.0 (–6.7 to –1.3)[a]**	115[49]	**–3.0 (–5.9 to –0.1)[a]**
Right atrial pressure (RAP) (mmHg)[c]	WMD	0	Data not available	115[49]	–1.0 (–2.5 to 0.5)	178[49]	**–1.5 (–2.8 to –0.3)[a]**	115[49]	–1.0 (–2.5 to 0.5)
Pulmonary vascular resistance (PVR) (dyn s/cm^5)[c]	WMD	0	Data not available	115[49]	**–270 (–402 to –138)[a]**	178[49]	**–256 (–349 to –163)[a]**	115[49]	**–270 (–402 to –138)[a]**
Cardiac index (l/min/m^2)[b]	WMD	0	Data not available	115[49]	**0.3 (0.1 to 0.5)[a]**	178[49]	**0.4 (0.2 to 0.5)[a]**	115[49]	**0.3 (0.1 to 0.5)[a]**
Safety									
Serious adverse events	RR	0	Data not available	304[37,48,49]	0.55 (0.27 to 1.12)	367[37,48,49]	0.65 (0.37 to 1.15)	115[49]	0.35 (0.10 to 1.23)

CI, confidence interval; FC, functional class; RR, relative risk; PAH, pulmonary arterial hypertension; WMD, weighted mean difference.
a Statistically significant result.
b Mean change from baseline; positive value favours sitaxentan.
c Mean change from baseline; negative value favours sitaxentan.

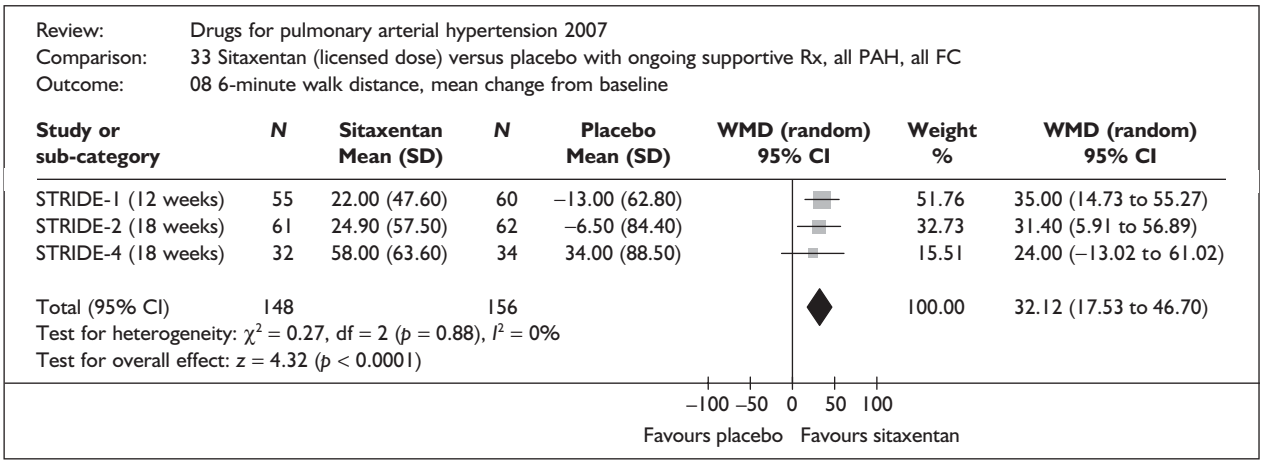

FIGURE 8 *Sitaxentan added to supportive treatment versus supportive treatment alone – change in 6-minute walk distance. CI, confidence interval; FC, functional class; PAH, pulmonary arterial hypertension; WMD, weighted mean difference.*

The mean 6MWD increased by 20 metres (SD 52) from baseline in the combined sitaxentan group ($n = 33$) and decreased by 38 metres (SD 84) in the placebo group ($n = 9$) after 12 weeks of treatment ($p = 0.027$). Significant improvements for sitaxentan-treated patients compared with placebo-treated patients were also observed in haemodynamic measures, including RAP, PVR and cardiac index. More sitaxentan-treated patients improved FC than placebo-treated patients (8/33 versus 1/9, $p = 0.14$). In contrast to the overall trial results, which showed no significant treatment effect in all six domains of the SF-36, significant improvements in the physical functioning and role–physical domains were observed.

The authors also compared data from the CTD-APAH population with data from the IPAH population within the trial.[61] No significant differences between the two cohorts were observed in any of the efficacy measures. Significant improvements in the physical functioning domain of the SF-36 were also observed in the IPAH subgroup.

Summary and discussion

- Three RCTs comparing sitaxentan with placebo with ongoing supportive treatment were identified. All three trials (STRIDE-1,[49] STRIDE-2,[48] STRIDE-4[37]) were industry-sponsored, international, double-blind studies with a study duration of 12–18 weeks. The licensed dose for sitaxentan (100 mg once daily) was investigated in all of the trials.
- Methods of randomisation and allocation concealment were adequate in all three trials. ITT analysis was used in STRIDE-1[49] and STRIDE-4,[37] but not in STRIDE-2.[48] The potential bias due to exclusion of a small number of patients from efficacy analysis in STRIDE-2[48] was unclear, but the impact on the pooled results of the meta-analysis is likely to be small.
- All three trials included mixed populations of patients with IPAH, CTD-APAH and PAH associated with CHD. The mean 6MWD at baseline ranged from 337 metres[48] to 398 metres.[49] Patients were of mixed FC, with 66% and 59% in FCIII at baseline for STRIDE-1[49] and STRIDE-2[48] respectively. The majority of patients (61%) in STRIDE-4 were in FCII at baseline.
- Data stratified by FC were available only for the outcome of change in FC. Results presented in this section were largely based on a patient population with mixed FC.
- Compared with supportive treatment alone, sitaxentan at its licensed dose (added to supportive treatment) significantly reduced the risk of clinical worsening, increased exercise capacity (6MWD), and improved FC and haemodynamic outcomes (mPAP, PVR and cardiac index) in PAH populations with mixed FC. Improvement in FC was observed in FCIII patients, but this did not reach statistical significance.
- Post hoc analysis suggested that the treatment effects of sitaxentan observed in the subgroup of CTD-APAH were similar to those observed in the whole trial population.[61] No significant differences were found between the IPAH and CTD-APAH subgroups across various efficacy outcomes. The additional positive finding in physical health-related quality of life in the post hoc analysis needs to be interpreted with caution and requires further confirmation in future studies with prospectively planned analysis.

Sildenafil

Quantity and quality of included studies

Sildenafil was investigated in six of the included RCTs. Four of these [SUPER-1 (Sildenafil Use in Pulmonary Arterial Hypertension study),[53] Bharani *et al*.,[35] Sastry *et al*.,[54] Singh *et al*.[55]] compared sildenafil with placebo in patients with ongoing supportive treatment (patients in Bharani *et al*.[35] appeared to have stopped previous vasodilator therapy before entering the study). Another trial (PACES-1[38]), identified through manufacturer submission, compared sildenafil with placebo in patients with ongoing epoprostenol and supportive treatment. The characteristics of these five studies are summarised in *Table 26*. Sildenafil was compared with bosentan in a further study by Wilkins and colleagues (SERAPH),[57] which will be described later in this chapter [see Direct (head-to-head) comparisons].

The SUPER-1[53] and PACES-1[38] trials were industry-sponsored international studies that randomised 278 and 267 patients respectively. The clinical study reports (commercial-in-confidence) for both trials were made available to the assessment group by Pfizer. The study duration was 12 weeks for SUPER-1[53] and 16 weeks for PACES-1. The studies by Bharani *et al*.,[35] Sastry *et al*.[54] and Singh *et al*.[55] were small ($n = 10$, 22 and 20 respectively) single-centre, cross-over trials conducted in India. The study by Sastry and colleagues[54] was sponsored by a not-for-profit organisation and the sponsorship for Bharain *et al*.[35] and Singh *et al*.[55] was not reported. The cross-over trials had a duration of 2[35]–6[54,55] weeks for each treatment period. The doses investigated in these trials varied, but only the SUPER-1 study[53] included a treatment arm using the licensed dose (20 mg three times daily). Above licensed doses of up to 80 mg three times daily were also investigated in the SUPER-1 trial[53] and in all of the other trials (see *Table 26*).

Both the SUPER-1[53] and PACES-1[38] trials recruited mixed PAH populations of IPAH and CTD-APAH. The SUPER-1 study also included 6% of patients with CHD. The majority of patients in both trials were in FCIII at baseline; there were 39% and 26% of patients in FCII at baseline for the SUPER-1 and PACES-1 trials respectively. The primary end point was change in 6MWD for both trials. Bharani *et al*.[35] recruited patients in FCII–IV at baseline with various types of pulmonary hypertension including PPH, PAH associated with Eisenmenger syndrome and other forms of pulmonary hypertension. Sastry *et al*. recruited exclusively PPH patients, the majority of which (82%) were in FCII at baseline.[54] Singh *et al*.[55] recruited mixed populations of IPAH and Eisenmenger syndrome patients and the study included a significant proportion of children (as young as 3 years old). Given the large proportion of the study populations being outside sildenafil's licensed indication in Bharani *et al*.,[35] Sastry *et al*.[54] and Singh *et al*.,[55] and their small sample sizes, the characteristics and study results of these three trials are only briefly listed/mentioned in the following sections and data from these studies were not meta-analysed.

Quality assessment of the five trials is summarised in *Table 27*. Both SUPER-1[53] and PACES-1[38] used adequate methods of randomisation and allocation concealment. ITT analysis was not used as the primary analysis, but was used as sensitivity analysis for a few outcomes. The proportion of patients who completed the trials was similar between treatment arms in SUPER-1, and was [Commercial-in-confidence information has been removed].

Because of the different nature of the comparisons between the trials, the results of SUPER-1 and PACES-1 will be described separately [see Direct (head-to-head) comparisons].

Sildenafil added to supportive treatment versus supportive treatment alone

This comparison was investigated in SUPER-1,[53] Bharani *et al*.,[35] Sastry *et al*.[54] and Singh *et al*.[55] As previously stated, results from the last three trials will only be briefly mentioned and will not be combined with results from SUPER-1[53] because of the minimal relevance of their study populations to this technology appraisal. The findings presented in this section are therefore mainly based on a single trial (SUPER-1[53]) rather than meta-analysis, but results will be presented in a format similar to previous sections. Planned comparisons and those actually available are summarised in *Table 28*. The results from SUPER-1 are listed in *Table 29* according to planned comparisons. Results for individual outcomes are described in the following subsections. As data stratified by FC were only available for the outcome of change in FC, results described were mainly drawn from data of mixed FC. Findings specifically for FCIII are stated separately when appropriate.

Survival

A total of four deaths were reported in the SUPER-1 trial (one in the placebo arm, one in the 20-mg arm and two in the 80-mg arm).[53] The number was too small to draw any conclusions.

TABLE 26 *Characteristics of included sildenafil trials*

Trial name/key paper (protocol number); location/ centres	Duration; design; number of patients randomised	Intervention[a]	Comparator[a]	Type of PAH	Functional class	Age (years), mean (SD, range); % female	Baseline exercise capacity and haemodynamic measures,[b] mean (SD)
Sildenafil vs placebo with ongoing supportive treatment							
SUPER-1/Galiè *et al*., 2005[53] (A1481140); international, 53 centres	12 weeks; double-blind, parallel; $n = 278$	Sildenafil (oral) 20 mg t.i.d. ($n = 69$), 40 mg t.i.d. ($n = 67$), 80 mg t.i.d. ($n = 71$)	Placebo ($n = 70$)	IPAH (63%), CTD (30%), repaired congenital S–P shunts (6%)	I (0.4%), II (39%), III (58%), IV (3%)	49 (15); 75%	6MWD: 344 (81); cardiac index: 2.4 (0.7); mPAP: 53 (15); PVR: 957 (509); RAP: 9 (5); SvO_2: NR
Bharani *et al*., 2003;[35] India, single centre	2×2 weeks (with washout period of ≥ 2 weeks); double-blind, cross-over; $n = 10$	Sildenafil (oral) 25 mg t.i.d.	Placebo	PPH (30%), Eisenmenger syndrome (30%), non-PAH (30%)[c]	II (33%), III (56%), IV (11%)	32 (15, 18–60); 56%	6MWD: 164; cardiac index: NR; mPAP: NR; PVR: NR; RAP: NR; SvO_2: NR
Sastry *et al*., 2004;[54] India, single centre	2×6 weeks (no washout period); double-blind, cross-over; $n = 22$	Sildenafil (oral) 25–100 mg t.i.d. depending on body weight[d] ($n = 10$ receiving sildenafil first)	Placebo ($n = 12$ receiving placebo first)	PPH (100%)	II (82%), III (18%)	NR (16–55); 55%	6MWD: NR; cardiac index: 2.8 (1.1); mPAP: NR; PVR: NR; RAP: NR; SvO_2: NR
Singh *et al*., 2006;[55] India, single centre	2×6 weeks with a 2-week washout period; double-blind, cross-over; $n = 20$	Sildenafil (oral) 25–100 mg t.i.d. depending on body weight	Placebo	IPAH (50%), Eisenmenger syndrome (50%)	II (40%), III (55%), IV (5%)	NR (3–45); 75%	6MWD: 262 (99); cardiac index: NR; mPAP: NR; PVR: NR; RAP: NR; SvO_2: NR

Trial name/key paper (protocol number); location/ centres	Duration; design; number of patients randomised	Intervention[a]	Comparator[a]	Type of PAH	Functional class	Age (years), mean (SD, range); % female	Baseline exercise capacity and haemodynamic measures,[b] mean (SD)
Sildenafil vs placebo with ongoing epoprostenol and supportive treatment							
PACES-1 (A1481141);[38] international, multicentre	16 weeks; double-blind, parallel; $n = 267$	Sildenafil (oral) started 20 mg t.i.d., uptitrated to 80 mg t.i.d. by week 8 if tolerated + ongoing epoprostenol (individualised optimal dose) ($n = 134$)	Placebo + ongoing epoprostenol (individualised optimal dose) ($n = 133$[e])	PPH (79%), CTD (21%)	$n = 257$; I (1%), II (26%), III (67%), IV (5%)	48 (13, 18–75); 80%	6MWD: NR; cardiac index: NR; mPAP: NR; PVR ($n = 164$): [Commercial-in-confidence information has been removed]; RAP: [Commercial-in-confidence information has been removed]; SvO_2: [Commercial-in-confidence information has been removed]

6MWD, 6-minute walk distance; CTD, PAH associated with connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; NR, not reported; PAH, pulmonary arterial hypertension; PPH, primary pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; S–P, systemic-to-pulmonary; SD, standard deviation; SvO_2, mixed venous oxygen saturation; t.i.d.: three times daily.

a With ongoing conventional therapy unless otherwise specified.

b Units are: 6MWD, metres; cardiac index, l/min/m^2; mPAP, mmHg; PVR, dyn s/cm^5; RAP, mmHg; SvO_2, %.

c Including two patients with interstitial lung disease and one patient with PAH associated with thromboembolism; information regarding one patient who did not complete the study was not reported.

d Patients weighing up to 25 kg received 25 mg three times daily; those weighing between 26 and 50 kg received 50 mg three times daily; and those weighing > 51 kg received 100 mg three times daily.

e Two of these patients did not receive any study medication.

TABLE 27 *Quality assessment of included sildenafil trials*

Study; duration	Truly random allocation (strata for randomisation)	Adequate allocation concealment	Blinding	Use of ITT analysis[a] (*n* included in analysis/*N* randomised)	% of patients completing the trial	Comments
Sildenafil vs placebo with ongoing supportive treatment						
SUPER-1/Galiè *et al.*, 2005;[53] 12 weeks	Yes (baseline 6MWD and cause of PAH)	Yes	Double-blind	Survival: yes; clinical worsening: yes; functional class: no (273/277); 6MWD: yes; haemodynamic: no (258/277); quality of life: N/A	Placebo: 97% (68/70); sildenafil 20 mg t.i.d.: 97% (67/69), 40 mg t.i.d.: 97% (65/67), 80 mg t.i.d.: 92% (65/71)	Primary analysis for 6MWD excluded patients without baseline and at least one post-baseline measurement ($n = 266$), but ITT analysis was performed as a sensitivity analysis
Bharani *et al.*, 2003;[35] 2×2 weeks	Unclear	Unclear	Double-blind	Survival: no death; clinical worsening: N/A; functional class: unclear; 6MWD: unclear; haemodynamic: unclear; quality of life: N/A	90% (9/10)	
Sastry *et al.*, 2004;[54] 2×6 weeks	Yes	Unclear	Double-blind	Survival: yes; clinical worsening: N/A; functional class: N/A; 6MWD: N/A; haemodynamic: N/A; quality of life: yes	At week 6: placebo: 92% (11/12); sildenafil: 90% (9/10)	
Singh *et al.*, 2006;[55] 2×6 weeks	Unclear	Yes	Double-blind	Survival: N/A; clinical worsening: N/A; functional class: unclear; 6MWD: unclear; haemodynamic: unclear; quality of life: N/A	Not reported	
Sildenafil vs placebo with ongoing epoprostenol and supportive treatment						
PACES-1;[38] 16 weeks	Yes (baseline 6MWD, PAH subcategory)	Yes	Double-blind	Survival: yes; clinical worsening: yes; functional class: no (257/265); 6MWD: no (250–[Commercial-in-confidence information has been removed]/265); haemodynamic: no ([Commercial-in-confidence information has been removed]/265); quality of life: no (234–242/265)	Placebo: 82% (108/131); sildenafil: 91% (122/134)	Patients with missing baseline 6MWT or no post-baseline 6MWT were excluded from the 6MWD analysis

6MWD, 6-minute walk distance; ITT, intention to treat; N/A, data not available; PAH, pulmonary arterial hypertension; t.i.d., three times daily.

a Defined as an analysis that includes all randomised patients (or all randomised patients who received at least one dose of study medication) according to the treatment group to which they were assigned, irrespective of actual treatment received or early withdrawal of treatment. N/A, data not available (outcome not measured in the trial or unclear if it was measured; analysis for the outcome not performed or unclear if it was performed). When analysis for the outcome was performed but the number of patients included was not reported, this was noted as 'unclear'. When ITT analysis was not used, the number of patients included in the analysis (or a range of numbers when more than one outcome was analysed/more than one analysis was performed with various numbers of patients used) over the number that should have been used in an ITT analysis is shown.

TABLE 28 *Comparison checklist – sildenafil added to supportive treatment versus supportive treatment alone*

Planned comparison	Population/doses/data to be included	Comparison listed	Comments and source of data
A. Primary analysis	All PAH, FCIII, licensed dose	Yes	Data stratified by FC were available only for the outcome of change in FC
B. Sensitivity analysis – mixed FC	All PAH, all FC, licensed dose	Yes	The comparison between sildenafil 20 mg three times daily and placebo from the SUPER-1 study[53] was included
C. Sensitivity analysis – mixed pulmonary hypertension	All pulmonary hypertension including categories 1–5 of the Venice 2003 classification, all FC, licensed dose(s)	No	SUPER-1[53] did not include pulmonary hypertension other than PAH
D. Sensitivity analysis – including above licensed doses	All PAH, all FC, licensed dose and above licensed doses	Yes	Data from all three sildenafil arms (20 mg, 40 mg and 80 mg three time daily) in the SUPER-1 study[53] were combined
E. Sensitivity analysis – excluding data designated as confidential	All PAH, all FC, licensed dose(s), excluding commercial-in-confidence and academic-in-confidence data	No	Not applicable (results from a single trial – data designated as confidential are highlighted)
F. Sensitivity analysis – excluding open-label trial	All PAH, all FC, licensed dose(s), excluding open-label trial	No	Not applicable
G. Subgroup analysis –IPAH	IPAH, all FC, licensed dose	No	Stratified data were not available. Data for mixed FC were available for 6MWD and were described in the text
H. Subgroup analysis – CTD-APAH	CTD-APAH, all FC, licensed dose	No	Stratified data were not available. Data for mixed FC were available for 6MWD and were described in the text

CTD-APAH, PAH associated with connective tissue disease; FC, functional class; IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension.

Time to clinical worsening

Clinical worsening was defined in the SUPER-1 trial[53] as death, transplantation, hospitalisation for PAH or initiation of additional therapies for PAH, such as intravenous epoprostenol or oral bosentan. Time-to-event analysis was carried out. No significant increase in time to clinical worsening or decrease in the incidence of clinical worsening was found in the sildenafil groups compared with the placebo group.

Functional class

Table 29 shows that the difference in the proportion of patients who maintained or improved FC between the placebo group and the sildenafil group(s) (20 mg three times daily or three doses combined) was in favour of sildenafil, but just failed to reach statistical significance. The proportion of patients having FC improved was significantly higher in the sildenafil 20 mg three times daily group than in the placebo group (mixed FC, RR = 3.91, 95% CI 1.55–9.88). The RR increased further when the two higher-dose sildenafil groups were included (mixed FC, RR = 4.97, 95% CI 2.09–11.79). The result of having FC improved specifically for FCIII patients [Commercial-in-confidence information removed].

Exercise capacity

A significant increase in 6MWD for the sildenafil 20 mg three times daily group compared with the placebo group was observed (38 metres, 95% CI 12–64). The increase appeared to be slightly larger with high doses, although the differences between doses were not statistically significant.

Quality of life

Quality of life outcomes were not reported in the published paper for SUPER-1[53] but were reported in Pfizer's submission to NICE. It stated that improvements in all domains of the SF-36 (physical functioning, role–physical, bodily pain, general health, vitality, social functioning, role–emotional and mental health) were observed in the sildenafil groups compared with the placebo group with the exception of role–physical for sildenafil 20 mg three times daily and role–emotional for sildenafil 40 mg three times daily. Statistical testing for these comparisons was not performed according to the study protocol, but the differences may not have

TABLE 29 *Results from SUPER-1: sildenafil added to supportive treatment versu s supportive treatment alone*

		Analysis (see comparison checklist)					
		A. Primary analysis		**B. Sensitivity analysis – mixed FC**		**D. Sensitivity analysis – including above licensed doses**	
PAH population		All PAH subcategories		All PAH subcategories		All PAH subcategories	
Functional class (FC)		FCIII		All FC		All FC	
Doses		Licensed dose (20 mg three times daily)		Licensed dose (20 mg three times daily)		Licensed dose and above (20 mg, 40 mg and 80 mg three times daily)	
Total no. eligible for analysis		74[53]		139[53]		277[53]	
No. included in analysis		0–74		130–139		258–277	
Outcomes	**Statistics**	***n***	**Effect size (95% CI)**	***n***	**Effect size (95% CI)**	***n***	**Effect size (95% CI)**
Efficacy							
Death	RR	0	Data not available	139[53]	1.01 (0.06 to 15.90)	277[53]	1.01 (0.11 to 9.60)
Clinical worsening	RR	0	Data not available	139[53]	0.43 (0.12 to 1.61)	277[53]	0.48 (0.19 to 1.22)
Functional class improved	RR	74[53]	[Commercial-in-confidence data has been removed]	138[53]	**3.91 (1.55 to 9.88)[a]**	273[53]	**4.97 (2.09 to 11.79)[a]**
Functional class maintained or improved	RR	74[53]	[Commercial-in-confidence data has been removed]	138[53]	1.08 (0.99 to 1.18)	273[53]	1.08 (0.99 to 1.17)
Withdrawal for any reason	RR	0	Data not available	139[53]	[Commercial-in-confidence data has been removed]	277[53]	[Commercial-in-confidence data has been removed]
6-minute walk distance (metres)[b]	WMD	0	Data not available	139[53]	**38 (12 to 64)[a]**	141[53d]	**42 (9 to 75)[a,d]**

Outcomes	Statistics	*n*	Effect size (95% CI)	*n*	Effect size (95% CI)	*n*	Effect size (95% CI)
Haemodynamics							
Mean pulmonary arterial pressure (mPAP) (mmHg)[c]	WMD	0	Data not available	130[53]	**–2.7 (–5.3 to –0.1)[a]**	258[53]	**–3.7 (–5.5 to –1.9)[a]**
Right atrial pressure (RAP) (mmHg)[c]	WMD	0	Data not available	130[53]	–1.1 (–2.7 to 0.5)	258[53]	–1.3 (–2.7 to 0.1)
Pulmonary vascular resistance (PVR) (dyn s/cm^5)[c]	WMD	0	Data not available	130[53]	**–171 (–311 to –31)[a]**	258[53]	**–225 (–341 to –109)[a]**
Cardiac index (l/min/m^2)[c]	WMD	0	Data not available	130[53]	0.2 (0.0 to 0.5)	258[53]	**0.3 (0.1 to 0.5)[a]**
Safety							
Serious adverse events	RR	0	Data not available	139[53]	0.85 (0.39 to 1.83)	277[53]	0.82 (0.44 to 1.51)

CI, confidence interval; PAH, pulmonary arterial hypertension; RR, relative risk; WMD, weighted mean difference.
a Statistically significant result.
b Mean change from baseline; positive value favours sildenafil.
c Mean change from baseline; negative value favours sildenafil.
d Data were insufficient for combining the three sildenafil doses; comparison between sildenafil 80 mg three times daily and placebo is shown.

been statistically significant in the bodily pain and role–emotional domains for any of the three doses according to the data presented. There appears to be no consistent pattern between the sildenafil doses and their effects on the various domains of the SF-36. The EuroQol 5 dimensions (EQ-5D) utility index was unchanged in the placebo and sildenafil 40 mg three times daily groups (mean change from baseline 0.0, 95% CI 0.0–0.1) and was slightly increased in the sildenafil 20 mg and 80 mg three times daily groups (0.1, 95% CI 0.1–0.2). Data specifically for FCIII patients were not available.

Haemodynamic measures

Table 29 shows that sildenafil at its licensed dose significantly reduced mPAP (–2.7 mmHg, 95% CI –5.3 to –0.1) and PVR (–171 dyn s/cm^5, 95% CI –311 to –31) compared with placebo in patients with mixed FC. Inclusion of above licensed doses consistently increased treatment effects across the haemodynamic measures and the increase in cardiac output also reached statistical significance.

Other effectiveness measures

There was no significant difference in the change in Borg dyspnoea index for the sildenafil groups compared with the placebo group.

Serious adverse events and other adverse events

The risk of experiencing at least one SAE was similar between treatment groups (mixed FC, RR = 0.82, 95% CI 0.44–1.51 for sildenafil groups combined versus placebo). Common adverse events that occurred more frequently in the sildenafil groups include: headache, flushing, diarrhoea, dyspepsia, pain in limb, myalgia and pyrexia.[53]

Subgroup analysis – PAH subcategories

Treatment effects on 6MWD among various subgroups of patients, defined according to demographic features, disease characteristics and baseline variables, were examined descriptively in the SUPER-1 study.[53] The treatment effect at the licensed dose did not differ significantly between PPH and CTD-APAH subgroups: 40 metres (95% CI 14–66) versus 55 metres (95% CI 25–85) respectively (test for heterogeneity: $\chi^2 = 0.55$, df = 1, $p = 0.46$).

Results from cross-over trials

All three short-term cross-over trials[35,54,55] reported significant improvements in exercise capacity and haemodynamic measures for sildenafil (at above licensed doses) compared with placebo.

Summary and discussion

- Four RCTs comparing sildenafil (added to supportive treatment) with supportive treatment alone were identified. The SUPER-1 study[53] was the pivotal trial for this comparison and was the only trial that investigated the licensed dose for sildenafil (20 mg three times daily). It was an international, double-blind study with a duration of 12 weeks. Three further single-centre, cross-over trials[35,54,62] included predominantly patients outside the scope of this technology appraisal and used sildenafil only at above licensed doses.
- Methods of randomisation and allocation concealment were adequate in SUPER-1.[53] The primary analyses reported in this study excluded some patients with missing data and thus were not based on the ITT principle. However, ITT analyses were performed as sensitivity analyses and the results were consistent with the primary analyses.
- The majority of patients included in the SUPER-1 study had IPAH. Patients with CTD-APAH and PAH associated with CHD were also included. The mean 6MWD at baseline was 344 metres. Patients were of mixed FC; 58% were in FCIII and 39% in FCII at baseline.
- Data stratified by FC were available only for the outcome of change in FC. Results presented below were largely based on a patient population of mixed FC.
- Compared with supportive treatment alone, sildenafil at its licensed dose (added to supportive treatment) demonstrated significant improvements in exercise capacity (6MWD), haemodynamic outcomes (mPAP and PVR) and certain domains of quality of life measures and improvement in FC in PAH populations with mixed FC. Above licensed doses up to 80 mg three times daily appear to increase the treatment effect for these outcomes, although the differences between doses were not statistically significant in the trial. No significant improvement in time to clinical worsening and the symptom of dyspnoea was observed.
- The treatment effect of sildenafil on 6MWD was similar in the PPH and CTD-APAH groups.

Sildenafil added to ongoing epoprostenol versus ongoing epoprostenol

This comparison was investigated in the PACES-1 trial.[38]This study remained unpublished at the time of completion of this technology assessment. Data presented in this section were largely obtained from Pfizer's submission to NICE for this technology appraisal. Additional data were sought from the

clinical study report (commercial-in-confidence) of this study, which was made available to the assessment group by Pfizer. The characteristics and quality assessment of the PACES-1 study are shown in *Tables 26* and *27* respectively.

As the results presented in this section were based on a single trial and the dose of sildenafil used (80 mg three times daily) was above its licensed dose, only a narrative summary of the study findings is provided. Most of the findings were based on the whole trial population, which included mixed types of PAH (IPAH and CTD-APAH) and mixed FC (I–IV).

Findings

Seven deaths occurred in the placebo group and one in the sildenafil group. The difference between groups just failed to reach statistical significance (RR = 0.14, 95% CI 0.02–1.12). Clinical worsening was defined in this trial as death, lung transplantation, hospitalisation due to PAH, initiation of bosentan therapy or change in epoprostenol dose because of clinical deterioration. Time-to-event analysis showed that a significantly lower proportion of patients treated with sildenafil 80 mg three times daily compared with those treated with placebo experienced clinical worsening (stratified log-rank test $p = 0.012$). The difference was also significant when analysed as a dichotomous outcome (RR = 0.36, 95% CI 0.16–0.77). Significantly fewer patients in the sildenafil group withdrew from the study compared with the placebo group (RR = 0.51, 95% CI 0.26–0.98).

The proportion of patients with FC improved or maintained was not significantly different between the sildenafil group and the placebo group (mixed FC, RR = 1.06, 95% CI 0.98–1.15; FCIII only, RR = 1.04, 95% CI 0.96–1.12), but significantly more patients treated with sildenafil had their FC improved (mixed FC, RR = 2.47, 95% CI 1.52–4.02; FCIII only, RR = 1.95, 95% CI 1.16–3.29). Patients treated with sildenafil also had a greater improvement in 6MWD (mean difference 26 metres, 95% CI 11–41) and in various domains (physical functioning, role limitation due to physical problems, bodily pain, general health, vitality, social functioning and mental health) of the SF-36 questionnaire (but not role limitation due to emotional problems). No significant differences were found between treatment groups in the change from baseline in Borg dyspnoea score (no change in median score in both groups) and the EQ-5D utility index (increased by 0.052 for the sildenafil group and by 0.022 for the placebo group). Significant reductions in mPAP, RAP and PVR were also observed in the sildenafil group compared with the placebo group. The analyses of all of the above outcomes (FC, 6MWD, Borg dyspnoea index, quality of life and haemodynamic measures) were not based on the ITT principle, and more patients in the placebo group than in the sildenafil group were excluded from the analyses.

SAEs were experienced by 29/134 patients in the sildenafil group and 39/131 in the placebo group (RR = 0.73, 95% CI 0.48–1.10). Common adverse events that occurred more frequently in the sildenafil group than in the placebo group included: headache, diarrhoea, nausea, flushing, dyspepsia and nasal congestion.

The mean change from baseline in 6MWD appeared to be greater in the subgroup of patients with IPAH (31 metres, 95% CI 14–49) than in the subgroup of patients with CTD-APAH (8 metres, –23 to 38); however, the difference was not statistically significant (test for heterogeneity $\chi^2 = 1.80$, df = 1, $p = 0.18$).

Summary and discussion

- One double-blind RCT (PACES-1[38]) compared sildenafil 80 mg three times daily (above licensed dose) with placebo in patients who were receiving ongoing epoprostenol and supportive treatment.
- Methods of randomisation and allocation concealment were adequate in PACES-1. ITT analysis was not used for most outcomes. More patients in the placebo group than in the sildenafil group were excluded from analyses because of missing data. The potential bias would be in favour of placebo if the excluded patients had worse outcomes.
- Results from PACES-1 indicated that patients treated with sildenafil 80 mg three times daily had a significantly lower risk of clinical worsening and a greater improvement in FC, 6MWD, some domains of quality of life measures and haemodynamic measures (mPAP, RAP and PVR). There were no significant differences between the sildenafil and placebo groups in changes in Borg dyspnoea score, the EQ-5D utility index and risk of SAEs.
- The trial included mixed PAH populations (IPAH and CTD-APAH) with mixed FC (67% FCIII). Changes in 6MWD were not significantly different between the IPAH and CTD-APAH groups. Results of changes in FC for patients in FCIII at baseline were similar to results of the overall trial population.

Direct (head-to-head) comparisons

Quantity and quality of included studies

Direct comparisons between the five technologies under assessment in this review were made in two of the included RCTs. Bosentan was compared with sitaxentan (both at the licensed dose) in the STRIDE-2 study.[48] The comparisons in this trial of both drugs with placebo have been included in the bosentan and sitaxentan sections respectively. Bosentan (licensed dose) was compared with sildenafil (above licensed dose) in a further study (SERAPH) by Wilkins and colleagues.[57] The characteristics of these two studies are summarised in *Table 30* (STRIDE-2[48] is listed again for the convenience of readers; only relevant treatment arms are listed). Additional comparisons involving combinations of the technologies under assessment (iloprost added to ongoing bosentan versus ongoing bosentan; epoprostenol plus bosentan versus epoprostenol alone) have been described in the iloprost and bosentan sections respectively.

The study characteristics and quality assessment of the STRIDE-2 study[48] have been described in previous sections. The SERAPH study[57] was a 16-week, single-centre trial that randomised 26 patients. It was conducted in the Hammersmith Hospital, London and was funded by the British Heart Foundation. The dose of sildenafil used was 50 mg twice daily for the first 4 weeks, uptitrated to 50 mg three times daily thereafter (above licensed dose). The trial recruited exclusively patients in FCIII at baseline and the majority of patients had IPAH (23/26) with the rest having CTD-APAH. The mean 6MWD at baseline was 297 metres. The primary end point for SERAPH was change in right ventricular mass from baseline as measured by cardiovascular magnetic resonance.[57]

The methods of randomisation and allocation concealment in the SERAPH study were adequate. Both ITT analysis and per-protocol analysis (including patients who completed the trial) were used. Except for one patient who died during the study, no patient was withdrawn from treatment.[57] The quality assessment for STRIDE-2 and SERAPH is summarised in *Table 31*.

Sitaxentan versus bosentan with ongoing supportive treatment

The results presented in this section are from STRIDE-2[48] rather than from meta-analysis, as this study was the only one that investigated this comparison. Planned comparisons and those actually performed are summarised in *Table 32*. Results are listed in *Table 33* according to the planned comparisons, followed by a paragraph summarising the findings. As STRIDE-2 included patients with mixed FC, and data stratified by FC were available only for the outcome of change in FC, the findings presented are mainly based on the results of mixed PAH populations. Findings specifically for FCIII are stated separately when appropriate.

Findings

No deaths occurred in either treatment group. The number of patients with the following events was larger in the bosentan arm than in the sitaxentan 100-mg arm: clinical worsening (9/60 versus 4/61), withdrawal for any reason (8/60 versus 4/61) and FC worsened (5/[Commercial-in-confidence information has been removed] versus 1/[Commercial-in-confidence information has been removed]). However, these numbers were small and the differences between groups were not statistically significant. The numbers of patients having FC improved and experiencing at least one SAE were similar between the two groups; in addition, the changes in 6MWD and Borg dyspnoea index were also similar between the two groups. Change in FC did not differ significantly between groups for patients in FCIII at baseline. Quality of life and haemodynamic outcomes were not measured in STRIDE-2.[48]

Sildenafil versus bosentan with ongoing supportive treatment

This comparison was investigated in the SERAPH study.[57] As the dose used in the study was above the licensed dose and the number of patients randomised was small ($n = 26$), only a narrative summary is provided below.

Findings

One death occurred in this trial. The patient who was assigned to sildenafil died suddenly at week 14. Clinical worsening and changes in FC were not reported in this trial. ITT analysis, in which the patient who died was assigned a 6MWD of 0 metres at week 16, showed no significant difference in the mean change from baseline in 6MWD between the sildenafil group (increased by 75 metres) and the bosentan group (increased by 59 metres) at week 16 (end of trial). The improvement in the sildenafil group increased to 114 metres in a per-protocol analysis excluding the patient who died, and the between-group difference became statistically significant ($p = 0.044$). The total number of patients who experienced at least one SAE was not reported. Hospital admissions or unscheduled

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TABLE 30 *Characteristics of included head-to-head trials*

Trial name/key paper (protocol number); location/ centres	Duration; design; number of patients randomised	Intervention[a]	Comparator[a]	Type of PAH	Functional class	Age (years), mean (SD, range); % female	Baseline exercise capacity and haemodynamic measures,[b] mean (SD)
STRIDE-2/Barst *et al.*, 2006[48] (FPH02); international, 55 centres	18 weeks; double-blind (open-label for bosentan), parallel; $n = 247$	Bosentan (oral) 125 mg b.d.[c] ($n = 60$);	Sitaxentan (oral) 100 mg o.d. ($n = 61$)	IPAH (59%), CTD (30%), congenital heart disease (11%)	II (37%), III (59%), IV (4%)	54 (15); 78%	6MWD: 337 (80); cardiac index: 2.4 (0.8); mPAP: 48 (14); PVR: 880 (560)[e] RAP: NR; SvO_2: NR
SERAPH/Wilkins *et al.*, 2005;[57] UK, single centre	16 weeks; double-blind, parallel; $n = 26$	Bosentan (oral) 125 mg b.d.[c] ($n = 12$)	Sildenafil (oral) 50 mg t.i.d.[d] ($n = 14$)	IPAH (88%), CTD (12%)	III (100%)	43 (NR, 27–62); 81%	6MWD: 297 (82); cardiac index: 2.3 (0.1); mPAP: NR; PVR: NR; RAP: NR; SvO_2: NR

6MWD, 6-minute walk distance; b.d., twice daily; CTD, PAH associated with connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; NR, not reported; o.d., once daily; PAH, pulmonary arterial hypertension; PPH, primary pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; S–P, systemic-to-pulmonary; SD, standard deviation; SvO_2, mixed venous oxygen saturation; t.i.d.: three times daily.

a With ongoing conventional therapy unless otherwise specified.

b Units are: 6MWD, metres; cardiac index, l/min/m^2; mPAP, mmHg; PVR, dyn s/cm^5; RAP, mmHg; SvO_2, %.

c 62.5 mg twice daily for the first 4 weeks.

d 50 mg twice daily for the first 4 weeks.

e Converted from mmHg/l/min (Wood units).

TABLE 31 *Quality assessment of included head-to-head trials*

Study; duration	Truly random allocation (strata for randomisation)	Adequate allocation concealment	Blinding	Use of ITT analysis[a] (*n* included in analysis/*N* randomised)	% of patients completing the trial	Comments
STRIDE-2/ Barst *et al.*, 2006;[48] 18 weeks	Yes	Yes	Double-blind for sitaxentan and open-label for bosentan (outcome assessor blinded)	Survival analysis: N/A; clinical worsening: yes; functional class: no [Commercial-in-confidence information has been removed];[b] 6MWD: no [Commercial-in-confidence information has been removed];[a] haemodynamic: not measured; quality of life: not measured	Bosentan: 87% (52/60); sitaxentan 100 mg: 93% (57/61)	Patients who did not have a valid post-baseline 6MWT were excluded from efficacy analysis [Commercial-in-confidence information has ben removed]
SERAPH/ Wilkins *et al.*, 2005;[57] 16 weeks	Yes	Yes	Double-blind	Survival analysis: N/A; clinical worsening: N/A; functional class: N/A; 6MWD: yes; haemodynamic: yes; quality of life: yes	Bosentan: 100% (12/12); sildenafil: 93% (13/14)	ITT analysis was performed and reported, although the main results table in the paper excluded the patient who died during the trial

6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; ITT, intention to treat; N/A, data not available.

a Defined as an analysis that includes all randomised patients (or all randomised patients who received at least one dose of study medication) according to the treatment group to which they were assigned, irrespective of actual treatment received or early withdrawal of treatment. N/A, data not available (outcome not measured in the trial or unclear if it was measured; analysis for the outcome not performed or unclear if it was performed). When analysis for the outcome was performed but the number of patients included was not reported, this was noted as 'unclear'. When ITT analysis was not used, the number of patients included in the analysis (or a range of numbers when more than one outcome was analysed/more than one analysis was performed with various numbers of patients used) over the number that should have been used in an ITT analysis is shown.

b Numbers refer to bosentan and sitaxentan 100-mg arms only.

TABLE 32 *Comparison checklist – sitaxentan versus bosentan with ongoing supportive treatment*

Planned comparison	Population/doses/data to be included	Analysis carried out	Comments and source of data
A. Primary analysis	All PAH, FCIII, licensed dose	Yes	Data stratified by FC were available only for the outcome of change in FC
B. Sensitivity analysis – mixed FC	All PAH, all FC, licensed dose	Yes	All data from relevant treatment arms were included
C. Sensitivity analysis – mixed pulmonary hypertension	All pulmonary hypertension including categories 1–5 of the Venice 2003 classification, all FC, licensed dose(s)	No	STRIDE-2[48] did not include patients outside category 1 of the Venice 2003 classification
D. Sensitivity analysis – including above licensed doses	All PAH, all FC, licensed dose and above licensed doses	No	No above licensed dose was used in STRIDE-2[48]
E. Sensitivity analysis – excluding data designated as confidential	All PAH, all FC, licensed dose(s), excluding commercial-in-confidence and academic-in-confidence data	No	Not applicable. Data were from only one trial. Confidential data are highlighted
F. Sensitivity analysis – excluding open-label trial	All PAH, all FC, licensed dose(s), excluding open-label trial	No	Not applicable (the bosentan arm was open-label in STRIDE-2[48])
G. Subgroup analysis –IPAH	IPAH, FCIII, licensed dose(s)	No	No data specifically for patients with IPAH were available
H. Subgroup analysis –CTD-APAH	CTD-APAH, FCIII, licensed dose(s)	No	No data specifically for CTD-APAH were available

CTD-APAH, PAH associated with connective tissue disease; FC, functional class; IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension.

visits were required for three patients in the bosentan group and one patient in the sildenafil group. Right ventricular mass (the primary end point) was reduced in both groups, but only significantly in the sildenafil group compared with baseline. The differences between the two groups in right ventricular mass and all other measures including haemodynamic, hormonal and quality of life (Kansas City Cardiomyopathy Questionnaire) measures were not statistically significant.

Summary and discussion

- Two RCTs included a direct comparison between the technologies under assessment in this report. The STRIDE-2 trial[48] was an 18-week, international study sponsored by the manufacturer of sitaxentan and compared sitaxentan (licensed dose) with bosentan (licensed dose) with ongoing supportive treatment. The SERAPH study[57] was a 16-week, single-centre UK study sponsored by the British Heart Foundation and compared sildenafil (above licensed dose) with bosentan (licensed dose) with ongoing supportive treatment. The bosentan arm in STRIDE-2 was open-label, whereas SERAPH was a double-blind study.
- Methods of randomisation and allocation concealment were adequate in both trials. ITT analysis was used in SERAPH[57] but not in STRIDE-2.[48] The potential bias due to exclusion of a small number of patients from the efficacy analysis in STRIDE-2[48] was unclear, but the impact is likely to be small.
- STRIDE-2 included mixed populations of patients with IPAH, CTD-APAH and PAH associated with CHD with mixed FC (59% FCIII).[48] SERAPH included exclusively patients in FCIII predominantly with IPAH.
- For the comparison between sitaxentan and bosentan at licensed doses, no significant differences between the two treatment groups were found in any of the outcomes examined. Data stratified by FC were available only for the outcome of change in FC, and the results for FCIII patients only were similar to the overall trial results.
- For the comparison between sildenafil (above licensed dose) and bosentan (licensed dose), no significant differences between the two treatment groups were found in any of the outcomes examined. However, the sample size for this trial was small ($n = 26$) and it might not be sufficiently powered to detect clinically important differences.

TABLE 33 *Results from STRIDE-2: sitaxentan versus bosentan with ongoing supportive treatment*

		Analysis (see comparison checklist)			
		A. Primary analysis		**B. Sensitivity analysis – mixed FC**	
PAH population		All PAH subcategories		All PAH subcategories	
Functional class (FC)		FCIII		All FC	
Doses		Licensed dose (sitaxentan 100 mg once daily; bosentan 125 mg twice daily)		Licensed dose (sitaxentan 100 mg once daily; bosentan 125 mg twice daily)	
Total no. eligible for analysis		71[48]		124[48]	
No. included in analysis		69		[Commercial-in-confidence information has been removed]–122[48]	
Outcomes	**Statistics**	***n***	**Effect size (95% CI)**	***n***	**Effect size (95% CI)**
Efficacy					
Death[a]	RR	0	Data not available	121[48]	Not estimable (no death)
Clinical worsening[a]	RR	0	Data not available	121[48]	0.44 (0.14 to 1.34)
Functional class maintained or improved[b]	RR	69[48]	1.06 (0.96 to 1.16)	121[48]	1.07 (0.99 to 1.17)
Functional class improved[b]	RR	69[48]	0.78 (0.27 to 2.22)	[Commercial-in-confidence information has been removed][48]	[Commercial-in-confidence information has been removed]
Withdrawal for any reason[a]	RR	0	Data not available	[Commercial-in-confidence information has been removed][48]	0.49 (0.16 to 1.55)
6-minute walk distance (metres)[c]	WMD	0	Data not available	[Commercial-in-confidence information has been removed][48]	2 (–22 to 26)
Borg dyspnoea index[d]	WMD	0	Data not available	[Commercial-in-confidence information has been removed][48]	[Commercial-in-confidence information has been removed]

		Analysis (see comparison checklist)			
		A. Primary analysis		**B. Sensitivity analysis – mixed FC**	
Haemodynamics					
Mean pulmonary arterial pressure (mPAP) (mmHg)[d]	WMD	0	Not measured	0	Not measured
Right atrial pressure (RAP) (mmHg)[d]	WMD	0	Not measured	0	Not measured
Pulmonary vascular resistance (PVR) (dyn s/cm^5)[d]	WMD	0	Not measured	0	Not measured
Cardiac index (l/min/m^2)[c]	WMD	0	Not measured	0	Not measured
Safety					
Serious adverse events[a]	RR	0	Data not available	122[48]	[Commercial-in-confidence information has been removed]

CI, confidence interval; FC, functional class; PAH, pulmonary arterial hypertension; RR, relative risk; WMD, weighted mean difference.
a RR < 1 favours sitaxentan and RR > 1 favours bosentan.
b RR > 1 favours sitaxentan and RR < 1 favours bosentan.
c Mean change from baseline; positive value favours sitaxentan and negative value favours bosentan.
d Mean change from baseline; negative value favours sitaxentan and positive value favours bosentan.

- Results from SERAPH[57] demonstrated the importance of using ITT analysis and the potential impact of excluding randomised patients from analysis, particularly when the sample size is small.

Ongoing studies

Several ongoing studies were identified through the formal searches and scrutiny of the manufacturer submissions. These are documented for information in Appendix 6, *Table 74*.

More evidence from RCTs regarding the use of combination therapy will become available in the next few years. This includes the addition of inhaled iloprost to sildenafil (NCT00302211), bosentan to sildenafil (NCT00303459), and sildenafil to bosentan (NCT00323297). This review should be updated when the results from these trials are reported.

In addition, an RCT (NCT00091715) of bosentan versus placebo in patients with mild PAH (FCII at baseline) has been completed. There are also RCTs of other emerging treatments for PAH that have recently been completed or are ongoing. More treatments for PAH may become available and the licensed indications for existing treatments may be amended in view of the emerging evidence. The scope of any future review may need to be changed accordingly.

Long-term studies

Scrutiny of the manufacturer submissions revealed a number of long-term follow-up studies. These are documented in Appendix 7, *Tables 75* and *76*. Those studies that reported data for change/no change in FC and/or mortality data stratified by FC were utilised to inform the independent economic assessment (see Chapter 4).

Overview and discussion of clinical effectiveness

Comparison of each of the five technologies with placebo/control with ongoing supportive treatment

This comparison is the main focus of this technology assessment and is also where the vast majority of RCT evidence lies. *Table 34* summarises the results of relevant meta-analyses and individual studies (when only one trial provided relevant data) for each of the five technologies under assessment for selected key outcomes. The results show that significant improvements in FC, 6MWD and haemodynamic measures have been clearly demonstrated in PAH populations for each of the technologies compared with placebo/control, although the volume of evidence varies between technologies. The findings for the other outcomes were less clear-cut. The main findings for this comparison are discussed below.

Survival

All of the RCTs included in this review were of a duration of 18 weeks or less. Death generally occurred more frequently in the placebo/control groups than in the treatment groups, but the numbers were very small within each trial. The epoprostenol trial by Barst and colleagues[11] was an exception and was the only RCT that demonstrated a significant survival benefit within a trial. The pooled RRs for death were in favour of each of the technologies (except for sildenafil for which the result was based on two deaths in a single trial), but did not reach statistical significance as confidence intervals were wide.

A recent meta-analysis[63] of treatments for pulmonary hypertension (i.e. a wider population than just PAH) reported a RR of death of 0.70 (95% CI 0.41–1.22) compared with control. The analysis pooled all disease-modifying technologies for pulmonary hypertension including those outside this technology assessment. The merits of this are debatable. However, the estimated non-significant 30% reduction in mortality led the authors to question the survival benefit offered by the technologies for pulmonary hypertension, and in particular whether the trials were adequately powered or of a long enough duration to adequately measure survival. The findings of this assessment report are in agreement with this conclusion.

Despite some methodological issues with this meta-analysis[63] (e.g. the head-to-head trial SERAPH[57] was included in the analysis with the bosentan arm being treated as a control), its finding is consistent with the finding of this technology assessment in that the overall direction of effect was in favour of active treatments and was consistent across different types of drugs. The key questions are therefore whether the magnitude of the effect varies between drugs and whether it changes over time. Unfortunately these questions are unlikely to be answerable with existing evidence because of the small numbers of deaths that occurred in the RCTs

and their short duration. Increasing evidence from long-term observational studies (see Appendix 7) agrees with the potential survival benefit of these treatments observed during short-term trials, but unbiased comparison between drugs using observational data is difficult to achieve because of differences in patient populations, entry criteria, treatments offered and methods of follow-up.

In addition to the small numbers of patients/events and short duration of study, interpretation of results from RCTs in relation to mortality as well as other outcomes needs to take into account the following issues.

Patient populations

Trials varied in their population mix in terms of types of PAH and FC at baseline. Although limited within- and between-trial comparisons shown in this assessment report did not demonstrate significant differences between subcategories of PAH, these comparisons were limited by the small number of patients within each subcategory and thus the low statistical power to detect genuine differences between the subgroups. It should be noted that baseline mortality rates between different subcategories of PAH are different. Very limited data from trials included in this report have also shown that results from the subset of patients in FCIII at baseline were generally similar to the overall trial results, which included patients with mixed FC. From a statistical point of view it is worth emphasising that a certain level of association between data sets is to be expected when one set of data (i.e. FCIII only) is compared with another set of data that includes the former (i.e. data for the whole trial population including that for FCIII and other FC). Conclusive results with regard to whether the treatment effect varied by FC can only be obtained from comparisons between mutually exclusive subgroups (e.g. FCII versus FCIII) or analysis of individual patient data using appropriate statistical tests. These were not carried out in this assessment report as evaluating the clinical effectiveness of the treatments outside their licensed indications (in terms of FC) is beyond the scope of the assessment. Nevertheless, similar problems of (lack of) availability of data stratified by FC and small patient numbers within each FC would have prevented such comparisons in most cases.

Although there appears to be limited statistical heterogeneity within many of the pooled analyses, there was considerable clinical heterogeneity between some of the populations enrolled in and between trials.

In addition to the varied population mix within each trial, the awareness of the condition of PAH within the medical community has risen in the past few years. Consequently, patients enrolled in the trials conducted in 1990s were likely to have been at different stages of the disease from those enrolled in the trials conducted in the past few years, even if they were designated the same FC at baseline. This is apparent when the mean age, baseline 6MWD and haemodynamic measures are compared between trials (particularly for epoprostenol trials compared with others). However, it is still clear that patients are generally being diagnosed well after the onset of symptoms[64] and thus there is a considerable delay in patients being first seen at a designated centre.

One further issue relates to the inclusion criteria of the trials. Again, the major difference was between epoprostenol trials and other trials, but important differences also existed between some of the other trials in terms of use of baseline FC and 6MWD as inclusion criteria. A common feature for nearly all trials was the requirement of patients to be stable on supportive treatment for a certain period of time (usually 4 weeks or longer) before study entry. The trials therefore essentially excluded unstable and therefore potentially sicker patients whom are frequently seen in clinical practice. This could have an implication for the generalisability of the results from the trials.

Comparator

Although supportive treatment was the common comparator across the trials, the standard of care is likely to have changed over time and may vary between countries. Consequently the results of the trials may not be directly comparable. In terms of survival benefit, if epoprostenol did reduce mortality, as the limited evidence suggests, it would be more difficult for the other trials to demonstrate a reduction in mortality as patients who deteriorated in the control groups would have been given epoprostenol as a rescue therapy, which may have prevented/delayed death.

Whether a placebo was used in the control arm may also have affected the response in control groups because of the placebo effect (when placebo was used) and possible bias in the provision of care and assessment of outcome (when placebo was not used), although this would be less of an issue for the outcome of survival.

In brief, limited evidence from RCTs (and observational studies) suggests that various

TABLE 34 *Overview of evidence from RCTs for the clinical effectiveness of the five technologies (licensed doses) under assessment compared with placebo and/or supportive care*

Drug and population	Death, RR (95% CI)	Clinical worsening, RR (95% CI)	FC improvement, RR (95% CI); NNT (95% CI)	6MWD, WMD[a] (95% CI)	Quality of life[b]	Haemodynamics, WMD[c] (95% CI)
Epoprostenol						
Mixed PAH, mixed FC	0.37 (0.09 to 1.57) [3]	No data	**10.58 (3.07 to 36.50); 2.2 (1.6 to 3.6, I^2 = 69%)[d] [3]**	**81 (45 to 117)[d] [3]**	Chronic Heart Failure Questionnaire (+) [1]; Nottingham Health Profile (+/–) [1]	mPAP: **–6.3 (–8.7 to –3.9)[d] [3];** RAP: **–2.4 (–4.1 to –0.7)[d] [2];** PVR: **–427 (–548 to –306)[d] [3];** cardiac index: **0.6 (0.4 to 0.8)[d] [2]**
PPH, mixed FC	0.18 (0.03 to 1.18) [1]	No data	**7.45 (2.55 to 21.77); 1.9 (1.1 to 5.9, I^2 = 82%)[d] [2]**	**58 (6 to 110)[d] [2]**	Same as above	mPAP: **–6.8 (–10.6 to –3.0)[d] [2];** RAP: –2.3 (–5.1 to 0.5) [1]; PVR: **–401 (–613 to –189)[d] [2];** cardiac index: **0.6 (0.2 to 0.9)[d] [1]**
PPH, FCIII	No stratified data	No data	No stratified data	No stratified data	No stratified data	No stratified data
PPH, FCIV	No stratified data	No data	No stratified data	No stratified data	No stratified data	No stratified data
CTD-APAH, mixed FC	0.79 (0.22 to 2.77) [1]	No data	**42.25 (2.62 to 680.61); 2.6 (2.0 to 4.0)[d] [1]**	**100 (55 to 144)[d] [1]**	No data	mPAP: **–6.0 (–9.0 to –2.9)[d] [1];** RAP: **–2.5 (–4.6 to –0.4)[d] [1];** PVR: **–440 (–588 to –292)[d] [1];** cardiac index: **0.6 (0.4 to 0.8)[d] [1]**
Iloprost						
Mixed PH, mixed FC	0.58 (0.14 to 2.46) [2]	0.42 (0.15 to 1.15) [1]	**1.98 (1.13 to 3.48); 8.3 (4.5 to 33.3, I^2 = 0%)[d] [2]**	**36 (12 to 60)[d] [1]**	EQ-5D VAS (+) [2]; EQ-5D health state score (–) [1]; SF-12 (–) [1]; MLHF Questionnaire (–) [1]	mPAP: **–4.4 (–6.7 to –2.1)[d] [1];** RAP: **–2.2 (–3.5 to –0.9)[d] [1];** PVR: **–335 (–421 to –249)[d] [1];** cardiac index: no data
PPH, mixed FC	0.52 (0.05 to 5.55) [1]	No stratified data	**3.19 (1.11 to 9.11); 5.9 (3.1 to 33.3)[d] [1]**	No stratified data	No stratified data	No stratified data
PPH, FCIII	No stratified data	No stratified data	3.71 (0.83 to 16.61) [1]	No stratified data	No stratified data	No stratified data
CTD-APAH, mixed FC	No stratified data	No stratified data	No stratified data	No stratified data	No stratified data	No stratified data

Drug and population	Death, RR (95% CI)	Clinical worsening, RR (95% CI)	FC improvement, RR (95% CI); NNT (95% CI)	6MWD, WMD[a] (95% CI)	Quality of life[b]	Haemodynamics, WMD[c] (95% CI)
Bosentan						
Mixed PAH, mixed FC	0.23 (0.03 to 1.47) [4]	0.43 (0.15 to 1.24) [3], $I^2 = 62\%$	**1.51 (1.05 to 2.15); 7.1 (4.0 to 50.0, $I^2 = 46\%$)[d] [4]**	**41 (24 to 58) [4]**	No data	mPAP: **–5.9 (–9.3 to –2.5)[d] [2];** RAP: –3.0 (–9.0 to 3.0) [2], $I^2 = 89\%$; PVR: **–414 (–596 to –232)[d] [1];** cardiac index: **1.0 (0.7 to 1.3)[d] [1]**
Mixed PAH, FCIII	No death [2]	0.08 (0.00 to 1.39) [1]	2.08 (0.97 to 4.46) [3]	59 (20 to 99) [2]	No data	Same as above
IPAH, mixed FC	No stratified data	No stratified data	No stratified data	No stratified data	No stratified data	No stratified data
CTD-APAH, mixed FC	No stratified data	No stratified data	No stratified data	22 (–32 to 76) [2]	No stratified data	No stratified data
Sitaxentan						
Mixed PAH, mixed FC	0.20 (0.01 to 4.15) [3]	**0.33 (0.12 to 0.87) [d] [3]**	**1.74 (1.12 to 2.70); 10 (5 to infinity, $I^2 = 21\%$)[d] [3]**	**32 (18 to 47) [3]**	SF-36 (–) [1]	mPAP: **–3.0 (–5.9 to –0.1)[d] [1];** RAP: –1.0 (–2.5 to 0.5) [1]; PVR: **–270 (–402 to –138)[d] [1];** cardiac index: **0.3 (0.1 to 0.5)[d] [1]**
Mixed PAH, FCIII	No stratified data	No stratified data	1.53 (0.74 to 3.17) [2]	No stratified data	No stratified data	No stratified data
IPAH, mixed FC	No stratified data	No stratified data	2.02 (0.88 to 4.60) [1][a]	**34 (7 to 61) [d,e] [1]**	No stratified data	No stratified data
CTD-APAH, mixed FC	No stratified data	No stratified data	2.18 (0.31 to 15.24) [1][a]	**58 (0 to 116) [d,e] [1]**	No stratified data	No stratified data

continued

TABLE 34 *Overview of evidence from randomised controlled trials for the clinical effectiveness of the five technologies (licensed doses) under assessment compared with placebo and/or supportive care (continued)*

Drug and population	Death, RR (95% CI)	Clinical worsening, RR (95% CI)	FC improvement, RR (95% CI); NNT (95% CI)	6MWD, WMD[a] (95% CI)	Quality of life[b]	Haemodynamics, WMD[c] (95% CI)
Sildenafil						
Mixed PAH, Mixed FC	1.01 (0.06 to 15.90) [1]	0.43 (0.12 to 1.61) [1]	**3.91 (1.55 to 9.88); 4.8 (3.0 to 11.1)[d] [1]**	**38 (12 to 64)[d] [1]**	SF-36 (+/–) [1]; EQ-5D current health state VAS (+) [1]; EQ-5D utility index (?) [1]	mPAP: **–2.7 (–5.3 to –0.1)[d] [1];** RAP: –1.1 (–2.7 to 0.5) [1]; PVR: **–171 (–311 to –31)[d] [1];** cardiac index: 0.2 (0.0 to 0.5) [1]
Mixed PAH, FCIII	No stratified data	No stratified data	2.55 (0.91 to 7.18) [1]	No stratified data	No stratified data	No stratified data
IPAH, mixed FC	No stratified data	No stratified data	No stratified data	**40 (14 to 66)[d] [1]**	No stratified data	No stratified data
CTD-APAH, mixed FC	No stratified data	No stratified data	No stratified data	**55 (25 to 85)[d] [1]**	No stratified data	No stratified data

6MWD, 6-minute walk distance; CI, confidence interval; CTD-APAH, PAH associated with connective tissue disease; EQ-5D, EuroQol 5 dimensions; FC, functional class; IPAH, idiopathic pulmonary arterial hypertension; MLHF, Minnesota Living with Heart Failure; NNT, number needed to treat; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RR, relative risk; SF-12, Short-Form 12; SF-36, Short-Form 36; VAS, visual analogue scale; WMD, weighted mean difference.

Note: Numbers in square brackets indicate the number of trials.

a Weighted mean difference for change from baseline, metres.

b '+' indicates that there was significant improvement versus placebo/control in all domains; '+/–' indicates that significant improvement versus placebo/control was found only in some of the domains; '–' indicates that no significant improvement was found in any of the domains; '?' indicates that improvement was observed but statistical significance was unclear.

c Weighted mean difference for change from baseline: mPAP, mean pulmonary arterial pressure (mmHg); RAP, right atrial pressure (mmHg); PVR, pulmonary vascular resistance (dyn s/cm^5); cardiac index (l/min/m^2).

d Statistically significant result.

e Includes above licensed dose.

treatments for PAH confer survival benefit, although it is difficult to quantify the treatment effects and to ascertain whether differences exist between drugs. However, it is unlikely that the survival benefit demonstrated in the epoprostenol trial by Barst and colleagues[11] [prevention of eight deaths over 12 weeks for every 40 patients treated, number needed to treat (NNT) = 5, 95% CI 3–14] would be replicated in future trials because epoprostenol has since been used as a standard treatment for severe PAH. Interpretation of results from RCTs needs to take into account the relatively small sample sizes and short duration of these studies, and differences in patient populations and comparators (supportive treatment) between trials and over time.

Clinical worsening

Clinical worsening events were not defined or reported in any of the epoprostenol trials. A significant reduction in clinical worsening events and/or an increase in time to clinical worsening was demonstrated in individual trials of bosentan,[43,45] the pooled results of sitaxentan trials and the pooled results of bosentan trials (excluding STRIDE-2[48]). Fewer clinical worsening events occurred in the active treatment arms than in the placebo arms in the pivotal trials for iloprost (AIR study[41]) and sildenafil (SUPER-1[53]), but the results did not reach statistical significance.

Most points already discussed in relation to survival are also applicable to clinical worsening events. An additional issue for this outcome is that different definitions of clinical worsening have been used in different trials. It is likely that both the severity of disease in study participants at baseline and the definition of clinical worsening adopted in the trials had an impact (in addition to the treatment effect) on the event rates for clinical worsening. Standardisation of the definition in future trials would be helpful for comparison of results between trials.

Changes in functional class

All five technologies demonstrated a significant benefit compared with placebo/control with regard to having an improved FC on treatment. One issue that needs to be highlighted in relation to this outcome is the substantial variations between trials in the response rates in the placebo/control groups. The differences between trials may partly be attributable to the differences in the mix of FC at baseline. However, even when limiting the data to patients in FCIII at baseline, the proportion of patients having their FC improved still ranged from 29% (19/65) in BREATHE-1[45] (bosentan trial) to 6% (2/36) in the AIR study[41] (iloprost trial). Again, the differences in trial populations and standard of (supportive) care need to be considered when interpreting the results. Within the context of RCTs, the nature of FC being a subjective outcome means that there was a possibility of misclassification of FC at baseline. Interpretation of baseline FC and outcomes related to FC changes should therefore be made in conjunction with objective outcome measures such as 6MWD.

The variations in the response rates in the placebo/control groups between trials mean that calculating the NNT, assuming a common 'baseline risk' across different technologies or even within a drug, may be problematic. The NNTs presented in *Table 34* were calculated according to the pooled risk differences of the trials contributing to the data for each technology. Therefore they should not be compared against each other and should be interpreted with great caution, particularly when substantial heterogeneity in risk differences is shown ($I^2 \geq 50\%$).

In contrast to the significant effect on improving FC, most technologies, except sitaxentan, failed to demonstrate a statistically significant effect on having FC improved or maintained (i.e. not worsened). This was unexpected and was in part due to some of the trials failing to report changes in FC other than improvement (i.e. proportion of patients having FC maintained or worsened), and consequently the smaller number of patients included in the analysis of this outcome. Furthermore, it is likely that the exclusion of patients with unstable conditions from these trials made it more difficult for these studies to demonstrate the benefit of reducing FC deterioration within the short duration of the trials.

6-Minute walk distance

All five technologies demonstrated a significant effect compared with placebo/control on increasing exercise capacity as measured by 6MWT. The mean difference between the treatment and placebo/control groups appeared to be greatest in two of the epoprostenol trials[33,39] (approximately 100 metres). The between-group difference varied from approximately 30 to 75 metres in the other trials, with wide confidence intervals because of the high variability between individual patients. Again, values from different trials are not directly comparable because of differences in patient populations in terms of types of PAH, baseline FC and exercise capacity. For example, a ceiling effect in 6MWD (those patients with milder disease/higher baseline 6MWD had less scope for

improvement) was observed in a post hoc analysis of the STRIDE-1 study (sitaxentan trial).[50,51]

Whether ITT analysis was used and the methods for imputing missing data can also have a substantial impact on the reported group means and differences for 6MWD, particularly in trials of small sample size. Excluding patients who had no post-baseline 6MWT would almost certainly bias the results. Different methods of imputing data (e.g. last observation carried forward; assuming no change compared with baseline; assuming a 6MWD of 0 for missing observations), however, could produce different results. Interpretation of trial results and comparison between studies therefore requires great caution.

Quality of life

The volume of evidence from RCTs with regard to the impact of treatment on health-related quality of life varied between technologies. No data were reported in the trials for bosentan. Other trials used different tools and the findings seemed inconclusive (see *Table 34*). Two studies measured the EQ-5D utility index (AIR study for iloprost;[41] SUPER-1 study for sildenafil[53]); there was an improvement of approximately 0.1 (on a scale of 0–1) compared with placebo in both trials.

Haemodynamic measures

All five technologies demonstrated significant effects on haemodynamic measures, which are important indicators of PAH disease progression and/or survival.[5,65,66] In the context of clinical trials these measures were most susceptible to missing observations and were usually not analysed by ITT. Consequently, statistically significant findings in these outcomes may better be treated as 'proof of concept' for PAH treatment. The magnitude of the reported group means and differences, however, may not be clinically useful.

Serious adverse events and withdrawal for any reasons

The potential harm associated with any treatment for PAH needs to be weighed against the potential worsening of the disease without treatment. Worsening of PAH frequently incurs events that are classified as SAEs and may require withdrawal from RCTs. Effective treatments for PAH with an acceptable safety profile would therefore be expected to demonstrate a reduced risk of SAEs and withdrawal for any reason compared with placebo/control.

Data on the total number of patients experiencing at least one SAE were not available for the three epoprostenol trials[11,33,39] and two of the bosentan trials.[43,45] The pooled data for the other two bosentan trials[47,48] showed a significant reduction in the risk of experiencing at least one SAE for bosentan compared with placebo, but the pooled results (or result from the only trial) for other technologies failed to demonstrate a significant risk reduction. A significant reduction in the risk of withdrawal for any reason was observed in individual trials for epoprostenol[11] and iloprost[41] and in the pooled results for sitaxentan.

Poor reporting of the outcomes and the small number of patients with the events are possible reasons for the lack of consistent findings for these outcomes across technologies (contrary to some of the efficacy outcomes). Further evidence from comparative trials is needed as these drugs have different adverse effect profiles and differences between drugs in the maintenance of patients on treatment and the overall risk–benefit profile cannot be ruled out.

Direct comparisons between the five technologies under assessment

Only two of the included RCTs directly compared one of the technologies under assessment against another. The STRIDE-2 trial[48] was the only trial that used licensed doses for both treatments being compared. No statistically significant difference was found between sitaxentan and bosentan for all major outcomes. The main concern in interpreting the results from this study was the lack of blinding for the bosentan arm only. Although assessors for efficacy outcomes were blinded, potential bias introduced by the differential blinding of investigators and patients could not be ruled out. Another head-to-head trial (SERAPH[57]) compared an above licensed dose for sildenafil with bosentan at its licensed dose and was relatively small in its sample size. Again, no significant differences were found for any of the outcomes measured in the trial when ITT analysis was used.

A total of 10 different head-to-head comparisons would have been possible for the five technologies under assessment when used as monotherapy. The number of possible comparisons would increase further if combinations of these drugs are also considered. However, given the influence of routes of administration, the speediness of action and potential adverse effects of different technologies (plus costs) on patients' and physicians' preferences, direct comparisons between epoprostenol/iloprost and the three oral

treatments are likely to be neither feasible nor clinically relevant.

Although very limited data from the aforementioned trials did not identify significant differences between sitaxentan and bosentan, and between sildenafil and bosentan, these trials may have been underpowered to detect clinically relevant differences because of their sample sizes and duration. Indeed, [Commercial-in-confidence information has been removed] were reported in the long-term extension of the STRIDE-2 trial (which was not included in this review as the patients in each of the treatment groups had varied durations of exposure to the drugs because of the study design). Sufficiently powered, long-term, head-to-head RCTs (preferably double-blind and independently funded) of the three oral treatments therefore remain a high priority for future research. However, the limited patient pool may make undertaking such trials difficult.

No indirect comparisons or mixed treatment comparisons between the five technologies were planned or performed in this review. Many issues that would affect comparability between results of individual trials have been highlighted in the previous section. In addition, there appeared to be no single outcome measure that could adequately represent the overall effectiveness of individual treatments. Together with the relatively small volume of available evidence, indirect comparisons and mixed treatment comparisons are unlikely to provide conclusive results and could potentially generate misleading findings.

Treatment involving combination of the technologies under assessment

A few RCTs have explored the use of combinations of the technologies under assessment. The BREATHE-2 study compared the combination of epoprostenol plus bosentan with epoprostenol alone in patients who required the initiation of epoprostenol treatment.[47] No significant differences were observed between groups. The sample size for this study was not large ($n = 54$) and the results were not conclusive. However, they do suggest caution in assuming greater benefit for combination therapy versus monotherapy.

Two trials (COMBI[58] and STEP[59]) compared iloprost with control/placebo in patients who were stable on bosentan and supportive treatment, but who remained symptomatic. Given the general preference of oral treatment over other routes, results from these two studies were probably more relevant to the actual use of inhaled iloprost in clinical practice than the results from studies that compared inhaled iloprost with supportive treatment in patients who had not received oral treatments. Inhaled iloprost demonstrated significant benefit compared with placebo in the STEP study,[59] but failed to demonstrate such benefit compared with control in the COMBI study[58] for all outcomes including 6MWD and changes in FC. It was difficult to determine whether the inconsistency arose from differences in study population, location, study design, the combination of these or any other factors.

Finally, results from the PACES-1 study[38] demonstrated a significant benefit of giving sildenafil to patients who were stable on epoprostenol. However, the dose used in this study was much higher than the licensed dose of sildenafil.

Specific issues related to this technology appraisal

Several potential problems that might affect our ability to address the decision problems outlined in the final scope of this technology appraisal were expected at the inception of the project and were highlighted in the review protocol as well as in Chapter 2 of this report. The major difficulty was that this assessment was undertaken for the licensed indications of individual technologies, and there was a mismatch between the license and available evidence. To this end this assessment report presents findings for whole trial populations (usually mixed populations of different PAH subcategories and/or FC), but also, when possible, evidence that is directly applicable to the licensed indication and evidence for specific subcategories of PAH (IPAH and CTD-APAH) (see *Table 34* and also results tables for individual technologies in Chapter 3).

It can be seen that, although the most inclusive (whole trial data) evidence is sufficiently robust for all of the technologies, the volume of available evidence reduces dramatically when only evidence directly applicable to the licensed indications is included (PPH FCIII and FCIV for epoprostenol; PPH FCIII for iloprost; PAH FCIII for bosentan, sitaxentan and sildenafil). When evidence is available the confidence intervals tend to be wider than those for the inclusive evidence and the results may no longer be significant. There are few data

for specific subcategories of PAH and little scope for comparison between them. In addition to the volume of evidence, all of the data were restrictive to a duration of 18 weeks or shorter. A possible lesson learned (amongst other explanations) from a 1-year trial of beraprost (not included in this assessment) suggests that observations made at 3 months may not last beyond this time. [67]

Furthermore, there are specific issues related to the evidence for individual technologies. For epoprostenol, all of the trials were conducted in the USA and in the 1990s. There is therefore a potential issue of the generalisability of the study results to the current UK context. For inhaled iloprost there is a fluctuation of drug effects because of the method of administration. Whether some of the outcomes measured immediately after inhalation can present the overall treatment benefit is questionable. In addition, conflicting results between some of the iloprost trials have been observed. For bosentan, the exceptionally high response for FC improvement in the placebo group in its pivotal trial (BREATHE-1[45]) and lack of stratified data from this trial for various outcomes increases the uncertainty of the pooled estimate presented in this report. For sildenafil, the bulk of its trial evidence is related to doses that are higher than the licensed dose (this also applies to evidence from observational studies). Beyond all this there is also a possible mismatch between the licensed indication of each drug and the actual use in clinical practice.

Chapter 4

Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

Searches

A comprehensive search for literature on the cost and cost-effectiveness of drugs for PAH was carried out.

The searches identified existing economic models and information on cost-effectiveness, costs and quality of life from the following sources:

- bibliographic databases: MEDLINE (Ovid) 1950 to February 2007, EMBASE (Ovid) 1980 to February 2007, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO) 1982 to February 2007, Cochrane Library [Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluation Database (NHS EED)] 2007 Issue 1, and Health Economic Evaluation Database (HEED) February 2007
- manufacturer submissions
- internet sites of national economic units.

Searches were not limited by date neither were there language restrictions. Full search strategies can be found in Appendix 2.2.

Study selection, data extraction and quality assessment strategy

The inclusion and exclusion criteria applied to the economic searches are shown in *Table 35*.

An experienced health economist applied the inclusion and exclusion criteria to papers, with checking by a second health economist. The quality of the eligible economic evaluation studies was assessed using the Consensus on Health Economic Criteria (CHEC)-list[68] and an adapted version of the Drummond and Jefferson *BMJ* criteria for economic evaluations.[69] Papers remaining in the review were read in detail and data extracted using a predesigned data extraction form. Data on the following were sought:

- study characteristics such as the study question, form of economic analysis, population, interventions, comparators, perspective, time horizon and modelling used
- clinical effectiveness and cost parameters, such as effectiveness data, health state valuations (utilities), resource use data, unit cost data, price year, discounting, key assumptions and productivity costs
- results and sensitivity analysis.

In addition, any papers related to quality of life of patients with PAH were read and, where relevant, utility data for PAH-related health states were extracted.

Results

Economic evaluations

A total of four economic evaluations meeting the inclusion criteria were identified, none of which were a UK study. All four evaluations met at least eight of the 10 Drummond and Jefferson quality assessment criteria and 16 of the 19 CHEC-list criteria. Full details can be found in Appendix 8. The characteristics and the main results of the economic evaluations are summarised in *Table 36*. Einarson *et al.*[70] and Narine *et al.*[71] both compared treprostinil with epoprostenol, and

TABLE 35 *Inclusion and exclusion criteria for the review on cost-effectiveness*

Study design	Cost–consequence analysis, cost–benefit analysis, cost-effectiveness analysis, cost–utility analysis, cost studies (UK only), quality of life studies
Population	Pulmonary arterial hypertension patients
Intervention	Intravenous epoprostenol, inhaled iloprost, bosentan, sitaxentan, sildenafil
Comparator	Placebo, supportive therapy, any intervention drug
Outcome	Quality of life estimates, cost estimates, cost-effectiveness

TABLE 36 *Summary of published economic analyses*

Economic analysis features	Einarson, 2005[70]	Highland, 2003[72]	Narine, 2005[71]	Wlodarczyk, 2006[73]
Country	Canada	USA	USA	Australia
Sponsor	Northern Therapeutics (distributor of treprostinil in Canada)	Not stated	United Therapeutics	Submissions to PBAC funded by Actelion Pharmaceuticals Australia
Choice of therapy	Treprostinil	Bosentan	Treprostinil	Bosentan
Comparator(s)	Epoprostenol	Treprostinil, epoprostenol	Epoprostenol	Conventional therapy
Patient characteristics	Two cohorts of patients of FCIII and FCIV	Cohort of 100 PAH patients	Two cohorts of 270 patients of FCIII and FCIV who have failed or who are not candidates for bosentan	Patients of FCIII or FCIV
Form of analysis	Cost-minimisation	Cost–utility	Cost-minimisation	Cost-effectiveness (cost per life-year gained)
Model used	Microsoft EXCEL spreadsheet	Markov model	Microsoft EXCEL spreadsheet	Individual patient level simulation
Time horizon of model	3 years	1 year	3 years	15 years
Cost year and currency	2003, Canadian $	2002, US $	2003, US $	2001/2, Australian $
Base-case results	Treprostinil gave savings of C$2,610,642 (60 patients over 3 years) (£1,364,959, 2006) and an average annual saving of C$14,504 (per patient per year) (£7583, 2006) from a health-care perspective	Bosentan less costly (cost savings of US$3,631,900) (£2,990,169, 2006) with a QALY gain (11 QALYs) for 100 patients	Treprostinil gave savings of US$37,433 (£27,252, 2006) per patient (over 3 years) and the average cost saving per patient per year was $12,478 (£9084, 2006)	ICER: A$55,927 per life-year gained (£23,657, 2006)

FC, functional class; ICER, incremental cost-effectiveness ratio; PAH, pulmonary arterial hypertension; PBAC, Pharmaceutical Benefits Advisory Committee; QALY(s), quality-adjusted life-year(s).

several of the authors were involved in both papers. In essence, the same model was used; however, one study considered Canadian costs[70] and the other considered US costs.[71] For simplicity these papers will be discussed in tandem as the model structure and data inputs are essentially the same. However, it should be noted that treprostinil is not a technology being evaluated as part of this assessment. The Highland *et al*. paper,[72] a US-based study, compared bosentan with treprostinil or epoprostenol, and Wlodarczyk and colleagues[73] from Australia also considered bosentan but in comparison to conventional therapy. Three out of the four studies had connections with industry; the exception was the study by Highland *et al.*[72] in which no reference was made to funding or conflicts of interests stated.

All four studies were model-based analyses. In the studies by Einarson *et al*. and Narine *et al*. a cost-minimisation analysis was conducted as they assumed that treprostinil and epoprostenol were clinically equivalent.[70,71] The Wlodarczyk *et al.* study, which describes the process of the Australian Pharmaceutical Benefits Scheme (PBS) listing for bosentan, conducted a cost-effectiveness analysis using survival as the outcome.[73] Only the model by Highland *et al.*[72] conducted a cost–utility analysis. This paper was not explicit about the population modelled in terms of FC, with the population described as a cohort of 100 PAH patients. The other papers all considered patients of FCIII and FCIV, although the Narine and Einarson model only considered patients who were non-responders to oral therapy.

The model presented in the Narine *et al*. and Einarson *et al*. papers was a decision-analytical spreadsheet model built in Microsoft EXCEL. This model followed a cohort of patients over a 3-year period and was built to represent a logical sequence of clinical practice for PAH patients. Highland *et al*. presented a Markov cohort model that followed patients over a 1-year period with a cycle length of 3 months, with health states based on FC. The model in the Wlodarczyk *et al*. study was an individual patient level simulation, run over a time horizon of 15 years with a cycle length of 6 months. Within the model patients could improve, stabilise or not respond to a therapy.

The effectiveness data used in the model presented by both Narine *et al*. and Einarson *et al*. were obtained from preliminary data analysis, expert clinical opinion and also non-comparative studies. The two therapies in question were assumed to be clinically equivalent, based on results of a 3-year clinical trial showing equal survival. Highland *et al*. obtained transition probabilities for bosentan from Rubin *et al*.[45] Values for treprostinil and epoprostenol were based on bosentan probabilities and adjusted by the RR of improvement in the 6MWT for each therapy obtained from other trials. The model presented by Wlodarczyk and colleagues obtained effectiveness data from two clinical trials[43,45] and a long-term open-label extension study provided by industry. Mortality data for conventional therapy were estimated using clinical data on haemodynamic parameters from a trial with long-term follow-up.[43,45] The data were entered into the NIH equation and mortality estimated using the survival model proposed by D'Alonzo *et al*.[5] Bosentan mortality data were obtained from the two clinical trials. In addition, data on withdrawal rates and the probability of hospitalisation were also estimated using trial data.

The analysis in Narine *et al*. was from a health-care perspective, with Einarson *et al*. widening the perspective that the analysis considered by including societal costs. Both models discounted costs only at a rate of 3%, as no measure of effectiveness was used. The models presented in the Wlodarczyk and Highland papers considered a health-care perspective only, with the former discounting costs and life-years at 5%. The Highland model did not require discounting as the time horizon was 1 year.

All four studies considered appropriate resource use items. These typically were the cost of the drugs, initiation of therapy, medical supplies, particularly those associated with the delivery of the drugs, primary and secondary care consultations, surgical and diagnostic procedures, including liver function tests for bosentan, and treatment of SAEs, in particular sepsis. Wlodarczyk *et al*. considered conventional therapy as the comparator, and this consisted of diuretics, oral anticoagulants, calcium channel blockers, oxygen therapy and digoxin. Unit costs were obtained from standard sources in all studies.

The model presented by both Einarson *et al*. and Narine *et al*. did not consider outcomes as the two therapies were considered to be of equal efficacy. The Wlodarczyk model considered outcomes in life-years and only the Highland model measured outcomes in quality-adjusted life-years (QALYs). The health state valuations were obtained from clinical experts. Using the EQ-5D questionnaire, a consensus was achieved on the extent of limitations in each of the five dimensions for each FC. Then the health state descriptions were adjusted for expected side effects associated with the treatments. An alternative set of values was also estimated by increasing FCI estimates by 0.04 and other estimates by this factor plus a further 0.02. A minimum of 0.1 was allowed for FCIV. The values produced are presented in *Table 37*.

The model used by the Einarson and Narine papers demonstrated savings when using treprostinil compared with epoprostenol. The analysis by Einarson *et al*. from a US perspective gave savings of US$37,433 over the 3-year time horizon, with an expected average cost saving per patient per year of US$12,478. The greatest savings were attributed to reducing hospitalisation for dose titration and treatment of adverse events, particularly sepsis. The savings reported from a Canadian perspective by Einarson *et al*. were C$2,610,642 overall, with an average annual saving of C$14,504 from a health-care perspective and C$15,452 from a societal perspective. Again, savings were attributed to reduced hospitalisations. Probabilistic sensitivity analysis (PSA) presented in both papers demonstrated almost a 100% probability of cost savings.

The results of the Highland *et al*. analysis, from a US perspective, showed bosentan to be dominant over epoprostenol. For a cohort of 100 patients, cost savings were US$3,631,900 with a QALY difference of 11. Sensitivity analyses included changing the RR of improvement and also using alternative utility values, but bosentan still remained cheaper and with greater QALYs. The Australian study by Wlodarczyk *et al*. demonstrated greater survival on bosentan than

TABLE 37 *Utility values in published quality of life papers by FC*

	Keogh et *al.*, 2007[84]	**Kirsch, 2000[76]**		**Highland et *al.*, 2003[72]**	
Source	SF-36; *n* = 177, PAH patients on bosentan	2-year TTO; *n* = 64, general population	10-year TTO; *n* = 64, general population	Clinician consensus using EQ-5D	
Health state	**Mean (±SD)**	**Mean (SD)**	**Mean (SD)**	**Bosentan**	**Epoprostenol**
FCI	0.73 (±0.09)	0.934 (0.093)	0.930 (0.093)	Base: 0.92; alternative: 0.96	Base: 0.68; alternative: 0.72
FCII	0.67 (±0.10)	0.782 (0.244)	0.765 (0.183)	Base: 0.75; alternative: 0.81	Base: 0.63; alternative: 0.69
FCIII	0.60 (±0.10)	0.553 (0.361)	0.509 (0.351)	Base: 0.27; alternative: 0.35	Base: 0.18; alternative: 0.26
FCIV	0.52 (±0.09)	0.371 (0.407)	0.284 (0.404)	Base: 0; alternative: 0.1	Base: 0; alternative: 0.1

EQ-5D, EuroQol 5 dimensions; FC, functional class; PAH, pulmonary arterial hypertension; SD, standard deviation; SF-36, Short-Form 36; TTO, time trade-off.

on conventional therapy, with 6.7 discounted life-years after 15 years for bosentan compared with 2.8 for conventional therapy. The discounted mean cost was A$234,618 for bosentan and A$18,287 for conventional therapy, giving an ICER of A$55,927 per QALY gained. After 5 years the ICER was a much higher A$84,231 per QALY gained. Sensitivity analyses considered issues such as continuation rules (addition of or switching to epoprostenol), and a series of one-way sensitivity analyses were conducted on many of the model parameters. Mortality was found to be a key variable that reduced the ICER, as was the inclusion of epoprostenol for a small proportion of patients.

Quality of life

A total of 16 quality of life studies (excluding the economic evaluation papers presenting quality of life) were identified; however, two of these[74,75] were subsequently found to be general commentary papers that did not present empirical data. Five papers presented values using standard tools to elicit health state utilities. The remaining nine papers considered generic or disease-specific quality of life measures, the most common being the SF-36. One further published paper[76] was identified from the manufacturer submissions, giving health state valuations for NYHA FCI–IV. This section will briefly describe the studies considering generic and disease-specific quality of life measures, and will concentrate on those studies containing utility values for health states.

Excluding those studies converting SF-36 values into utility values, quality of life was assessed using the SF-36 in a total of seven studies.[9,49,77–81] Chua *et al.*[81] also used the Minnesota Living with Heart Failure (MLHF) questionnaire and the Assessment of Quality of Life (AQoL) instruments. The MLHF tool was also used by Cenedese *et al.*[82] A paper published in 2006 by McKenna *et al.*[83] reported on the development of the disease-specific Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) questionnaire, the first PAH-specific tool. The EQ-5D was also administered in the validation stage; however, only correlations between the tools were presented.

Keogh *et al.*[84] considered the SF-36 and AQoL questionnaire in 177 patients receiving bosentan. Responses to certain items in the SF-36 were used to produce utility values for each FC. Two papers generated values using the EQ-5D. Olschewski *et al.*[41] conducted a study to evaluate the use of inhaled iloprost in patients with severe pulmonary hypertension compared with placebo. The questionnaire was administered at baseline and after 12 weeks, demonstrating an improvement in health state for patients on active therapy. However, utility values were not presented by FC, and at baseline there was a mix of FCIII and FCIV patients. Sitbon *et al.*[85] considered both the EQ-5D and SF-36 in 16 patients with HIV-associated PAH receiving bosentan for a total of 16 weeks. As in the previous study the questionnaire was administered at baseline and at the end of follow-up and demonstrated an improvement in quality of life on treatment.

Shafazand *et al.*[86] described quality of life in 53 patients with PAH, of whom 53% received

epoprostenol and 75% were in FCIII or FCIV. The tools administered in the study were the Nottingham Health Profile, the Congestive Heart Failure Questionnaire and the Hospital Anxiety and Depression Scale. In addition, the authors used the VAS and standard gamble methods to elicit preferences for current health. Results were presented for all patients and those taking and not taking epoprostenol. The standard gamble results showed little difference between the epoprostenol and non-epoprostenol groups; however, the VAS score gave a slightly lower value with no epoprostenol, and overall the VAS values were lower. One drawback of the utilities gained in the study is that they were directly elicited from patients rather than from the general population.

The paper by Groen *et al.*[87] presented a model of lung transplantation for patients with end-stage pulmonary disease, which included pulmonary hypertension. Utility values were derived from the EQ-5D questionnaire administered to patients on the waiting list of a lung transplantation programme every 3 months and after transplantation; however, the values for different periods of time on the waiting list were not related to any health state, for example FC or specific condition. Kirsch[76] considered the feasibility of defining a QALY from disease-specific data using the NYHA classifications using the time trade-off method (TTO) associated with the EQ-5D valuation method. The TTO valuations were conducted over a 2-year and a 10-year period for each of the health states (FC), and were elicited from a general population sample of 64 people via interview. Health state valuations by FC were also given in the paper by Highland *et al.*,[72] described earlier in this chapter, which presented a decision model comparing three treatments. For completeness the values used in this paper are presented in *Table 37* alongside all of the utility values presented in the other papers for each FC. *Table 38* presents the utility values for the other health states outlined in the papers.

Although four cost studies were identified, three[88–90] were not UK studies. The remaining study[91] concerned epoprostenol treatment in children alone and presented costs in US dollars. This population group is outside the remit of

TABLE 38 *Utility values in published quality of life papers, non-functional class (FC)-related health states*

	Olschewski *et al.*, 2002[41]	**Sitbon *et al.*, 2004[85]**	**Shafazand *et al.*, 2004[86]**	**Groen *et al.*, 2004[87]**
Source	EQ-5D; *n* = 203, PAH patients on iloprost or placebo	EQ-5D; *n* = 16, HIV-related PAH patients on bosentan	VAS, SG; *n* = 53, PAH patients, 53% taking epoprostenol	
Health state	**Mean (±SD)**	**Mean (±SD)**	**Mean (95% CI)**	
Iloprost baseline	0.49 (±0.28)			
Iloprost week 12	0.58 (±0.27)			
Placebo baseline	0.56 (±0.29)			
Placebo week 12	0.56 (±0.31)			
Bosentan baseline		0.37 (±0.43)		
Bosentan week 16		0.63 (±0.21)		
PAH patients, mix FC			SG: 0.71 (0.64–0.78); VAS: 0.58 (0.54–0.62)	
PAH patients, epoprostenol			SG: 0.72 (0.61–0.82); VAS: 0.60 (0.54–0.66)	
PAH patients, non–epoprostenol			SG: 0.71 (0.61–0.81); VAS: 0.56 (0.50–0.62)	
Pretransplantation:				
First 6 months				0.55
6–9 months				0.50
9–12 months				0.45
1 year				0.40

CI, confidence interval; EQ-5D, EuroQol 5 dimensions; PAH, pulmonary arterial hypertension; SD standard deviation; SG, standard gamble; VAS, visual analogue scale.

the appraisal and therefore this paper was also omitted.

Summary

The published economic evaluations used three different approaches to modelling, and none of the models produced results that are generalisable to the NHS. None of the studies were UK based, and only one considered QALYs as the outcome, with two studies only considering a cost-minimisation analysis. Two studies considered an intervention (treprostinil) that was not part of this appraisal and only one used conventional therapy as a comparator. However, the review of quality of life studies yielded several sets of health state utility values appropriate for use in the economic evaluation of intervention therapies for PAH.

Review of manufacturer cost-effectiveness submissions

A submission was received from each company; however, only four manufacturers included a model-based economic analysis. *Table 39* provides a brief summary of the four economic analyses provided.

GlaxoSmithKline submission (epoprostenol)

The submission for epoprostenol did not include any economic modelling. The report states that 'no formal cost-effectiveness analysis is available for epoprostenol'. However, information was given with regards to the pricing of the technology. The submission states that the drug is available at a discount [Commercial-in-confidence information has been removed] for this indication. [Commercial-in-confidence information has been removed].

Schering Health Care submission (iloprost)

A Markov model with a cohort of 100 patients was built to evaluate the cost-effectiveness of inhaled iloprost versus intravenous epoprostenol, with no supportive therapy comparator included in the model. The type of evaluation undertaken was a cost–utility analysis with outcomes measured in QALYs. The model had a time horizon of 20 years, with a cycle length of 3 months. The patient group modelled included those with a diagnosis of PPH of FCIII who had failed or were unable to tolerate oral therapy and who would otherwise have required intravenous epoprostenol. Age on initiation of treatment was 52 years.

Health states were based on the NYHA functional classification, with a starting state of FCIII and transitions to FCII or FCIV or death, or patients could remain in FCIII. In addition, there were also health states representing transplantation and post transplantation. In the first cycle of therapy no transition to transplantation or post transplantation was possible, and improvement of FC was only allowed in this cycle. When patients reached FCIV there was a switch of therapy to intravenous epoprostenol. The justification given for this was that it is the only licensed therapy for this indication.

Data on effectiveness were considered separately for the initial and subsequent periods. The initial period was set at 12 weeks, in line with randomised studies that followed patients for this time period. The base-case analysis used data from the AIR trial,[41] which was the largest randomised trial comparing iloprost with placebo. The trial reported FC change with treatment, and included a range of patients with primary or secondary pulmonary hypertension. Data on epoprostenol versus usual care were obtained from Barst *et al.*[11] However, as findings for the subgroup of patients in FCIII at baseline were not available, the percentage with improvement or deterioration from baseline in a mixed population of FCIII and FCIV was used. Additional analyses were undertaken using pooled data, using additional data from studies identified in their systematic review.

For subsequent periods of treatment, the D'Alonzo *et al.* study[5] was used as it reported the long-term survival of patients preceding widespread use of epoprostenol. Several studies on long-term survival were also identified for epoprostenol and iloprost and for each therapy this information was pooled. Using this data the rate of progression for actively treated patients was reduced to 69% of the rate of progression in untreated patients, so that survival after 5 years equalled that observed in the pooled analysis.

In the base-case analysis the utility values employed were those obtained from the AIR study.[41] The mean EQ-5D tariff was calculated for patients in FCII, FCIII and FCIV, using a repeated assessments model to take into account that individuals in the study provided multiple estimates. Values for transplant and post transplant were taken from an economic evaluation of lung transplantation.[92] Sensitivity analysis was undertaken on values

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TABLE 39 *Summary of methods used in industry economic analyses*

Submission features	Schering Health Care; iloprost trometamol (Ventavis®)	Actelion Pharmaceuticals; bosentan (Tracleer®)	Encysive Pharmaceuticals; sitaxentan sodium (Thelin®)	Pfizer; sildenafil (Revatio®)
Choice of therapy	Inhaled iloprost with switch to intravenous epoprostenol on reaching FCIV	Bosentan as first-line treatment	Sitaxentan as first-line treatment	Sildenafil as first-line treatment followed by iloprost or epoprostenol on failure
Comparator(s)	Intravenous epoprostenol	Historical care (30% intravenous prostaglandins, 70% supportive therapy); supportive therapy alone; intravenous prostaglandins	Bosentan; supportive care	Background therapy; each of the other four intervention therapies
Patient characteristics	Patients with primary pulmonary hypertension, FCIII, who are unable to tolerate oral therapy. Age on initiation 52 years	FCIII, age sampled from distribution. Separate analyses for IPAH patients and those with CTD	FCIII, age 18+years (STRIDE trial populations[48,95])	FCIII. Age 18+ years with primary or secondary PAH from SUPER-1[53] and SUPER-2[96] studies. Age on initiation 49 years
Form of analysis	Cost–utility analysis	Cost–utility analysis	Cost-effectiveness analysis (life-years gained)	Cost–utility analysis (vs background therapy); cost-minimisation analysis (vs four other intervention therapies)
Model used	Markov model (with cohort of 100 patients and cycle length of 3 months)	Discrete event simulation (run for 10,000 hypothetical patients)	Markov model (with cycle length of 1 week)	Markov model of two distinct parts: year 1; year 2 onwards (with cycle length of 12 weeks (×3) and 16 weeks (×1) for year 1 and yearly cycle for year 2 onwards)
Time horizon of model	20 years	Length of time on bosentan before 'clinical worsening' (i.e. death, change in treatment or need for transplantation)	5 years	30 years
Base-case results	Iloprost dominates epoprostenol alone (cost difference: £348,000; QALY difference: 0.04 per person)	IPAH: vs historical care, £21,000 per QALY; vs epoprostenol, bosentan dominates; vs supportive therapy, £84,000 per QALY CTD: vs historical care, £15,000 per QALY; vs epoprostenol, bosentan dominates; vs supportive therapy, £78,000 per QALY	Sitaxentan: vs bosentan, £19,531 per life-year gained; vs supportive care, £94,631 per life-year gained	Sildenafil vs background therapy, £22,058 per QALY CMA result: lowest cost for sildenafil

CMA, cost minimisation analysis; CTD, connective tissue disease; IPAH idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; QALY, quality-adjusted life-year.

derived from an alternative analysis of the AIR study data and on data obtained from two studies identified in a literature review.[72,76]

Resource use was estimated from a review of the literature and a panel of five experts from four specialist centres in the UK. Results were presented for each FC separately. Clinicians were asked about the conventional therapies they prescribed, the average doses and the proportion taking each therapy. Information was collected on NHS contacts such as the number of contacts with doctors and nurses at specialist and non-specialist centres, GP contacts and visits to A&E. In addition, rates and length of hospital admissions and use of day, residential and home care were collected. The frequency of adverse events during the first cycle of treatment was taken from the literature and unit costs attached to each event. It was assumed that, in subsequent cycles, adverse events would result in discontinuation of medication or be managed during routine consultations. Finally, the submission refers to a fixed fee system in which iloprost is provided at a fixed cost irrespective of the dose, thus allowing patients to be treated in a more 'economical manner'. This cost was included in the base-case analysis with the NHS price included in a sensitivity analysis. An NHS/personal social services (PSS) cost perspective was used and all costs were updated to 2006 prices. Costs and QALYs were discounted at 3.5%.

The base-case results showed that, for a cohort of 100 patients, treatment with inhaled iloprost (followed by intravenous epoprostenol in FCIV) compared with treatment with epoprostenol alone reduced costs by £34.8 million (£348,000 per person) and increased QALYs by 4 (0.04 QALYs per person). Therefore, iloprost was dominant versus epoprostenol alone. The authors noted that, although the reduction in costs was statistically significant, the difference in outcomes was close to zero. The PSA results demonstrated that, at a threshold of £30,000 per QALY gained, the probability of iloprost being cost-effective was 100%. Additional one-way sensitivity analyses were undertaken, with findings most sensitive to assumptions made about the proportion of patients improving with usual care. Results were also sensitive to the cost of drugs, but were less sensitive when the costs of managing PAH were included.

A number of limitations were discussed in the submission including problems with the evidence base, the paucity of direct comparisons in trials and the small number of patients involved. In addition, it was suggested that the assumption of no improvement in FC after the first cycle may not be realistic as 'some patients are maintained very well on active treatment'.

In conclusion, the key issue in this submission relates to the choice of comparator. Although the model results in the submission point to the cost-effectiveness of iloprost compared with epoprostenol, no comparison with supportive therapy was made. The submission argues that a comparator of epoprostenol is appropriate with the claim that it is consistent with UK clinical practice. This claim is, however, not substantiated and is not consistent with the position adopted by other manufacturers. The drug pricing assumptions are also noteworthy; as discussed, iloprost is assumed to have a fixed price regardless of dose.

Actelion submission (bosentan)

The model presented in this submission was a discrete event simulation, constructed in SIMUL8 software, which compared bosentan (as first-line treatment) with three comparators: 'historical care', supportive therapy and intravenous prostaglandins. Historical care is defined as 30% of patients receiving the lowest cost intravenous prostaglandins and the remaining 70% receiving supportive care. This definition was based on audit data from specialised PAH centres before the launch of bosentan. The submission states that 'treatment with supportive care alone is no longer a reasonable option'. The authors state that intravenous iloprost is historically the intravenous prostaglandin of choice but, because epoprostenol is cheaper, this is used in the model. In addition, epoprostenol efficacy data is also used for intravenous prostaglandins because of limited intravenous iloprost data.

The model considered 10,000 hypothetical FCIII PAH patients, with patients remaining in the model until 'clinical worsening' occurred, defined as death, a change in treatment through addition of or substitution of another intervention or the need for transplantation. Thus, costs and QALYs were not counted after a patient was deemed to have reached clinical worsening. If a patient achieved their life expectancy age without clinical worsening they were assumed to die from other causes. Two types of PAH were considered separately by the model: IPAH and CTD-APAH. Starting age was sampled from a distribution.

The model used data on the mean length of time on bosentan therapy before clinical worsening, using a combined data set of two pivotal RCTs[43,45]

plus data on long-term follow-up and a data set associated with additional papers by Williams *et al.*[93] and Denton *et al.*[44] Time on supportive therapy was calculated using the equation in the paper by D'Alonzo *et al.*[5] Survival models were constructed to consider time to clinical worsening by FC for IPAH and CTD-APAH. A Kaplan–Meier analysis was used, utilising all data irrespective of FC and type of PAH, using a Weibull model. The nature of the model meant that the time to clinical worsening and the time to death were sampled for each patient.

Utility data were obtained from two sources. Utilities from Keogh *et al.*[84] provided values in relation to FC, derived from SF-36 responses for bosentan treatment. Meads *et al.*[94] provided additional data on utilities, collected alongside the CAMPHOR disease-specific quality of life scale. Data were derived from a broad spectrum of PAH patients and, although about 60% were using bosentan, the remaining patients were taking alternative therapies. However, the assumption was made that the utilities applied regardless of treatment. They noted that this may overestimate the utility of patients on supportive therapy alone. No disutility associated with taking intravenous prostaglandins was included, which was likely to be favourable for this type of therapy. The Keogh data were used in the base case with results using the CAMPHOR utilities presented in the sensitivity analyses. Further analysis of the CAMPHOR data suggested an [Commercial-in-confidence information has been removed] in utility [Commercial-in-confidence information has been removed] in FCIII from taking no treatment to taking bosentan, and this was also included in the sensitivity analyses.

Resource use was assessed by an empirical costing study of bosentan use in 2006, which is currently unpublished. Information was obtained from multiple sources, including protocols, and much was obtained from a retrospective record review of patients from two specialist PAH centres. Costs were grouped into three periods: initiation of therapy, first year follow-up and second year follow-up. In the initiation of therapy period, resource use associated with diagnostic tests and procedures, hospitalisations, outpatient visits, equipment and consumables and other therapies was ascertained. For the follow-up periods the same items were assessed, with the exception of the exclusion of the diagnostic tests and procedures and the addition of home care delivery. Home care delivery costs were assumed to be 8% of the advanced therapy acquisition costs, based on input from one of the specialist centres. However, it was stated that this cost is negotiated centre by centre. A breakdown of the therapies forming the supportive care comparator was not given. In addition, it was not clear if the cost of a monthly liver function test is included in the costs for bosentan. Costs were for 2006 and a discount rate of 3.5% was applied to both costs and QALYs. It is assumed that the analysis was from an NHS/PSS perspective, although this was not explicitly stated.

In the base-case results for the IPAH group, the ICER for bosentan versus historical care was £21,000 per QALY gained. This rose to £84,000 per QALY for supportive therapy, and bosentan dominated when compared with intravenous prostaglandins (epoprostenol). The therapy was more cost-effective when considered in the CTD group alone, with an ICER of £15,000 per QALY versus historical care and £78,000 per QALY versus supportive therapy. Again, bosentan dominated intravenous prostaglandins. Results of the PSA for IPAH patients showed bosentan to have a 40% chance of being cost-effective compared with historical care at £20,000 per QALY, and a 90% chance of being cost-effective compared with historical care at £30,000; however, it was not cost-effective at either threshold when compared with supportive care. Analysis for CTD patients versus historical care gave 90% and 100% probabilities of bosentan being cost-effective for £20,000 and £30,000 per QALY thresholds, respectively; again, bosentan was not cost-effective at either threshold when the comparator was supportive therapy.

Use of the CAMPHOR utility data only marginally changed the overall results. However, bosentan did appear more cost-effective when the differential utility between patients on active treatment and patients not on active treatment was included. Additional sensitivity analyses considered the proportion of patients on intravenous prostaglandins, with bosentan becoming more cost-effective with a higher proportion and less cost-effective with lower proportions.

The submission concluded that treatment with supportive care is no longer a reasonable option. Therefore, taking historical care as the comparator, the submission argues that bosentan is cost-effective in the IPAH and CTD subgroups, which represent the majority of patients considered reflective of the entire Venice category 1 group.

In conclusion, the comparator issue again clearly comes through as being central to the cost-effectiveness result. The sensitivity analyses

undertaken as part of this submission (reported on page 42 of the submission) highlight this well. If the higher cost comparator of intravenous iloprost is used then, as expected, bosentan begins to look much more attractive. Another interesting issue in this submission relates to the modelling approach of counting costs and benefits only up until 'clinical worsening'. This will have understated the costs and QALY estimates, but it is not clear whether serious bias is introduced as a result of doing this.

Encysive submission (sitaxentan)

A Markov model was built to determine the cost-effectiveness of sitaxentan as first-line treatment when compared with supportive care and bosentan. The type of evaluation undertaken was a cost-effectiveness analysis with outcomes measured in life-years rather than QALYs. A cost–utility analysis was not undertaken, the justification being that 'there is limited information on quality of life in patients with PAH in the literature'. The model time horizon was 5 years with a cycle length of 1 week. The model followed a population of PAH patients of FCIII over the age of 18 years, based on trial populations from STRIDE-2[48] and STRIDE-2X.[95] Patients started in a predeterioration state and could remain in that state, deteriorate and move into a post-deterioration state, or die.

Data for STRIDE-2 and STRIDE-2X were pooled and two Weibull survival regressions (using an accelerated failure time model) were fitted to estimate the rates of FC deterioration and death of patients. Survival in the supportive care arm was obtained using the NIH survival equation in which mortality was related to haemodynamic measures.[5] This equation applied to IPAH and was derived from 3-year data. The rationale behind the short time horizon of 5 years was that the survival equation used for supportive care was derived from 3-year data, and so the authors did not consider it valid beyond 5 years. Deterioration in supportive care was handled in the accelerated failure time model by including treatment as a dummy variable, thus indicating when the treatment effect (from active treatment) should be applied in the equation.

Costs included in the analysis were drug costs and hospitalisation costs, with rate of hospitalisation and length of state for each health state determined from both STRIDE trials. As too little data were available in the bosentan arm to determine resource use post deterioration, sitaxentan data were used. Costs of supportive care were not included, and no description of what supportive care contained was provided. In addition, adverse event costs were not taken into account and, even though both bosentan and sitaxentan require monthly liver function monitoring, the cost of these additional tests was not included. All costs and life-years were discounted at a rate of 3.5% and an NHS/PSS perspective was stated, although no PSS costs were included. As the model only considered life-years gained, no utility values were required.

Base-case results showed sitaxentan to be more effective (3.32 life-years) than supportive care (2.70 life-years) or bosentan (2.45 life-years) but more expensive. The ICER was £94,631 per life-year gained for sitaxentan compared with supportive care, and £19,531 per life-year gained for sitaxentan compared with bosentan. PSA was also undertaken, with the results showing considerable uncertainty, particularly versus supportive care when sitaxentan had only a 44% chance of being cost-effective at £80,000 per life-year gained. The authors highlighted the uncertainty around the accuracy of the NIH equation as a predictive measure of survival for supportive care, and that little data were available for this therapy option. In addition, they also pointed out that the STRIDE trial data included patients with CTD and that this subgroup have a poorer prognosis, whereas the NIH equation uses data for IPAH patients who have a better prognosis.

The authors conclude that sitaxentan is at least as cost-effective as bosentan and that longer-term bosentan data suggest cost-effectiveness; thus, the submission therefore argues that sitaxentan is also likely to be so.

It is important to remember that the ICERs reported here relate to life-years gained and not QALYs. This is the only economic submission that failed to report results using QALYs. The model is described only briefly and the justification for some aspects of the analysis (e.g. the distributions used in the PSA) was not provided. The lack of comprehensiveness cost analysis data (e.g. the failure to include costs of supportive care or adverse events) was another negative. The choice of comparator again comes through as a key issue in considering cost-effectiveness – the ICERs are dramatically different depending on whether supportive care or bosentan is used as the comparator.

Pfizer submission (sildenafil)

The economic analysis conducted in this submission considered two types of analysis. The first analysis was a cost–utility analysis of sildenafil compared with background therapy. The second was a cost-minimisation analysis comparing all five interventions considered in the appraisal. The premise behind the cost-minimisation analysis was the 'absence of evidence that there any clinically meaningful efficacy differences' between the five intervention therapies.

The model presented was a Markov model with two distinct parts. In the first year the first three cycles were 12 weeks each, followed by one cycle of 16 weeks. From year 2 onwards a yearly cycle was used. The model population was patients aged 18 years and over with primary or secondary PAH in FCIII, conforming to the inclusion/exclusion criteria of the SUPER-1[53] and SUPER-2[96] studies. The start age of patients in the model was 49 years, which was the average age of patients in the SUPER-1 trial. Base-case results were presented for a time horizon of 30 years, representing remaining lifetime, and all patients had died by the age of 79 years.

Patients received initial treatment and switched to alternative therapy when that treatment failed and they deteriorated. Alternative treatment was iloprost or epoprostenol and patients remained on that therapy even if they deteriorated. Events and health states were based on changes in the 6MWD, with states representing improvement, no change and deterioration in 6MWD and death. An improvement in 6MWD was more than 39 metres compared with baseline, no change in 6MWD was between 0 and 39 metres greater than baseline and deterioration represented a reduction in distance walked. Health states also took into account whether patients were on the initial therapy or alternative therapy.

The main sources of data on clinical effectiveness and mortality for sildenafil were the SUPER-1 and SUPER-2 trials, with death rates extrapolated from unpublished clinical trial data.[97] Placebo-specific probabilities were used for supportive care. As all other therapies (except for supportive care) were assumed to be equally efficacious, sildenafil transition probabilities were used for all therapies.

Utility data were also obtained from the SUPER-1 and SUPER-2 trials, with values at baseline, week 12 and week 24 used for improvement, no change and deterioration. The data for week 24 were used for weeks 36 and 52. The submission points out that the value for deterioration at 12 weeks (0.62) was in fact higher than the baseline value (0.57) and stated that this was an 'apparent anomaly derived from the nature of utility measurement over time'. Therefore 'the utility value was averaged among all the patients in that particular health state at either baseline, 12 and 24 weeks'.

Resource use data were collected by a questionnaire administered by telephone interview with PAH experts, and the data were validated by a clinical expert with the use of patient profiles for the average FCIII patient. The resource use included was comprehensive and included adverse events, medication and co-medication, laboratory tests, diagnostic and therapeutic procedures, visits and consultations and ward admissions, all dependent on therapy and whether the patient was taking first-line therapy or in a state of deterioration. The cost of equipment required by the patient for inhalation was not included 'as the BNF mentions that it is on loan'. Supportive care was defined as use of warfarin and furosemide by 100% of patients. Intervention therapies were taken alongside standard co-medication with alternative therapy regimens depending on the intervention therapy and FC. Unit costs were obtained from standard sources, and the cost year was 2007. Cost and QALYs were discounted at 3.5%. The costs considered were NHS only, as the authors stated that there were no robust data for PSS resource use.

The results of the base-case analyses gave an ICER of £22,058 per QALY gained for sildenafil versus background therapy. The PSA, run for 1000 iterations, suggested that sildenafil had an 84% probability of being cost-effective at £30,000 per QALY gained and a 66% probability of being cost-effective at £20,000. In the cost-minimisation analysis, QALYs were assumed to be equivalent across intervention therapies as efficacy was assumed to be the same. Therefore total costs and an 'average cost per QALY' were presented for each therapy, with the lowest costs demonstrated by sildenafil. The sensitivity analysis considered results over a 1-year period, and the ICER for sildenafil compared with background therapy was lower at £15,252 per QALY gained. Total costs and average cost per QALY when compared with other intervention therapies also demonstrated sildenafil to be of lowest costs.

This submission does not provide adequate detail of the model structure, the data inputs or the analysis methods to allow a detailed critique of the economic model to be undertaken. Thus, it is difficult to have confidence in the results of the

cost–utility analyses. For example, the definition of 'background therapy', the comparator for the main analysis, is not precisely defined. However, in its favour, this is the only submission that has attempted a head-to-head comparison of all of the newer treatments, although the strong assumption was made of no effectiveness differences between treatments and so the analysis was simply a search for the lowest cost alternative. This assumption does not consider the absence of long-term published data for sildenafil at the licensed dose.

Summary of manufacturer submissions

The disparity in methods used between the different manufacturer submissions highlights the fact that there is as yet no consensus as to the most appropriate model to use for the current technology assessment. This partly reflects the fact that the technologies are aimed at somewhat different groups of patients. There is some variability in the modelling approach, but more importantly in the type of economic evaluation used, with cost per QALY and cost per life-year being offered as efficiency measures. One submission has performed a cost-minimisation analysis.

There is also wide variation in the methods used and sources of data for important model inputs such as survival estimates, quality of life (utility) scores and cost estimates.

Finally, a key issue is that of the appropriate comparator to be used. The various manufacturer submissions are, in effect, not all addressing the same policy question.

Independent economic assessment

This section provides details of a model developed by the assessment team and used to evaluate the cost-effectiveness of each active therapy within its licensed indication compared with supportive care over the effective lifetime of PAH patients (30 years).

Methods

Model description

A Markov model built in TREEAGE PRO® was developed to determine the cost-effectiveness of each intervention therapy with supportive care for PAH compared with supportive care alone. The population considered was adults with PAH (category 1 of the Venice 2003 clinical classification[1]) in NYHA/WHO FCIII (and NYHA/WHO FCIV for epoprostenol) for whom calcium channel blockers were inappropriate or no longer effective. One reference case analysis was conducted using data on all category 1 PAH patients. A separate analysis for idiopathic PAH alone was proposed but a lack of data prevented this.

The five intervention therapies considered within their licensed indications for FCIII were epoprostenol (administered by continuous intravenous infusion), iloprost (administered by inhalation) and the oral therapies of bosentan, sitaxentan and sildenafil, with epoprostenol also considered for FCIV. Only the first use of the interventions was considered, and initiation of any of the interventions after failure of another listed intervention was not considered, with the exception of epoprostenol for patients in FCIV. Therefore, for all treatments the starting state was FCIII with a further analysis conducted with a starting state of FCIV for epoprostenol.

The time horizon of the model was the effective lifetime of patients (30 years), and a starting age of 50 years was used to represent the average age of patients with the disease. The general mortality data were weighted to take into account the ratio of women to men with the disease (1.5:1). A time cycle of 12 weeks was chosen as being sufficiently short enough to capture the effect of treatment, and this time period was in line with that used in the trials for measurement of treatment effect. Health states were based on FC, with a starting health state of FCIII for all therapies and FCIV when the model was run for intravenous epoprostenol for this patient population.

In the first cycle of treatment patients could improve from their starting state FC to the adjacent FC. In all cycles patients could also remain in the same health state or deteriorate and move to the next FC. In addition, patients were also at risk from PAH-related mortality or an age-related death due to other causes. In the intervention arm, once a patient deteriorated and moved to FCIV, the patient switched to intravenous epoprostenol alone, with the first-line therapy discontinued. Although in clinical practice the first-line therapy is unlikely to be stopped, this appraisal considers the treatments within their licensed indications only and therefore this was the only option considered. Data on the effectiveness of combination therapies was not available and

therefore inclusion of combinations in FCIV would only have an impact on cost. In the supportive care arm, once deterioration to FCIV was reached, patients switched to intravenous epoprostenol. The only exception was for the model run concerning epoprostenol in FCIV patients and here the comparator was supportive care alone. For all active therapies patients also received supportive therapy.

As the model ran, costs and QALYs were accumulated dependent on the transitions between health states determining FC, therapy and survival. A half-cycle correction was applied. All costs and QALYS were discounted at the rate of 3.5% per year. The model is presented in *Figure 9*.

Estimation of model parameters

Treatment effect

Transition probabilities on supportive care were directly related to the intervention, with separate probabilities for epoprostenol, iloprost and the three oral therapies. The rationale behind this was that the supportive care group in question may have been different in the epoprostenol, iloprost and oral therapy trials and patient prognosis may have been less favourable in the epoprostenol and iloprost trials. For each therapy the effect of treatment was incorporated into a transition probability by applying the odds ratio for change in FC on treatment to the respective supportive care transition probability.

For the first cycle of 12 weeks, the transition probabilities and odds ratios for iloprost were obtained from data for the subset of FCIII, PPH patients in the AIR study[41] provided within the manufacturer submission. No appropriate transition data stratified by FC were available for epoprostenol. Of the three epoprostenol trials, data from Barst *et al*.[11] (PPH only, mixed FC) were regarded as the best option given that the study by Rubin *et al*.[39] was only of 8 weeks duration and that by Badesch *et al*.[33] included exclusively PAH patients with scleroderma, which is outside epoprostenol's license. Data from Barst *et al*.[11] were therefore used, but it had to be assumed that values from the whole trial population (74% FCIII, 26% FCIV) can be applied to both FCIII and FCIV (i.e. transition probabilities and odds ratios for improvement of at least one FC based on the whole trial population are used for both FCIII to FCII and FCIV to FCIII; the values for deterioration of at least one FC including deterioration to death based on the whole trial population are used for FCIII to FCIV). Similar rules were applied for other drugs for which FC-specific transition probabilities and odds ratios were not available (i.e. assuming same value for FCIV to FCIII and FCIII to FCII; for FCII to FCIII and FCIII to FCIV).

Transition probabilities for the supportive care for models of oral therapies were calculated using combined data from the placebo arms of Channick *et al*.[43] (bosentan), BREATHE-5[47] (bosentan), STRIDE-2[48] (sitaxentan and bosentan) and SUPER-1[53] (sildenafil). Apart from these trials, data for FCIII patients receiving supportive care were also available from the placebo arms of BREATHE-1[45] and STRIDE-4.[37] However, these data were not included as FC improvement (from FCIII to FCII) in the placebo arms of these two trials was exceptionally high (> 20%) at 12 weeks and was considered unrealistic in clinical practice according to the advice from clinical experts.

The source of odds ratios for bosentan treatment relative to supportive care was a pooled analysis that included data from Channick *et al*.[43] and BREATHE-5,[47] but excluded data from STRIDE-2[48] (bosentan arm only was open-label) and BREATHE-1[45] (data stratified by FC were not available for bosentan arms). The odds ratios for sitaxentan were obtained from a pooled analysis using data from STRIDE-2[48] and STRIDE-4,[37] but excluding data from STRIDE-1[49] (data stratified by FC were not available). The odds ratios for sildenafil were available from the SUPER-1 trial.[53]

Because of the paucity of data, the same values for the transition probabilities and odds ratios for FC improvement and FC deterioration were used for the first 12 weeks on treatment and beyond 12 weeks. Twelve-week data for FC deterioration in FCII patients in the placebo arms of the STRIDE-2[48] and SUPER-1[53] trials were used as an approximation of the transition probability for deterioration from FCII to FCIII beyond 12 weeks on supportive care.

Transition probabilities were entered into the model as beta distributions (*Tables 40* and *41*). Odds ratios were entered as lognormal distributions (*Tables 42* and *43*).

Mortality

Mortality comprised two components: age-related general population mortality and PAH-related mortality. It was assumed that there was an additional mortality due to PAH, dependent on FC and treatment. This was assumed to be constant for each cycle. Mortality in FCII was assumed to be the general population mortality only. Details of the method used and uncertainty around it appear

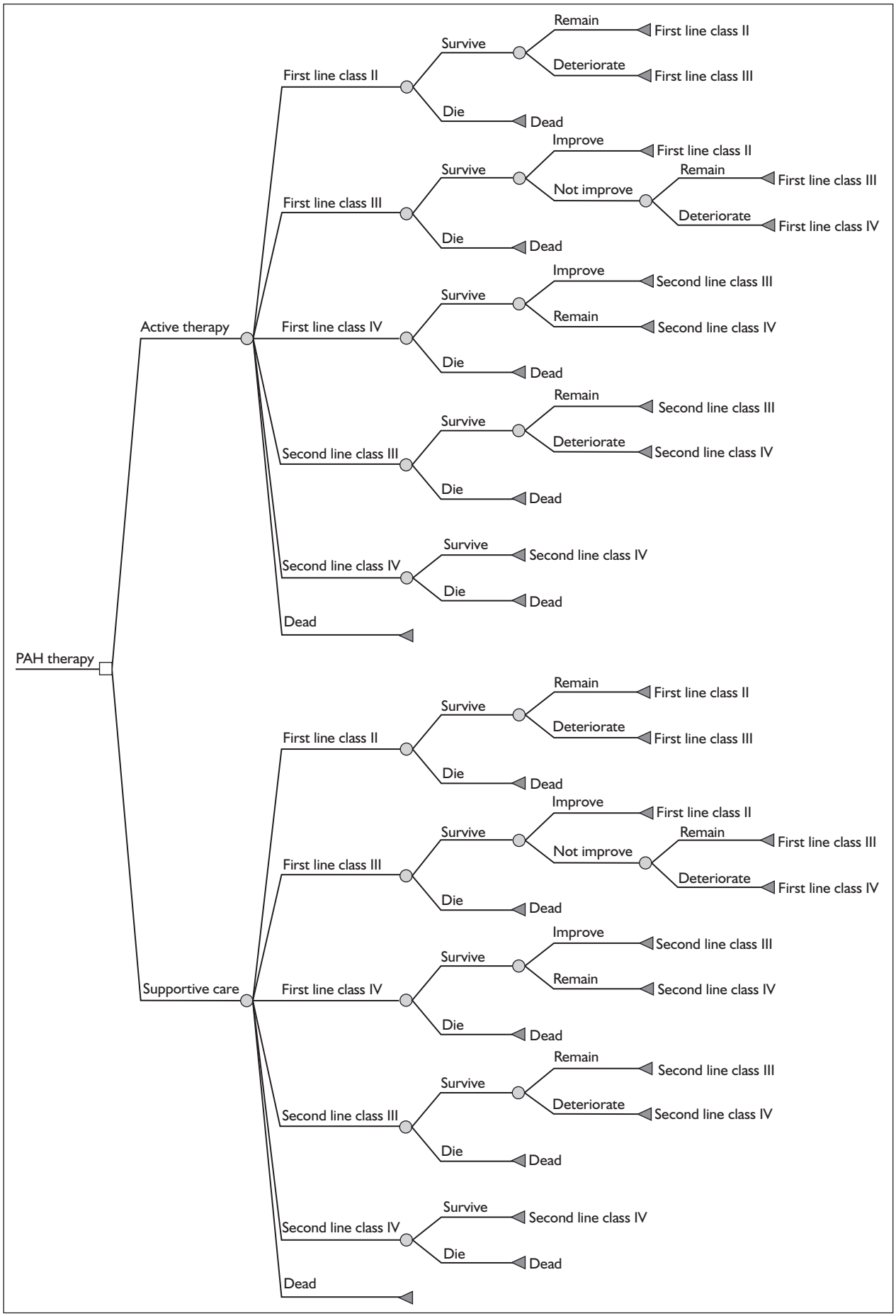

FIGURE 9 *Diagram of the decision model. PAH, pulmonary arterial hypertension.*

TABLE 40 *Transition probabilities for supportive care for the first 12 weeks*

	Functional class (FC) transition (*r*/*n*) (lower and upper confidence limits)		
Intervention	**FCIII to FCII**	**FCIII to FCIV[a]**	**FCIV to FCIII**
Epoprostenol (Barst *et al*., 1996[11])	0.025 (1/40) (0.001–0.090)	0.300 (12/40) (0.170–0.449)	0.025 (1/40) (0.001–0.090)
Iloprost (AIR[41])	0.056 (2/36) (0.007–0.149)	0.250 (9/36) (0.125–0.401)	–
Oral therapy (pooled Channick *et al*., 2001,[43] BREATHE-5,[47] STRIDE-2[48] and SUPER-1[53])	0.125 ([Commercial-in-confidence information has been removed]) (0.067–0.198)	0.094 ([Commercial-in-confidence information has been removed]) (0.044–0.159)	–

a Including FCIII to death (when occurred), except for STRIDE-2 for which it was unclear whether reported FCIII to FCIV included death.

TABLE 41 *Transition probabilities for supportive care beyond 12 weeks (using 12-week data)*

	Functional class (FC) transition (*r*/*n*) (lower and upper confidence limits)		
Intervention	**FCII to FCIII[a]**	**FCIII to FCIV**	**FCIV to FCIII**
Epoprostenol (Barst *et al*., 1996[11])	0.300 (12/40); (0.170–0.449)	0.300 (12/40); (0.170–0.449)	0.025 (1/40); (0.001–0.090)
Iloprost (AIR[41])	0.250 (9/36); (0.125–0.401)	0.250 (9/36); (0.125–0.401)	–
Oral therapy (STRIDE-2[48] and SUPER-1[53] for FCII to FCIII; Channick *et al*., 2001,[43] BREATHE-5,[47] STRIDE-2[48] and SUPER-1[53] for FCIII to FCIV)	0.127 ([Commercial-in-confidence information has been removed]); (0.054–0.226)	0.094 ([Commercial-in-confidence information has been removed]); (0.044–0.159)	–

a Using FCIII to FCIV for epoprostenol and iloprost.

TABLE 42 *Odds ratio by intervention for the first 12 weeks*

	Functional class transition (FC), odds ratio (lower and upper confidence limits)		
Intervention	**FCIII to FCII**	**FCIII to FCIV[a]**	**FCIV to FCIII**
Epoprostenol (Barst *et al*., 1996[11])	24.96 (3.11–200.14)	0.40 (0.13–1.20)	24.96 (3.11–200.14)
Iloprost (AIR[41])	4.41 (0.85–22.97)	0.29 (0.07–1.18)	–
Bosentan (pooled data from Channick *et al*., 2001[43] and BREATHE-5[47])	5.02 (1.35–18.65)	0.21 (0.03–1.76)	–
Sitaxentan (pooled data from STRIDE-2[48] and STRIDE-4[37])	2.08 (0.46–9.44)	0.18 (0.02–1.64)	–
Sildenafil (SUPER-1[53])	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	–

a Including FCIII to death (when occurred), except for STRIDE-2 for which it was unclear whether reported FCIII to FCIV included death.

in Appendix 9. Transition probabilities for PAH-related mortality were entered in the model as beta distributions. The 12-week mortality rates for the intervention therapies are presented in *Table 44*. The corresponding mortality rates for supportive care are presented in *Table 45*.

TABLE 43 *Odds ratios by intervention beyond 12 weeks*

	Functional class (FC) transition, odds ratio (lower and upper confidence limits)		
Intervention	**FCII to FCIII (using same as FCIII to FCIV)**	**FCIII to FCIV**	**FCIV to FCIII**
Epoprostenol (Barst *et al.*, 1996[11])	0.40 (0.13–1.20)	0.40 (0.13–1.20)	24.96 (3.11–200.14)
Iloprost (AIR[41])	0.29 (0.07–1.18)	0.29 (0.07–1.18)	–
Bosentan (pooled data from Channick *et al.*, 2001[43] and BREATHE-5[47])	0.21 (0.03–1.76)	0.21 (0.03–1.76)	–
Sitaxentan (pooled data from STRIDE-2[48] and STRIDE-4[37])	0.18 (0.02–1.64)	0.18 (0.02–1.64)	–
Sildenafil (SUPER-1[53])	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	–

TABLE 44 *Rates for additional pulmonary arterial hypertension-related mortality for all therapies (per 12 weeks)*

Treatment	**FC**	**Per-cycle mortality (95% CI)**	**Beta distribution**
Epoprostenol, iloprost (pooled data from Sitbon *et al.*, 2002,[66] Sitbon *et al.*,2005,[98] McLaughlin *et al.*, 2002[65])	III	0.021 (0.017–0.025)	$n = 5000$, $r = 105$
Epoprostenol (pooled data from Sitbon *et al.*, 2002,[66] McLaughlin *et al.*, 2002[65])	IV	0.056 (0.044–0.069)	$n = 1250$, $r = 70$
Bosentan (Sitbon *et al.*, 2005[98])	III	0.010 (0.006–0.015)	$n = 1600$, $r = 16$
Sitaxentan, sildenafil (pooled data from STRIDE-1X[99] and STRIDE-2X[100]	III	0.011 (0.004–0.023)	$n = 450$, $r = 5$

CI, confidence interval; FC, functional class.

TABLE 45 *Mortality on supportive care by intervention therapy (per 12 weeks)*

Treatment	**FC**	**Mortality on supportive care (95% CI)**	**Beta distribution**
Epoprostenol	III	0.051 (0.041–0.069)	$n = 950$, $r = 48$
Epoprostenol	IV	0.129 (0.103–0.156)	$n = 600$, $r = 77.5$
Iloprost	III	0.069 (0.056–0.093)	$n = 700$, $r = 48$
Oral therapies	III	0.058 (0.006–0.116)	$n = 66$, $r = 3.84$

CI, confidence interval; FC, functional class.

Resource use and costs

The resource use was broadly concerned with the initiation and ongoing costs of each therapy, contacts with primary and secondary health care, adverse events and use of wider social services including palliative care. The perspective adopted for the reference case is that of the NHS/PSS, and a price year of 2006 was applied.

The cost of each of the therapies in question was calculated using *British National Formulary* (*BNF*) prices for March 2007,[26] using the licensed dose (*Table 46*). For bosentan, in the first month of treatment it was assumed that the dose was 62.5 mg twice a day, with a dose of 125 mg twice a day for subsequent months. For inhaled iloprost and intravenous epoprostenol, for which the actual doses vary, estimates of average doses from clinical opinion were used. The amount of inhaled iloprost varies from patient to patient; however, as one vial is 10 µg and a patient opens a vial each time they nebulise, the cost of a 10-µg vial (£14.15) was used for each inhalation. It was assumed that a patient nebulised seven times a day. The amount of epoprostenol required for infusion was approximately 15–20 ng/kg/min at the end of the

TABLE 46 *Costs of therapies*

Therapy	Dose, mean (range)	Unit cost (per 4 weeks) (£) (SD)
Epoprostenol:		
Year 1	17.5 (15–20) ng/kg/min	4282.94 (305.92)
Year 2	40 (30–50) ng/kg/min	9789.59 (1223.70)
Iloprost	10-μg vial seven times a day	2773.40
Bosentan	125 mg twice daily	1541.00
Sitaxentan	100 mg once daily	1540.00
Sildenafil	20 mg three times daily	348.60

SD, standard deviation.

first year, and an average of 17.5 ng/kg/min was used for the first year. Although it was assumed that the dose in the first months would be much lower (the iloprost manufacturer submission uses values of 2.2 ng/kg/min at baseline and 14.1 ng/kg/min at 3 months), comparison with this industry data demonstrated that using this mean over the whole year would not be inappropriate. An average dose of 40 ng/kg/min was used for the second and subsequent years as the range was between 30 and 50 ng/kg/min. A standard deviation around the point estimate was estimated by assuming that the difference between the mean and an upper (or lower) limit equalled two standard deviations. The cost per mg of the drug was £86.71 and an average patient weight of 70 kg was applied.

Further information was provided by the manufacturers with regards to the cost contract with the NHS. GlaxoSmithKline stated that epoprostenol was available at a discount [Commercial-in-confidence information has been removed] for this indication, [Commercial-in-confidence information has been removed]. Schering Health Care referred to a fixed fee system called VENTafee, in which iloprost was provided at a fixed cost of £7400 (excluding VAT) per quarter irrespective of the dose. For both drugs the *BNF* price was included in the reference case, with the price of the alternative arrangements included in a sensitivity analysis. This equates to £2269.13 for 4 weeks of iloprost and [Commercial-in-confidence information has been removed] per 4 weeks for the first and subsequent years of epoprostenol respectively.

The therapies included in the definition of supportive care were warfarin, furosemide, digoxin and oxygen and it was assumed that all patients would be on each therapy. This is likely to be an overestimate; however, the costs of supportive therapies are small in comparison with the intervention therapies. In addition, when supportive care was not used in conjunction with an active therapy, it was assumed that the patient was hospitalised until death in FCIV. Supportive therapy was assumed to be given to patients irrespective of being on active therapy, but the intensity of supportive therapy was dependent on FC, particularly oxygen therapy. The proportion of patients requiring oxygen in each FC was obtained from the iloprost manufacturer submission, with rates of 5%, 27% and 71% for FCII, FCIII and FCIV respectively. An assumption was made that all patients in FCIV taking supportive therapies would only be on oxygen. The intensity of oral supportive therapies may also increase with worsening FC; however, this level of detail was not available and therefore a standard dose for each drug was used. As the cost of these oral therapies was deemed very low, the impact of dose changes would be negligible. All units and costs are presented in *Table 47*.

The cost of warfarin therapy includes not only the drug but also regular monitoring to ensure that the patient lies within their therapeutic INR range, thus reducing the risk of thrombolic or haemorrhagic events. As there are different models of care for monitoring, an average cost per visit was used from a trial of 617 patients[101] and applied to an assumed average frequency of a monitoring visit every 4 weeks.

For each active therapy an initiation cost was required. In the case of the three oral therapies the model assumed that the patient was on a day ward as a day case and any education by a nurse was assumed to be part of this day case cost. The unit cost used was that of a day case with cardiac catheterisation as this procedure would take place at this visit. An additional initiation cost for bosentan and sitaxentan was a liver function test. Patients commencing inhaled iloprost or

TABLE 47 *Costs of supportive therapies*

Therapy	Average dose per day	Cost per 4 weeks (£)
Warfarin	5 mg once daily	1.47
Furosemide	100 mg once daily	3.59
Digoxin	125 mg once daily	2.40
Oxygen:		0.66 per unit
FCII (5% uptake)	2 ml	1.84
FCIII (27% uptake)	2 ml	9.94
FCIV (71% uptake)	2.3 ml	30.06
FCIV (100% uptake, supportive therapy only)	2.3 ml	42.34

FC, functional class.

intravenous epoprostenol therapy required a longer period of time in hospital and training in order to use the drug delivery system safely. For inhaled iloprost it was assumed that patients were admitted for 3 days with a specialist nurse spending 2 hours a day with the patient for training. Initiation costs for intravenous epoprostenol were higher as it was assumed that a patient would spend approximately 12 days in hospital. Much training is required to ensure that patients are familiar with mixing the drugs and keeping all equipment sterile to reduce the risk of infection. Therefore it was assumed that a specialist nurse would spend 2 hours a day, 5 days a week training the patient. In addition, the cost of the insertion of a central venous catheter for intravenous administration of epoprostenol was also included. The unit cost used here was an elective inpatient stay for catheterisation of 2 days. Therefore the cost of the additional 10 days was calculated using the daily inpatient rate. Other costs may be applicable to patients at initiation of therapy, particularly with regard to standard tests for PAH patients; however, these were not included as they were assumed to apply for all therapies.

Ongoing costs were attributed to each drug to take into account a service fee, which includes delivery of the drug and providing any equipment required for drug delivery. Costs presented here are strictly confidential. Because of the possibility of liver toxicity when taking bosentan or sitaxentan it was assumed that patients had a liver function test every 4 weeks. In addition, each therapy was associated with a number of adverse events, varying in severity and most common in the first period of taking therapy. However, it was decided that the model should only consider the most severe (and therefore costly) adverse events. Therefore only line infection and sepsis while on intravenous epoprostenol were considered, with 17% (line infection) and 4% (sepsis) of patients suffering these events over a 3-month period.[11,39]

Primary and secondary care resource use was assumed to be related to FC. Social care and palliative care were also included in resource use, again related to FC. No published data were available on resource use; however, information was available in the iloprost industry submission, obtained from the research carried out by Schering Health Care. The overall costs per FC are presented in *Table 48*. NHS contacts included seeing hospital physicians and nurses, GP visits and A&E attendance. Personal and social services included residential, day and home care and hospice visits. Hospitalisations considered stays in general wards and intensive care and coronary care units and associated A&E attendance. Full details of resource use and unit costs used by this industry submission are presented in the Appendix 10. As the model assumes that patients on supportive care alone in FCIV will be hospitalised until death, the same resource use for FCIV was used except that the average hospitalisation costs were excluded and replaced by a cost of ongoing inpatient care for all patients at £188 a day.

Unit costs were obtained from a number of standard sources and are presented in *Table 49*. Drug costs were obtained from the most recent *BNF* (March 2007).[26] Staff costs and the cost of an inpatient stay were obtained from the *Unit Costs of Health and Social Care*.[102] Costs of procedures were obtained from NHS reference costs for 2005/6.[103] Warfarin monitoring costs were obtained from a trial dataset presented in Jowett *et al.*[101] and were inflated to 2006 costs. Other costs, for example liver function tests, were obtained from estimates used in the industry submissions.

TABLE 48 *Primary and secondary care resource use (cost per 4 weeks in £)*

Functional class	NHS contacts	Hospitalisations	Personal and social services	Total
II	42.44	19.01	4.91	66.36
III	68.87	85.86	54.83	209.56
IV	89.05	601.93	709.38	1400.36

TABLE 49 *Unit costs*

Resource item	Unit cost (£)	Source
Initiation costs		
Day ward	838	NHS reference costs 2005/6[103] [day cases, cardiac catheterisation and angiography without complications (HRG code E14)]
Inpatient day	188	Curtis and Netten[102] (patient rehabilitation, general inpatient cost, cost per bed day)
Specialist nurse (per hour)	37	Curtis and Netten[102] [nurse advanced (including clinical nurse specialist) (including qualifications)]
Central venous catheter insertion for intravenous therapy	1648	NHS reference costs 2005/6[103] [elective inpatient, cardiac catheterisation and angiography without complications (2-day stay) (HRG code E14)]
Additional costs		
Service contracts (per year):		
Epoprostenol	9464	Costs estimated through expert contact
Iloprost	5512	
Bosentan, sitaxentan, sildenafil	542	
Liver function test	22.47	London Clinic pathology price list 2003–4 (from sildenafil submission)
Sepsis	2011	NHS reference costs 2005/6[103] [non-elective inpatient, septicaemia (HRG code S12)]
Catheter site infection	1321	NHS reference costs 2005/6[103] [non-elective inpatient, other non-viral infections (HRG code S15)]
Warfarin monitoring visit	10.39	Jowett *et al.*[101]

HRG, Healthcare Resource Group.

Estimation of quality-adjusted life-years

As the model health states were based on FC, utility values also based on FC were sought from the literature and manufacturer submissions. Valuations based on FC were available from two quality of life studies,[76,84] one economic evaluation[72] and the iloprost and bosentan manufacturer submissions.[41,94] The data in the AIR study were analysed further to provide utility scores by FC, and values presented in the iloprost submission. The data presented here are from the simple pooling analysis. The data from Meads *et al.*[94] remains academic-in-confidence. The values used in the Highland *et al.* model[72] were not utilised here as the values were gained by clinical consensus and a valuation of 0 was given for FCIV, i.e. the same as death, which was not deemed to be appropriate for this cost-effectiveness analysis. The values from Keogh *et al.*[84] were used in the base case as this study has the largest sample size and is not academic-in-confidence. However, it should be noted that, although the patient population comprised bosentan patients, the model assumes that these values are applicable for all therapies. The utility values were entered into the model as beta distributions (*Table 50*). Alternative values were used in the sensitivity analysis to investigate the impact on overall results (*Table 51*).

TABLE 50 *Base-case utility values from Keogh* et al.[84]

Health state	Mean (SD)	α	β
Functional class II	0.67 (0.1)	14.144	6.966
Functional class III	0.60 (0.1)	13.800	9.200
Functional class IV	0.52 (0.09)	15.504	14.311

SD, standard deviation.

TABLE 51 *Alternative utility values*

	Meads *et al.*[94]	Kirsch 2000,[76] 2-year TTO	Kirsch 2000,[76] 10-year TTO	Olschewski *et al.*, 2002[41]
Health state	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Functional class II	[Academic-in-confidence information has been removed]	0.782 (0.031)	0.765 (0.023)	0.75 (0.193)
Functional class III	[Academic-in-confidence information has been removed]	0.553 (0.045)	0.509 (0.044)	0.61 (0.254)
Functional class IV	[Academic-in-confidence information has been removed]	0.371 (0.051)	0.284 (0.051)	0.44 (0.291)

SD, standard deviation; TTO, time trade-off.

Model assumptions

Odds ratios were calculated for the deterioration from FCIII to FCIV for each therapy, to be applied to supportive care transition probabilities. In the absence of suitable mortality data for supportive care alone, it was assumed that the odds ratios for deterioration could also be used as odds ratios for mortality.

Although lung transplantation is an option available to PAH patients in FCIV, this was not included as an event in this model as very few PAH patients actually have a transplant

Bosentan is licensed at 125 mg twice daily and 250 mg twice daily, and consideration of the dose taken was required for the drug costs. Advice from clinical experts indicated that very few patients are on the 250-mg twice daily dose, as liver toxicity is greater and no significant improvement is seen on this higher dose. Accordingly, the model assumed that all patients were taking 125 mg twice daily.

Assessment of cost-effectiveness

The main results are presented as mean costs and QALYs from 10,000 simulations for the alternative policy options considered. Incremental costs and QALYs and, when appropriate, an estimate of the incremental cost per QALY are shown. Cost-effectiveness acceptability curves (CEACs) are included to give a measure of the uncertainty reflected in the model. Some exploration of the contribution of individual model parameters to this uncertainty is reported.

Non-reference case analyses

Additional model runs were undertaken to consider the three main issues. First, there was an investigation of the effect on the results of running the model for shorter time horizons of 10 and 20 years. Second, alternative therapy costs supplied by the manufacturers for inhaled iloprost and intravenous epoprostenol were incorporated. Finally, as there was more than one set of utility values to apply to the health states, those values not used in the reference case were explored.

Results

A separate comparison is presented for each intervention therapy in addition to supportive care versus supportive care alone (with switching to epoprostenol in FCIV) for FCIII, and for epoprostenol in addition to supportive care versus

supportive care alone in FCIV. All model results are presented separately for each therapy, with the reference case results presented first followed by the non-reference case analyses.

As discussed, non-reference case analyses considered three main issues: time horizon, alternative drug price and alternative health state utility values. The reference case analysis had a time horizon of 30 years to represent effective lifetime and therefore shorter time horizons of 20 years and 10 years were also considered. The reference case analysis used the list price for drugs and therefore alternative model runs were undertaken to consider the lower price of epoprostenol, as stated in the industry submission for this drug, and the fixed fee scheme for iloprost, again as stated in the relevant manufacturer submission. Finally, four alternative sets of health states values were used so that values used in the manufacturer models were also used in the assessment group model. The full results of these analyses can be found in Appendix 12.

Epoprostenol in addition to supportive care versus supportive care alone, functional class III

Reference case

Table 52 presents 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 £277,000 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.

Analysis of the effect of single parameters in the reference case shows that in many cases the cost and QALY differences change significantly, but in

TABLE 52 *Epoprostenol with supportive care versus supportive care alone, functional class III*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	479,000		2.056		
Epoprostenol	697,000	218,000	2.843	0.787	277,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

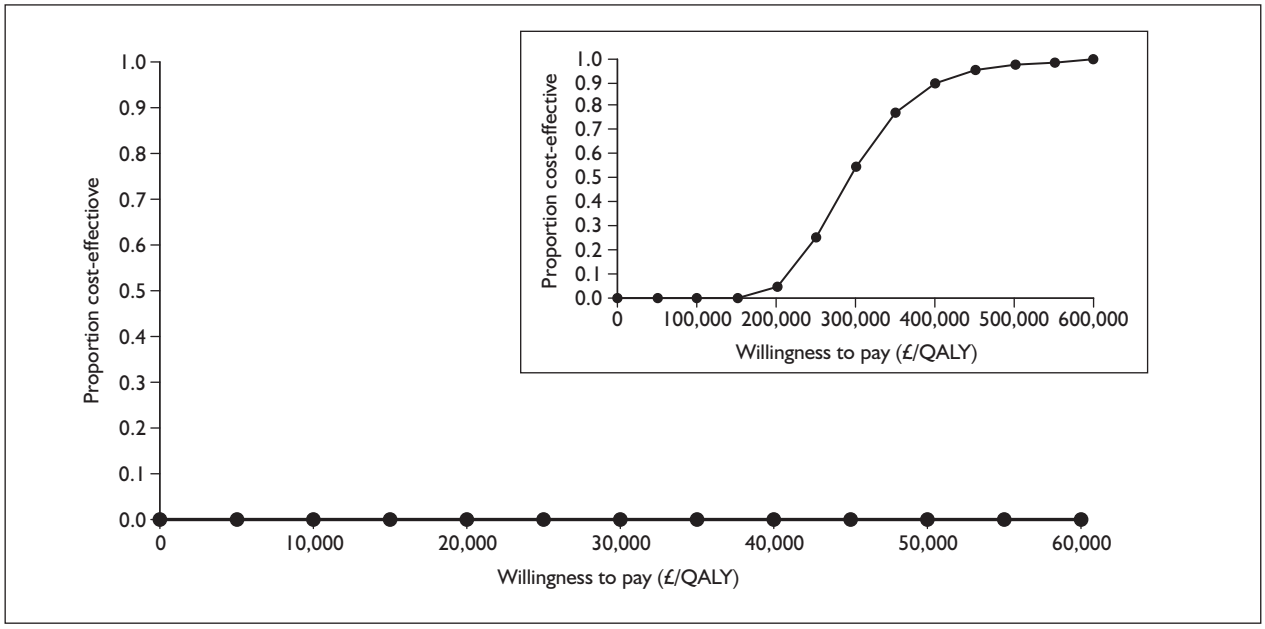

FIGURE 10 *Cost-effectiveness acceptability curve for epoprostenol with supportive care versus supportive care alone, functional class III. Inset graph shows a larger x-axis scale. QALY, quality-adjusted life-year.*

TABLE 53 *Non-reference case analyses for epoprostenol with supportive care versus supportive care alone, functional class III*

Scenario	Cost difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective at £20,000/QALY	Probability cost-effective at £30,000/QALY
Reference case	218,000	0.787	277,000	0	0
Alternative time horizon:					
20 years	216,000	0.779	277,000	0	0
10 years	189,000	0.683	277,000	0	0
Alternative epoprostenol price	83,000	0.787	106,000	0	0
Alternative health state utility values:					
Meads *et al.*[94]	218,000	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	0	0
Kirsch 2000,[76] 2-year TTO	218,000	0.831	262,000	0	0
Kirsch 2000,[76] 10-year TTO	218,000	0.799	272,000	0	0
Olschewski *et al*. 2002[41]	218,000	0.853	256,000	0	0

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TTO, time trade-off.

TABLE 54 *Epoprostenol with supportive care versus supportive care alone, functional class IV*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	128,000		0.829		
Epoprostenol	531,000	403,000	2.003	1.174	343,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

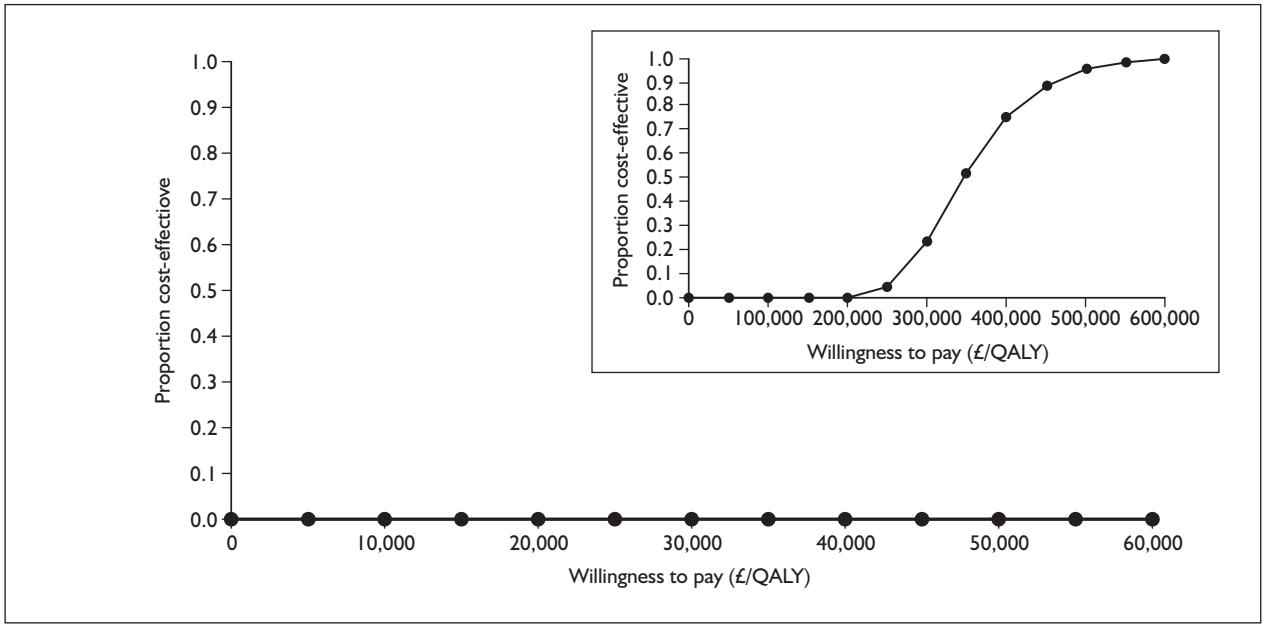

FIGURE 11 *Cost-effectiveness acceptability curve for epoprostenol with supportive care versus supportive care alone, functional class IV. Inset graph shows larger x-axis scale. QALY, quality-adjusted life-year.*

the same direction, so that the difference in ICER is small. Full details are in Appendix 11.1.

Non-reference case analyses

Table 53 presents the results of the additional analyses undertaken. The only variable that affected the ICER was the alternative (and lower) epoprostenol price, which reduced the ICER from £277,000 per QALY to £106,000 per QALY.

Epoprostenol with supportive care versus supportive care alone, functional class IV

Reference case

In FCIV, epoprostenol has a much greater cost than supportive care alone and produces just over one extra QALY, resulting in an ICER of £343,000 per QALY gained (*Table 54*). At the £20,000 and £30,000 per QALY thresholds, the probability of epoprostenol being cost-effective is zero in both cases (*Figure 11*).

Analysis of the effect of single parameters in the reference case shows that in most cases the cost and QALY differences change noticeably, but in the same direction, so that the difference in ICER is small. Full details are in Appendix 11.2.

Non-reference case analyses

Table 55 presents the results of the additional non-reference case analyses. The majority of analyses made very little impact to the overall ICER. The two alternative health state data sets presented in Kirsch *et al.*[76] gave a much higher ICER for epoprostenol in FCIV, and using the lower price as stated by the manufacturer reduced the ICER to £96,000 per QALY gained.

TABLE 55 *Non-reference case analyses for epoprostenol with supportive care versus supportive care alone, functional class IV*

Scenario	Cost difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective at £20,000/QALY	Probability cost-effective at £30,000/QALY
Reference case	403,000	1.174	343,000	0	0
Alternative time horizon:					
20 years	401,000	1.167	344,000	0	0
10 years	368,000	1.058	348,000	0	0
Alternative epoprostenol price	113,000	1.174	96,000	0	0
Alternative health state utility values:					
Meads *et al.*[94]	403,000	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	0	0
Kirsch 2000,[76] 2-year TTO[a]	402,000	0.895	449,000	0	0
Kirsch 2000,[76] 10-year TTO[a]	402,000	0.726	554,000	0	0
Olschewski *et al.* 2002[41]	403,000	1.049	384,000	0	0

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TTO, time trade-off.
a Small variations in the difference in cost are due to the use of different random number sets.

TABLE 56 *Iloprost with supportive care versus supportive care alone, functional class III*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	434,000		1.958		
Iloprost	537,000	103,000	2.975	1.017	101,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

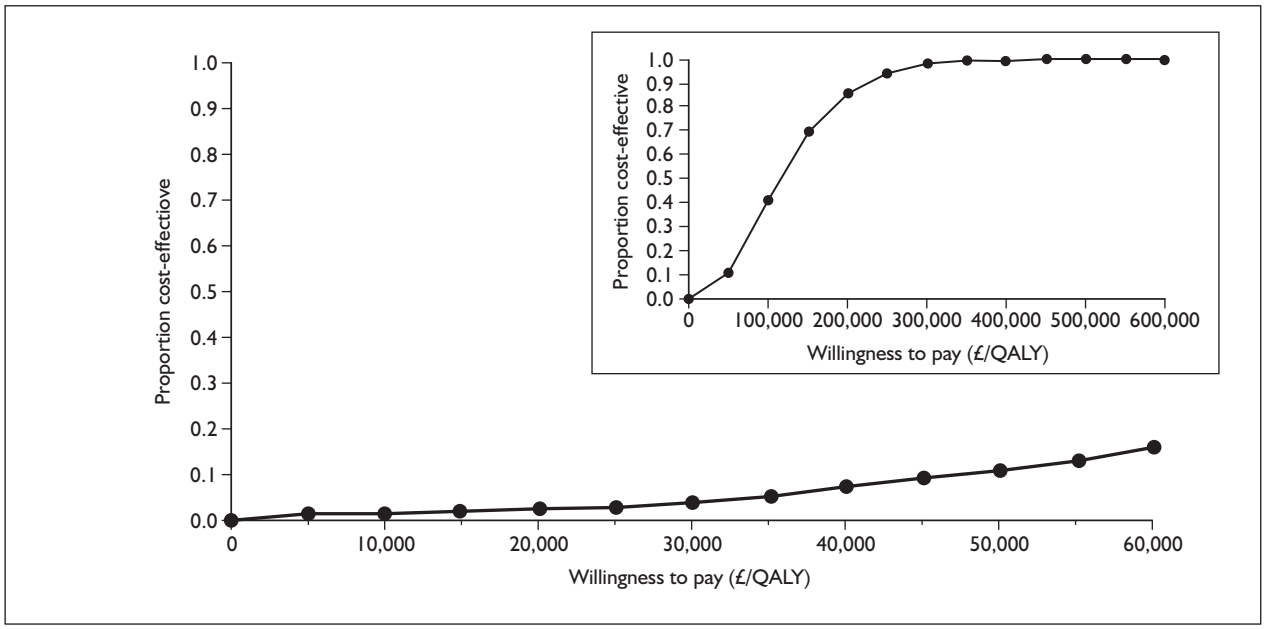

FIGURE 12 *Cost-effectiveness acceptability curve for iloprost with supportive care versus supportive care alone, functional class III. Inset graph shows larger x-axis scale. QALY, quality-adjusted life-year.*

TABLE 57 *Non-reference case analyses for iloprost with supportive care versus supportive care alone, functional class III*

Scenario	Cost difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective at £20,000/ QALY	Probability cost-effective at £30,000/ QALY
Reference case	103,000	1.017	101,000	0.03	0.05
Alternative time horizon:					
20 years	99,000	0.999	99,000	0.03	0.06
10 years	68,000	0.844	81,000	0.12	0.16
Alternative epoprostenol price	102,000	1.017	101,000	0	0
Alternative iloprost price	87,000	1.017	85,000	0.06	0.10
Alternative iloprost and epoprostenol prices	86,000	1.017	85,000	0	0
Alternative health state utility values:					
Meads *et al.*[94]	103,000	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	0.03	0.04
Kirsch 2000,[76] 2-year TTO[a]	102,000	1.030	99,000	0.03	0.05
Kirsch 2000,[76] 10-year TTO[a]	102,000	0.975	104,000	0.03	0.05
Olschewski *et al.* 2002[41]	103,000	1.074	96,000	0.03	0.06

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TTO, time trade-off.
a Small variations in the difference in cost are due to the use of different random number sets.

Iloprost with supportive care versus supportive care alone, functional class III

Reference case

Table 56 presents 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 £101,000 per QALY gained. The CEAC presented in *Figure 12* shows that at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, iloprost has a probability of being cost-effective of 3% and 5% respectively.

Analysis of the effect of single parameters in the reference case shows that the odds ratio for deterioration from FCIII to FCIV after the first cycle makes the most difference to the ICER. Even so, the lowest ICER for any decile group in this parameter is over £30,000 per QALY. Full details are in Appendix 11.3.

Non-reference case analyses

The results of the additional analyses, presented in *Table 57*, show that none has a significant effect on the overall ICER. Reducing the time horizon to 10 years changed the ICER to £81,000 per QALY, and using the lower price for iloprost reduced the ICER to £85,000 per QALY.

Bosentan in addition to supportive care versus supportive care alone, functional class III

Reference case

Table 58 presents the reference case results for bosentan, with the intervention more expensive than supportive care alone and producing a greater amount of QALYs, resulting in an ICER of £27,000 per QALY gained. The CEAC in *Figure 13* demonstrates that bosentan has a 41% chance of being cost-effective at £20,000 per QALY and a 54% chance at £30,000 per QALY.

Analysis of the effect of single parameters in the reference case shows that the result is highly sensitive to two parameters. Full details are in Appendix 11.4.

The results relating to the odds ratio for deterioration from FCIII to FCIV after the first cycle vary from bosentan dominating the comparator in the most favourable decile group (in which the odds ratio is < 0.053) to an ICER of

TABLE 58 *Bosentan with supportive care versus supportive care alone, functional class III*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		2.201		
Bosentan	436,000	93,000	5.696	3.494	27,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

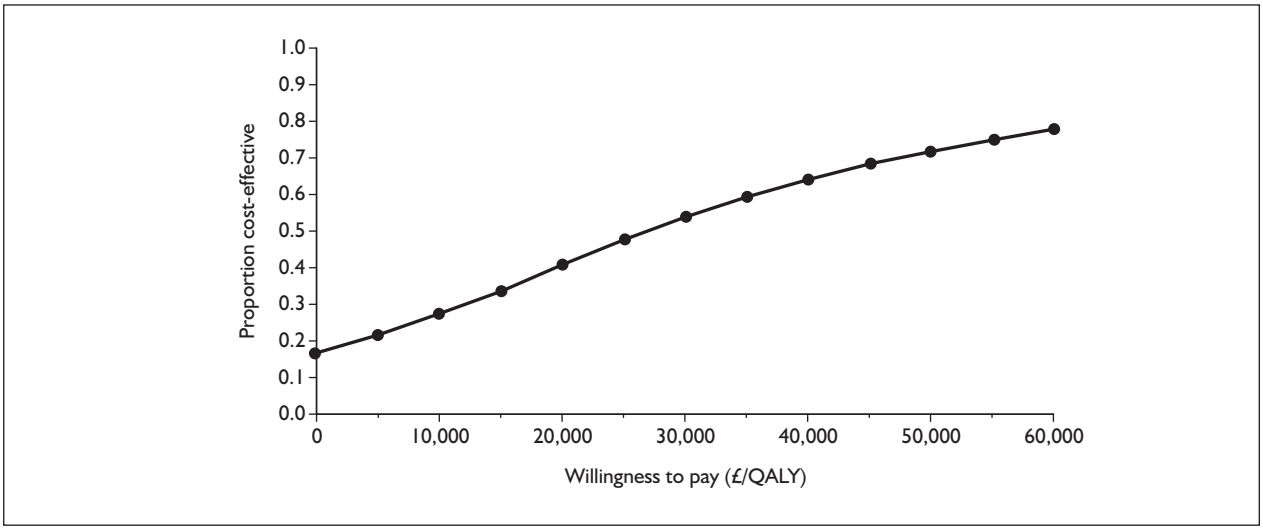

FIGURE 13 *Cost-effectiveness acceptability curve for bosentan with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

TABLE 59 *Non-reference case analyses for bosentan with supportive care versus supportive care alone, functional class III*

Scenario	Cost difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective at £20,000/QALY	Probability cost-effective at £30,000/QALY
Reference case	93,000	3.494	27,000	0.41	0.54
Alternative time horizon:					
20 years	66,000	3.108	21,000	0.49	0.60
10 years	–8,000	1.964	Dominates	0.70	0.76
Alternative epoprostenol price	137,000	3.494	39,000	0.03	0.20
Alternative health state utility values:					
Meads *et al.* [94]	93,000	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	0.40	0.52
Kirsch 2000,[76] 2-year TTO[a]	92,000	3.700	25,000	0.43	0.56
Kirsch 2000,[76] 10-year TTO[a]	92,000	3.549	26,000	0.42	0.55
Olschewski *et al.* 2002[41]	93,000	3.774	25,000	0.43	0.55

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year. TTO, time trade-off.
a Small variations in the difference in cost are due to the use of different random number sets.

£90,000 per QALY in the least favourable (odds ratio > 0.86). The ICER was greater than £30,000 per QALY in the top five decile groups (odds ratio > 0.21).

The higher the mortality rate in FCIII on supportive care the greater the difference in both costs and QALYs between bosentan and the comparator. The variation in costs is far higher than the variation in QALYs. This is probably because, comparatively, more people are surviving to be treated with epoprostenol in FCIV in the bosentan arm. The higher the mortality rate on supportive care the greater this difference becomes. The effect is that the results also vary from dominance in the most favourable decile group (mortality per cycle less than 0.0254, corresponding to annual mortality less than 10.5 per cent) up to £49,000 per QALY in the least favourable group (annual mortality rate > 35.5%). The ICER was greater than £30,000 per QALY in the top five decile groups (annual mortality rate > 21.3%).

Non-reference case analyses

Additional analyses for bosentan are presented in *Table 59*. Reducing the time horizon to 20 years changed the ICER from £27,000 to £21,000 per QALY, and a further reduction in the time horizon to 10 years meant that bosentan was cheaper and therefore dominated supportive care alone. Here, the probability of bosentan being cost-effective at £20,000 per QALY increased to 70%. Reducing the price of epoprostenol increased the cost difference substantially, therefore making bosentan less cost-effective at £39,000 per QALY, with only a 3% chance of it being cost-effective at £20,000 per QALY and a 20% chance at £30,000 per QALY. Changing the set of utility values used has very little impact on the overall result.

Sitaxentan in addition to supportive care versus supportive care alone, functional class III

Reference case

Compared with supportive care alone, sitaxentan provided an additional 3 QALYs but at greater cost, resulting in an ICER of £25,000 per QALY gained (*Table 60*). The CEAC presented in *Figure 14* demonstrates that, at thresholds of £20,000 and £30,000 per QALY gained, the probability of sitaxentan being cost-effective is 45% and 56% respectively.

Analysis of the effect of single parameters in the reference case shows that the result is highly sensitive to three parameters. Full details are in Appendix 11.5.

TABLE 60 *Sitaxentan with supportive care versus supportive care alone, functional class III*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		2.201		
Sitaxentan	419,000	76,000	5.289	3.087	25,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

The results relating to the odds ratio for deterioration from FCIII to FCIV after the first cycle vary from sitaxentan dominating the comparator in the most favourable decile group (in which the odds ratio is < 0.042) to an ICER of £120,000 per QALY in the least favourable (odds ratio > 0.76). The ICER was over £30,000 per QALY in the top four decile groups (odds ratio > 0.24).

The lower the mortality rate in FCIII on treatment, the greater the difference in both costs and QALYs between sitaxentan and the comparator. The variation in costs is far higher than the variation in QALYs, with the effect that the results vary from an ICER of £2500 per QALY in the most favourable decile group (mortality per cycle > 0.0176, corresponding to annual mortality rate > 7.4%) up to £37,000 per QALY in the least favourable group (annual mortality rate < 2.3%). The ICER was over £30,000 per QALY in the worst three decile groups (annual mortality rate < 3.5%).

Similarly, the higher the mortality rate in FCIII on supportive care, the greater the difference in both costs and QALYs between sitaxentan and the comparator. The variation in costs is again far higher than the variation in QALYs, with the effect that the results vary from dominance in the most favourable decile group (mortality per cycle less than 0.0254, corresponding to annual mortality rate < 10.5%) up to £50,000 per QALY in the least favourable group (annual mortality rate > 35.5%). The ICER was over £30,000 per QALY in the top four decile groups (annual mortality rate > 23.9%).

Non-reference case analyses

The additional analyses presented in *Table 61* show the same trend for sitaxentan as previously demonstrated for bosentan. Reducing the time horizon to 20 years reduced the ICER from £25,000 per QALY to £19,000 per QALY, and running the model for 10 years further changed the result and sitaxentan was dominant. Incorporating a reduced price for epoprostenol resulted in a much larger ICER of £40,000 per QALY. Again, changing the set of utility values used has little impact on the ICER.

Sildenafil in addition to supportive care versus supportive care alone, functional class III

Reference case

Compared with supportive care alone, sildenafil is less costly and more effective and therefore dominates supportive care (*Table 62*). The CEAC

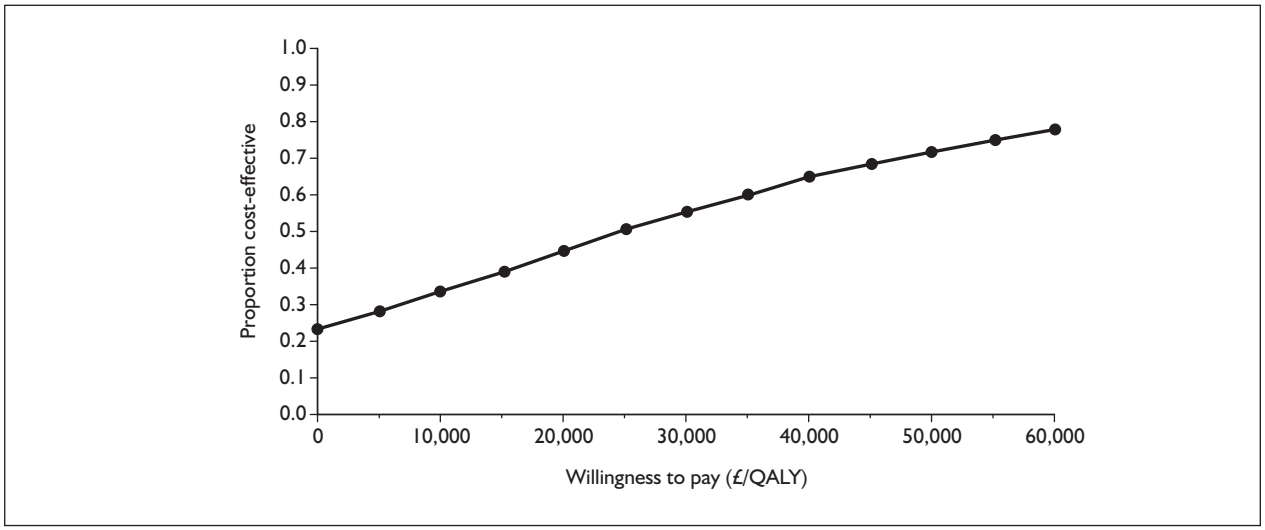

FIGURE 14 *Cost-effectiveness acceptability curve for sitaxentan with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year*

TABLE 61 *Non-reference case analyses for sitaxentan with supportive care versus supportive care alone, functional class III*

Scenario	Cost difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective at £20,000/QALY	Probability cost-effective at £30,000/QALY
Reference case	76,000	3.087	25,000	0.45	0.56
Alternative time horizon:					
20 years	52,000	2.755	19,000	0.51	0.61
10 years	–11,000	1.754	Dominates	0.69	0.74
Alternative epoprostenol price	122,000	3.087	40,000	0.06	0.23
Alternative health state utility values:					
Meads *et al.*[94]	76,000	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	0.44	0.54
Kirsch 2000,[76] 2-year TTO[a]	75,000	3.700	24,000	0.45	0.56
Kirsch 2000,[76] 10-year TTO[a]	75,000	2.997	25,000	0.44	0.54
Olschewski *et al.* 2002[41]	76,000	3.294	23,000	0.46	0.56

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year. TTO, time trade-off.
a Small variations in the difference in cost are due to the use of different random number sets.

TABLE 62 *Sildenafil with supportive care versus supportive care alone, functional class III*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		2.201		
Sildenafil	307,000	–36,000	5.436	3.235	Dominates

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

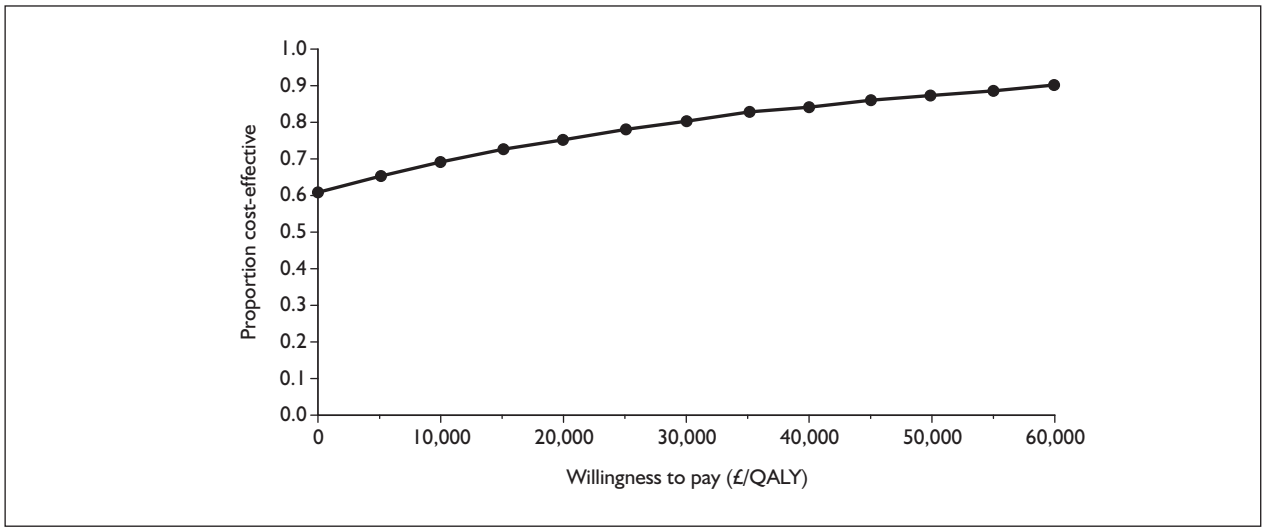

FIGURE 15 *Cost-effectiveness acceptability curve for sildenafil with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year*

presented in *Figure 15* shows that, at all threshold values, sildenafil is at least 60% cost-effective, and has a probability of being cost-effective of 75% at £20,000 per QALY and 78% at £30,000 per QALY.

Analysis of the effect of single parameters in the reference case shows that the sildenafil option remained dominant over its comparator except for variation in three parameters. Full details are in Appendix 11.6.

In the case of the odds ratio for deterioration from FCIII to FCIV after the first cycle, sildenafil remained dominant in six decile groups (in which the odds ratio is < 0.26), but the ICER reached £70,000 per QALY in the least favourable decile group (odds ratio > 0.83). The ICER was over £30,000 per QALY in the top two decile groups (odds ratio > 0.50).

The lower the mortality rate in FCIII on treatment, the greater the difference in both costs and QALYs between sildenafil and the comparator. In this case sildenafil remained dominant over the comparator in all but the least favourable decile group, in which the ICER was still below £2000 per QALY.

Similarly, the higher the mortality rate in FCIII on supportive care, the greater the difference in both costs and QALYs between sildenafil and the comparator. In this case sildenafil ceased to dominate the comparator in the top three decile groups, but the ICER still remained below £20,000 per QALY in all groups.

Non-reference case analyses

The results of the additional analyses included in *Table 63* show that, for almost all scenarios, sildenafil remains dominant over supportive care alone. Reducing the time horizon to 20 years and 10 years increases the cost saving with sildenafil and therefore increases the probability of the intervention being cost-effective. Running the model with alternative health state utility values had no impact on the overall result. The scenario incorporating the lower price for epoprostenol gave an ICER of £3700.

Discussion

All intervention therapies alongside supportive care led to a QALY improvement compared with supportive care alone; however, the cost-

TABLE 63 *Non-reference case analyses for sildenafil with supportive care versus supportive care alone, functional class III*

Scenario	Cost difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective at £20,000/ QALY	Probability cost-effective at £30,000/ QALY
Reference case	–36,000	3.235	Dominates	0.75	0.78
Alternative time horizon:					
20 years	–53,000	2.878	Dominates	0.78	0.82
10 years	–95,000	1.823	Dominates	0.86	0.88
Alternative epoprostenol price	12,000	3.235	3700	0.79	0.87
Alternative health state utility values:					
Meads *et al*.[94]	–36,000	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	0.75	0.80
Kirsch 2000,[76] 2-year TTO[a]	–34,000	3.376	Dominates	0.76	0.81
Kirsch 2000,[76] 10-year TTO[a]	–34,000	3.227	Dominates	0.75	0.80
Olschewski *et al*. 2002[41]	–36,000	3.480	Dominates	0.75	0.81

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s); TTO, time trade-off.
a Small variations in the difference in cost are due to the use of different random number sets.

effectiveness ratios vary considerably. It should be emphasised that, as the interventions are largely used in different populations, comparison between therapies is not appropriate.

Sensitivity of modelling results and non-reference case analyses

As described earlier, the model was run for a number of non-reference case scenarios, with time horizon appearing to have the greatest impact on results. All drugs other than epoprostenol showed more favourable results when the time horizon was shortened. This is likely to be because the downstream effects omitted are greater on the active treatment arm, in which overall survival is greater.

The ICERs for bosentan, sitaxentan and sildenafil, but not iloprost, are sensitive to the price of epoprostenol. The price of epoprostenol is particularly important when a technology is compared with supportive care in FCIII. If the technology was effective (delaying transition to FCIV) and much cheaper than epoprostenol, reducing the price of epoprostenol will make the technology less cost-effective as the cost of supportive care will greatly reduce and the cost of the technology (including epoprostenol in FCIV) will reduce but much less so (as less patients are going to FCIV). Iloprost is more expensive than the oral therapies but results in a smaller QALY difference; patients on iloprost get to FCIV quicker than on oral therapies, but slightly less so than on supportive care. Therefore the price of epoprostenol has a significant impact on the cost of both the iloprost and supportive care arms. Thus, while the cost in both arms is reduced, there is little overall impact on the difference in cost.

In addition to the non-reference case analyses described and discussed above, further analyses were undertaken at the request of the NICE Appraisal Committee to explore various non-reference case scenarios. These included:

1. assuming that patients in FCIV (for both the active treatment and supportive care arms) receive supportive care only (without epoprostenol)
2. for the three oral treatments assuming the same mortality rates on treatment and on supportive care as those for epoprostenol in FCIII
3. for the three oral treatments exploring the minimal 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 £20,000, £30,000 and £40,000 per QALY
4. assuming that no death occurs while patients stay in FCIII
5. assuming that patients on supportive care alone in FCIV receive only intermittent care as required for respite until death rather than hospitalisation until death
6. for the three oral treatments combining the above assumptions 1 and 2
7. for the three oral treatments combining the above assumptions 1, 2 and 5.

These additional analyses were carried out based on the reference case, with the specific assumption(s) altered in each scenario. Further descriptions of these additional analyses, their results and brief comments on the results are presented in Appendix 13.

Overall, these additional analyses further confirmed the crucial impact of the cost associated with epoprostenol use in FCIV on the cost-effectiveness of the oral treatments for FCIII patients. The assumption with regard to whether patients in FCIV on supportive care alone (without epoprostenol) are hospitalised until death or receive intermittent care has a very small impact on ICERs. Paradoxically, the analyses also suggested that survival benefits conferred by the oral treatments were inversely related to their cost-effectiveness in most instances (i.e. the greater the reduction in the odds of death on treatment compared with the odds of death on supportive care, the less cost-effective the treatment is). These results, while needing to be interpreted within the context and limitation of the model, are not unexpected: if a treatment reduces death in FCIII, more patients will live longer and eventually enter FCIV, which incurs substantial treatment costs that impact on the overall cost-effectiveness of the treatment. When the cost of epoprostenol in FCIV is taken out of the equation, however, the ICERs appear to be no longer sensitive to assumptions regarding survival benefits of the oral treatments according to the result of additional analysis 6.

Limitations and uncertainties associated with the choice of outcome measure, availability of data and model assumptions

The challenge in assessing the cost-effectiveness of the technologies for the treatment of PAH is well acknowledged for a number of reasons, but most notably because of the lack of appropriate data. The approach of using change in FC as the key outcome measure along with the need for making

various assumptions and extrapolating short-term data are some practical solutions in the absence of better alternatives. These assumptions are explicitly stated and extensive sensitivity analyses have been carried out as described in the previous sections. There are additional limitations and uncertainties that may not be fully captured in the sensitivity analyses. These will be discussed below.

The transition probabilities for supportive care and the odds ratios for the relative treatment effects of individual drugs used in the model require data related to change of FC stratified by patients' initial FC at the start of treatments. Despite the request from the assessment group to the companies for such data for all eligible trials, stratified data were not supplied for many trials. In some cases data were completely absent and various assumptions have to be made (such as using equal values for FCII to FCIII and FCIII to FCIV and for FCIV to FCIII and FCIII to FCII; and use of first cycle values for subsequent cycles). The direction of potential bias introduced by these assumptions is difficult to predict. In other cases data were available from only some, but not all of the trials that would have been included. This could also introduce bias towards the estimation of model parameters. For example, BREATHE-1[45] was not included in the estimation of pooled odds ratios for bosentan as FCIII data for the bosentan arms were not available for this trial. Given the high response rate for FC improvement in its placebo arm, inclusion of this trial would have reduced the pooled odds ratio for FC improvement with resultant less favourable ICERs.

While determining the transition probabilities of FC improvement/worsening for FCIII patients receiving supportive care alone (the comparator in the base case), data were sought from the control groups in the trials of the technologies under assessment. Separate data for FCIII and FCIV were not available for epoprostenol and data from a trial with a mixed FCIII and FCIV population was used instead. For the remaining four drugs, FC-specific data were available. Despite all being in FCIII at baseline, the proportion of patients who had their FC improved at 12 weeks varied widely between studies, from 5.6% (2/36) in the AIR study (iloprost)[41] and 9.1% (1/11) in Channick *et al.*[43] (bosentan) to [Commercial-in-confidence information has been removed] in STRIDE-4[37] (sitaxentan) and 29.2% (19/65) in BREATHE-1 (bosentan). The differences may reflect the varied severity (within FCIII) of patient populations included in the trials, particularly between the epoprostenol and iloprost trials and the trials of the three oral treatments. The different mix of subcategories of PAH within each trial and the relatively small numbers upon which the proportions were based may also contribute to the apparent variation. However, it is likely that the exceptionally high responses observed in the BREATHE-1 and STRIDE-4 studies were partly attributable to the Hawthorne effect (patients who enter a trial perform better irrespective of treatment received because of increased attention/standard of care) and possibly misclassification of FC (into a more severe FC) at study screening so that patients could be entered into a trial. Data from these two trials were therefore not used in the calculation of transition probabilities for supportive care. Sensitivity analysis shows that the results are not sensitive to the response rate in the supportive care arm; rather, it is the odds ratio between treatment and comparator (supportive care) that is critical.

The model assumes that improvement in FC occurs only in the first cycle (12 weeks). In the industry submission by the manufacturer of sitaxentan, a 'delayed first efficacy response beyond the 12-week study' in the STRIDE-1X study was mentioned. Such phenomenon, however, did not appear to have been observed in subsequent sitaxentan long-term studies. Similarly, few patients who were classified as FCIII after 4 months of bosentan treatment subsequently improved to FCII during long-term follow-up.[104] The assumption that no FC improvement occurs beyond the first cycle therefore seems reasonable and was agreed by our clinical experts.

The model is based on the use of FC alone as the description of a patient's current health state. Even with such a limited set of health states it has been difficult to populate the model with appropriate data for the transition probabilities within the model.

It would be highly desirable to use a more refined classification of health states. In a model-based cost–utility analysis it is desirable that the health states used are reasonable for both prognostic value and measurement of utility scores. Probably the most appropriate measure for this purpose would be to group patients into bands by 6MWD. This would, however, require the collection of appropriate data. Such data were not available to the assessment team; accordingly, any analysis based on such a model would be highly speculative in nature.

It should be noted that data such as mean improvement in walking distance or proportion improving from a varied starting point are of limited use for a realistic model. What would be needed for such a model is a longitudinal data set of sufficient size to allow a serious attempt to measure transition probabilities between states over an appropriately long period of time.

There is also the problem that the very short randomisation period of the trials has necessitated the assumption that treatment effects are preserved far beyond the timing of the trials.

For the above reasons the PSA is likely to have considerably underestimated the full uncertainty in the decision to be made. No attempt has been made to impose a correlation structure on the parameter distributions used in the model. Finally, any attempt at value of information analysis would lead to results that would not be meaningful.

Chapter 5

Assessment of factors relevant to the NHS and other parties

The technologies in this assessment report are already being widely used for the treatment of PAH in the NHS and are seen as key interventions in the process of stabilising the deterioration in patient health.

Designated specialist centres

Services for PAH are provided through the NCG designated centres. As most PAH patients are already seen at these centres, and the technologies of this assessment are already in use for PAH patients, there should be limited impact on the centres.

Primary care trusts

Apart from services for children, drug costs are not funded by the NCG services but locally by, for example, application to patients' primary care trusts (PCTs). National guidance recommending the use of disinvestments from the technologies in this assessment will add clarity to this funding process.

There is some information to suggest that the concentration of PAH patients may be higher closer to the designated centres. Whether this is related to more ready identification of patients who live in the proximity of a centre or the fact that patients move to be closer to a centre is unclear. However, it could mean that a greater financial burden for funding PAH drug treatment occurs close to as opposed to distant from a centre.

National guidelines

A consensus statement on the management of pulmonary hypertension in the UK and Ireland has recently been published.[31] In addition, the ESC is in the process of updating their guidelines for publication in 2009. These guidelines are likely to have a wider scope and include drugs outside this technology appraisal. Although this technology assessment report aims to critically appraise and synthesise the best available evidence pertinent to the decision problems defined in Chapter 2 (see Decision problem), it is beyond the report's remit to make any recommendations regarding treatment choices and service provisions for the technologies being assessed.

Disinvestment

A potential difficulty is that the five technologies of this assessment are currently being used within the NCG centers to treat PAH. If a decision is made not to recommend the use of one or more of the technologies then this disinvestment will need to be carefully managed. This is particularly important given the uncertainties around the clinical risk and the effects of withdrawal of the technologies on the patient.

Other interventions

Several other technologies targeted at modifying the PAH disease process are in development or are already available, but have yet to be licensed in the UK. Some of these are already being used in the designated PAH centres. To ensure equity these technologies, once licensed, may need to be assessed in updates to this assessment report. These technologies are likely to be included in the UK/EU guidelines being drawn up by expert groups.

Budget impact

The budget impact of each technology is difficult to accurately assess because of the absence of information on the number of PAH patients in England and Wales, the number in each FC, the numbers in each FC likely to be administered a given intervention, the doses given and also the fact that some of the fees associated with delivery of some of the interventions are commercially sensitive. However, accepting these uncertainties it is possible to indicate the magnitude of the annual impact for each technology for a range of patient population sizes. These are highlighted in Appendix 14 (*Figures 142–144*). The values

presented do take drug (licensed doses) and administration costs into consideration, but not additional monitoring and underlying supportive care as these were considered to be of relatively minimal cost compared with the technologies.

The data on current English (including Welsh) usage of the technologies (see Chapter 1, Current usage of technologies in the NHS, and Appendix 1) were considered to represent the approximate total number of patients likely to receive epoprostenol, iloprost inhaled or an oral technology. Using this data the magnitude of the budgetary impacts for each technology per annum is:

- [Commercial-in-confidence information has been removed]

Many patients are receiving treprostinil off licence at present, which may be reducing the number of patients on epoprostenol.

It should be remembered that for oral treatments the total pool of currently treated patients is approximately [Commercial-in-confidence information has been removed] and thus if all three oral technologies are utilised the total budget impact will be considerably less than the sum of the individual budgetary impacts above as most patients are receiving monotherapy and a smaller number dual and triple therapy.

Chapter 6
Discussion

Statement of principal findings

Clinical effectiveness

Overall quantity and quality of evidence

A total of 20 RCTs, most of good quality, were included in this assessment. The majority of them had a duration of 12–18 weeks and compared one of the technologies (intravenous epoprostenol, inhaled iloprost, bosentan, sitaxentan and sildenafil) added to supportive treatment with supportive treatment alone. Only a small number of trials compared the technologies against each other or investigated the use of combinations of these technologies.

Many of the trials included patient populations (in terms of FC and types of PAH) and doses that were outside the licensed indications of the technologies. Only very limited data examining specific types (subcategories) of PAH were available. Existing data do not suggest significant differences in treatment effects between subcategories of PAH, but studies are likely to be underpowered to detect clinically important differences.

Data stratified by FC were scant. Assessment of treatment effects stratified by FC could not be reliably conducted with the available evidence. This is particularly problematic when findings from the clinical effectiveness review were to be used to inform the economic modelling, which requires FC-specific data.

Monotherapy added to supportive treatment versus supportive treatment

All of the technologies, when added to supportive treatment at their licensed doses, have for the most part been shown to be more effective than supportive treatment alone in improving exercise capacity, symptoms of PAH and haemodynamic measures. The volume of evidence and patient populations included in the trials, however, varied between technologies.

The clinical effectiveness of intravenous epoprostenol (added to supportive treatment) compared with supportive treatment alone was demonstrated in open-label RCTs that included patients of mixed FC (mainly FCIII and FCIV).[11,33,39] Effectiveness has been shown in both patients with PPH[11,39] and patients with scleroderma.[33]

The clinical effectiveness of inhaled iloprost (added to supportive treatment) compared with supportive treatment alone was shown in a double-blind RCT[41] that included patients of mixed FC (FCIII and FCIV) with mixed types of pulmonary hypertension including non-PAH. An additional open-label RCT[36] also demonstrated effectiveness, but only for some of the measured outcomes.

The clinical effectiveness of bosentan (added to supportive treatment) compared with supportive treatment alone was demonstrated in double-blind RCTs[43,45,47] that included patients predominantly of FCIII and in an additional sitaxentan RCT that included open-label bosentan.[48] The effectiveness of bosentan has been shown in mixed PAH populations of IPAH and CTD-APAH[43,45] and in patients with PAH associated with Eisenmenger syndrome.[47]

The clinical effectiveness of sitaxentan (added to supportive treatment) compared with supportive treatment alone was demonstrated in double-blind RCTs[37,48,49] that included patients of mixed FC (predominantly FCII and FCIII) with mixed types of PAH including IPAH, CTD-APAH and PAH associated with CHD.

The clinical effectiveness of sildenafil (added to supportive treatment) compared with supportive treatment alone was demonstrated in a double-blind RCT[53] that included patients of mixed FC (predominantly FCII and FCIII) with mixed types of PAH including IPAH, CTD-APAH and PAH associated with CHD. For sildenafil in particular there is more data for above licensed doses than for the licensed dose.

Direct comparison

Only two RCTs have directly compared the technologies against each other. The STRIDE-2 study[48] compared sitaxentan with bosentan (both at licensed dose) for 18 weeks. The SERAPH study[57] compared sildenafil (above licensed dose) with bosentan (licensed dose). No significant difference between the drugs was observed in any outcome in

both trials. However, the sample size for SERAPH was small and there was an issue of differential blinding in STRIDE-2 (bosentan being the only open-label arm).

Combination therapy

Use of combinations of the technologies (including adding one to another) was investigated in four RCTs.[38,56,58,59] A double-blind RCT[56] showed no benefit of using the combination of bosentan plus intravenous epoprostenol compared with intravenous epoprostenol alone in patients of mixed FC (FCIII and FCIV) with mixed types of PAH (IPAH, CTD-APAH).

One double-blind RCT[41] showed that inhaled iloprost added to ongoing bosentan and supportive treatment was more effective than ongoing bosentan and supportive treatment in patients (mainly FCIII) with mixed types of PAH. However another open-label RCT[58] that included patients of FCIII with IPAH failed to demonstrate this.

A further double-blinded RCT[38] showed that sildenafil 80 mg three times daily (above licensed dose) added to ongoing epoprostenol and supportive care was more effective than ongoing epoprostenol and supportive care in patients of mixed FC (predominantly FCII and FCIII) with mixed types of PAH (IPAH and CTD-APAH).

Cost-effectiveness

None of the four published economic evaluations produced results that were generalisable to the NHS, as none were UK based, only one considered QALYs and only one compared the intervention with supportive care alone.

There was no consensus in the manufacturer submissions on the most appropriate model structure for the technology assessment, with variability seen in the type of economic evaluation, the methods used and the data sources. In addition, the same comparator was not used in all submissions and therefore they were not all addressing the same policy question.

The independent economic assessment demonstrated that all intervention therapies led to an improvement in QALYs, but the cost-effectiveness ratios varied considerably. The reference case analysis gave an ICER of £277,000 per QALY for intravenous epoprostenol with supportive care versus supportive care alone in FCIII and an ICER of £343,000 in FCIV. For FCIII only, the ICER was £101,000 per QALY for inhaled iloprost, £27,000 per QALY for bosentan and £25,000 per QALY for sitaxentan. Sildenafil with supportive care dominated supportive care alone (i.e. more effective and less costly). The analyses for iloprost, bosentan, sitaxentan and sildenafil were based on an assumption that all patients switch to intravenous epoprostenol upon deterioration to FCIV. Comparison between intervention therapies is not appropriate because of different target populations.

The reference case represents the full drug cost of epoprostenol. Sensitivity analyses were carried out using a reduced epoprostenol cost, which appears to be the price paid by the designated centres. The ICERs for the three oral treatments, but not for iloprost, were sensitive to the costs of epoprostenol. The lower the cost was for epoprostenol, the less favourable the ICERs were for bosentan and sitaxentan. Sildenafil no longer dominated supportive care when the cost for epoprostenol was lowered. These analyses suggest that the key driver of cost-effectiveness for the use of oral treatments in FCIII patients is the avoidance or delay of the high treatment costs that would be incurred when patients reach FCIV.

Because of the lack of stratified data to populate the model, and in some cases a complete absence of data, a number of assumptions had to be made and therefore bias may have been introduced by these assumptions. In addition, the data used for the model were from trials of short duration containing few patients. Therefore a longitudinal data set of a sufficient number of patients would be of great benefit to future modelling in this clinical condition.

Strengths and limitations of the assessment

Strengths of the assessment

- This assessment strictly adhered to its remit and did not cover technologies outside the scope of the technology appraisal, but which are being used in clinical practice, such as subcutaneous treprostinil and intravenous iloprost. Nor did it include technologies under development such as ambrisentan. Furthermore this assessment only considered each technology within its licensed indication. Evidence in relation to the use of these technologies outside their current licensed indications such as treating patients with milder disease (FCII) was not assessed.

- This assessment focused on evidence from RCTs, which were considered to be the most robust and the least subject to bias.
- A comprehensive literature search was performed. Submissions from the manufacturer were scrutinised and several unpublished trials were included. Additional data were obtained from clinical study reports. The assessment is likely to be the most up-to-date and comprehensive compared with the existing literature.
- Extensive reporting of the RCTs was undertaken and comprehensive analyses were carried out to highlight the mismatches between the licensed indications (the scope of the technology appraisal) and the available evidence.
- There was considerable clinical input into the model.
- Evidence from meta-analyses of RCTs (or individual RCTs when only one trial was available) was used to inform the parameters of the treatment effects in economic modelling.
- Trials included in the assessment were of short duration. Long-term observational studies were not systematically reviewed because of time/resource constraints; however, data were sought from all such studies cited in manufacturer submissions to inform the economic evaluation. In part, clinicians often make treatment decisions based on available long-term data rather than solely on the RCTs. The duration of the trials may be too short to demonstrate some of the possible biologically plausible effects of the technologies on disease processes.
- For both clinical effectiveness and cost-effectiveness considerable sensitivity analyses were undertaken.

Limitations of the assessment

- Although the assessment group requested and had access to unpublished trial data, the provision of such data stratified by FC and PAH subcategory was voluntary. The assessment was therefore limited by what was made available to the assessment group.
- This assessment report focused mainly on outcome measures for effectiveness. Only very limited outcomes related to safety were investigated as reporting of adverse events in the RCTs according to seriousness was relatively poor, and analysis of specific adverse events irrespective of seriousness was considered of little use in technology assessment given the seriousness of the disease itself.
- The primary purpose of this report was to provide an independent evaluation of the evidence to inform the NICE technology appraisal. As such, the scope of this report has to be in keeping with the scope of the technology appraisal. It is therefore inappropriate for this report to consider issues that are beyond the scope of the technology appraisal, such as the use of drugs or doses not currently licensed.

Uncertainties

- Whether the improvements in FC, exercise capacity and haemodynamic measures on treatment shown in the RCTs last beyond the duration of these trials, and whether these improvements translate into long-term benefits for survival and quality of life, remain uncertain. Although an increasing volume of evidence from observational studies supports the possibility of long-term benefits from the use of these technologies, the possibility of attenuation of treatment effect over time cannot be ruled out.
- Because of the lack of data stratified by FC, several assumptions with regard to change in FC had to be made for both the technologies and the comparator (supportive care) in the economic model. These include assuming the same treatment effects (odds ratios) for patients in different FC in terms of FC improvement and deterioration, and assuming that the treatment effect in preventing FC deterioration (from FCIII to FCIV) was the same as the treatment effect in preventing death. These assumptions require further validation.
- There is also considerable uncertainty with regard to whether the changes in FC sufficiently capture the overall impact of treatment on patients' quality of life. FC is a very blunt and to an extent subjective tool.
- The vast majority of the RCTs undertaken are placebo controlled and therefore unable to answer questions regarding which technologies are better. Thus, there is a need for head-to-head comparisons for patients in FCIII and in particular for the three oral technologies (bosentan, sitaxentan and sildenafil).

Generalisability

- Most trials excluded patients with unstable conditions. The patients who are seen in clinical practice are likely to be sicker and more unstable than those included in the trials.

- Finding the costs of the technologies (including associated services) for this assessment was not without difficulty. Variations in the costs between regions/centres inevitably affect the cost-effectiveness. Furthermore, the economic modelling suggested that the cost-effectiveness of the three oral treatments depends to some extent on the cost of epoprostenol. For example, as epoprostenol is the treatment of choice when patients deteriorate to FCIV, patients on less effective treatment (such as supportive care) will on average go on to epoprostenol earlier than those on more effective treatment (technologies). Thus, the time spent on epoprostenol will be different between the technologies and the total cost attributable to epoprostenol will be different between them. The unit cost of epoprostenol can therefore influence the ICER of compared treatments/technologies.
- This assessment considers only the use of the technologies for intentional long-term treatment in PAH. It does not consider the use of the technologies for treatment in other specific circumstances, such as bridging treatment for those patients who are awaiting a heart/lung transplantation but deteriorating on other treatment(s).

Other relevant factors

- Interpretation of results from RCTs needs to take into account the relatively small sample sizes and short duration of these studies, and differences in patient populations and comparator (supportive treatment) between trials and over time.
- Indirect comparisons and mixed treatment comparisons between the five technologies were not undertaken. These were unlikely to produce any conclusive results given the amount of evidence currently available, and could be potentially inappropriate because of the differences in trial design and study population between the technologies, and their different places in the treatment pathway.

Chapter 7
Conclusions

All five of the technologies (intravenous epoprostenol, inhaled iloprost, bosentan, sitaxentan and sildenafil), when added to supportive treatment and used at the licensed dose(s), have been shown to be more effective than supportive treatment alone in RCTs that included patients of mixed FC with mixed types of PAH. The volume of evidence and patient populations included in the trials varied between the technologies. Current evidence does not allow adequate comparisons between the technologies nor for the use of combinations of the technologies.

Independent economic evaluation suggests that bosentan, sitaxentan and sildenafil may be cost-effective by standard thresholds and that iloprost and epoprostenol may not.

Implications for service provision

Given the uncertainties listed in Chapter 6 there is evidence from the clinical effectiveness and cost-effectiveness analysis that may be sufficiently robust to allow a decision to be made on whether to recommend the use or otherwise of each of the five technologies as an adjunct to supportive care (compared with supportive care alone). There is insufficient evidence because of the lack of head-to-head comparisons to undertake the same for the merits of one technology over another.

All five technologies are currently used in the NHS. As requests for funding for the technologies for adult patients are currently made on an individual patient basis to the respective PCT any recommendation about the use of the technologies will impact on this process; a positive recommendation should make positive funding decisions easier, and a negative recommendation the opposite.

There is insufficient evidence with regard to whether any of the treatments are more effective for specific subcategories of PAH and on the effectiveness of combinations of technologies, the benefits of which cannot be assumed without being adequately tested in RCTs.

The findings of the review of cost-effectiveness of these technologies may require further confirmation as substantial uncertainty exists because of the paucity of data and consequently the large number of assumptions that need to be made. In particular, the differential cost-effectiveness between the oral treatments needs to be confirmed as current analysis was not designed for comparison between the technologies. If confirmed the use of the most cost-effective oral treatment(s) could potentially reduce overall treatment costs to the NHS. On the other hand, if technologies that are not considered as cost-effective according to the generally accepted threshold are withdrawn it would have a substantial impact on patients who are currently treated with these technologies and would also raise ethical issues as it could be argued that there is no exchangeable alternative treatment available for patients who require these treatments after failing oral therapies. Furthermore, as the findings suggested that the cost-effectiveness of oral treatments is highly dependent upon the cost of epoprostenol, any changes in the cost and/or availability of epoprostenol and the licensing of new treatments that occupy a similar place in the treatment pathway (i.e. if cheaper treatments with similar effectiveness to epoprostenol were licensed for patients in FCIV) would have knock-on effects on the cost-effectiveness of the other technologies.

Suggested research priorities

Being a very rare disease there is only a very limited pool of patients with PAH that can be enrolled in trials. There are always going to be more research priorities than available numbers of patients to investigate them and this is always going to limit the power of any study. Furthermore, there is also going to be competition for patients for the investigation of even newer technologies than are included in this assessment. These issues need to be considered alongside the research priorities listed below:

- Trials are required of the comparative effectiveness of the technologies. This seems most pressing for the three oral therapies (bosentan, sitaxentan and sildenafil) given their

similar places in the treatment pathway and the possibility of differential clinical effectiveness/ cost-effectiveness between them. Such trials would allow for direct clinical effectiveness and cost-effectiveness analyses.

- Trials are required of mono- versus dual and triple therapy across all of the technologies. Some of these are already in progress.
- Any future RCTs should ideally have a longer duration and measure clinically meaningful outcomes (see point below). The RCTs to date have been relatively short term, typically 12–18 weeks, and this is a relatively short period over which to measure any benefit on survival. However, recruitment to such trials with the possibility of patients receiving placebo may be difficult and raises ethical issues. Ethical issues should not be a problem though for well-designed head-to-head comparisons.
- 6MWT and other parameters routinely measured in the trials as the key end points have not been adequately evaluated and it is unclear how clinically meaningful any changes in them are. Further work is required in this area including the exploration and validation of existing and new end points
- Trials should report data in a disaggregated manner. Many trials report only aggregate data for change in parameters, usually for the whole trial population and often for mixed FC. The availability of data collected at baseline and subsequent follow-ups (and data on changes from baseline to follow-ups) stratified by subpopulation of PAH and by FC or the availability of individual patient data would greatly help future analyses. Data in this format from existing trials were requested for this assessment report, but for the most part were not provided/available.
- There is a great deal of variability between some of the existing trials with regard to improvement while receiving supportive care alone. Such variability needs to be explored to ascertain the underlying cause so that this can be fed into the design of future studies.
- There is no information currently available on sequencing of technologies. Although probably a lower priority than the above this is still an important research question. Therefore, studies assessing the feasibility of replacing an ongoing treatment that failed to provide adequate control of the disease with a new treatment rather than adding the new treatment to the existing treatment are required.
- In the absence of trials and prospective long-term controlled studies, data from well-run comprehensive national patient registries may be helpful in understanding further disease progression, the long-term response to treatment and survival.

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Contribution of authors

YFC was lead reviewer for the clinical effectiveness section of this report and also contributed to the discussion, conclusions and other sections. SJ reviewed existing economic evaluations and manufacturer submissions and undertook the independent economic evaluation along with PB. Both wrote and edited the economic sections of the report. KM contributed to the background section, identified clinical effectiveness data for the economic model from long-term studies and assisted in other areas of the clinical effectiveness section. CH acted as a methodological advisor and deputised for DM. SG and JPZ acted as clinical experts giving extensive advice and contributed to the drafting of the report. AFS devised and undertook all searches. JR undertook study selection (with YFC and DM) and assisted with data extraction for the clinical effectiveness sections. DM acted as project manager and senior reviewer on the report, wrote and edited sections of the report and takes responsibility for the overall content.

About the 'home unit'

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively undertake research synthesis to produce health technology assessments. Most of our members are based in the Public Health, Epidemiology and Biostatistics Unit, University of Birmingham; however, other members are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Unit, University of Birmingham.

WMHTAC produces systematic reviews, health technology assessments and economic evaluations for NETSCC, HTA, NICE and the health service in the West Midlands. WMHTAC also undertakes methodological research on research synthesis and provides training in systematic reviews and health technology assessment.

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Appendix 1

National Pulmonary Hypertension Service census. Distribution of patients and current UK usage of the technologies

Current usage data are taken from the National Pulmonary Hypertension Service census submitted as part of the submission for this technology appraisal by the Royal College of Physicians.[30] The data in this census are confidential. The census provides data on year-on-year numbers of patients under the care of the service centres and utilisation of the technologies. The census covers all types of pulmonary hypertension not only PAH and therefore figures may be greater than those for the PAH population. Conversely, not all PAH patients may be being seen at a designated centre. Further details about the designated centres can be found in Chapter 1 (see Current usage of technologies in the NHS).

Figure 16 details the total number of patients seen at designated pulmonary hypertension centres in England and Scotland by year since 2004.

Key summary data (*Table 64*) and data on mono-, dual and triple therapy utilisation by adults and children in England and Scotland (*Tables 65–67* respectively) are selectively reproduced below for the year 2006–7.

FIGURE 16 *Total numbers of patients under the care of the National Pulmonary Hypertension Service. Data from [Academic-in-confidence information has been removed] UK centres. [Academic-in-confidence information has been removed]. Data was collected to the 31 March each year and excluded patients who had been discharged, died or not been seen since 1 April of the previous year. [Academic-in-confidence information has been removed].*

TABLE 64 *Summary data of patients, their location and type of treatment in the National Pulmonary Hypertension Service 2006-7*

Summary data	English patients[a]	Scottish patients	UK children	Total UK patients[a]
Patients attending the National Pulmonary Hypertension Service	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Patients on disease-targeted monotherapy	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Patients on disease-targeted dual/triple therapy	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Patients on any disease-targeted therapy	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Transplants	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]

a [Academic-in-confidence information has been removed.]

TABLE 65 *Patients receiving monotherapy, their location and specific treatment in the National Pulmonary Hypertension Service 2006–7*

Name of therapy	English patients[a]	Scottish patients	UK children	Total UK patients
Epoprostenol (i.v.)	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Treprostinil (s.c.)	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Treprostinil (i.v.)	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Iloprost (i.v.)	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Iloprost (nebulised)	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Bosentan	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Sitaxentan	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Sildenafil	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Trial drug[b]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Total	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]

i.v., intravenous; s.c., subcutaneous.
a [Academic-in-confidence information has been removed].
b [Academic-in-confidence information has been removed].

TABLE 66 *Patients receiving dual therapy, their location and specific treatment in the National Pulmonary Hypertension Service 2006–7*

Name of therapy	Total English patients[a]	Total Scottish patients	UK children	Total UK patients[a]
Bosentan and sildenafil	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Sitaxentan and sildenafil	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Bosentan + epoprostenol (i.v.)	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Bosentan + iloprost (i.v. or nebuliser)	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Bosentan + treprostinil (s.c. or i.v.)	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Sildenafil + iloprost (i.v. or nebuliser)	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Sildenafil + treprostinil (s.c. or i.v.)	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Sildenafil + epoprostenol (i.v.)	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Trial drug[b]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Total	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]

i.v., intravenous; s.c., subcutaneous.
a [Academic-in-confidence information has been removed].
b [Academic-in-confidence information has been removed].

TABLE 67 *Patients receiving triple therapy, their location and specific treatment in the National Pulmonary Hypertension Service 2006–7*

Name of therapy	English patients[a]	Scottish patients	UK children	Total UK patients[a]
Bosentan + sildenafil + epoprostenol (i.v.)	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Bosentan + sildenafil + iloprost (i.v. or nebuliser)	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Bosentan + sildenafil + treprostinil (s.c. or i.v.)	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Treprostinil (s.c.) + bosentan + sildenafil + iloprost (nebuliser)	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Total	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]

i.v., intravenous; s.c., subcutaneous.
a [Academic-in-confidence information has been removed].

Appendix 2

Literature search strategies

Appendix 2.1 Clinical effectiveness searches

Source – Ovid MEDLINE(R), 1950 to February Week 2 2007

1. hypertension pulmonary/(15980)
2. pah.mp. (6334)
3. pulmonary hypertension.mp. (15783)
4. pulmonary arterial hypertension.mp. (1610)
5. pulmonary artery hypertension.mp. (459)
6. or/1–5 (27823)
7. (epoprostenol or flolan or prostacyclin).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (15446)
8. (iloprost or ventavis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1817)
9. (bosentan or tracleer).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1012)
10. (sitaxentan or thelin).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (7)
11. (sildenafil or revatio).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2706)
12. or/7–11 (19556)
13. 6 and 12 (1582)
14. randomized controlled trial.pt. (229118)
15. controlled clinical trial.pt. (74075)
16. randomized controlled trials.sh. (46851)
17. random allocation.sh. (56772)
18. double blind method.sh. (89402)
19. single blind method.sh. (10586)
20. or/14–19 (388897)
21. (animals not human).sh. (3987213)
22. 20 not 21 (356739)
23. clinical trial.pt. (431735)
24. exp clinical trials/(186384)
25. (clin$adj25 trial$).ti,ab. (125601)
26. ((singl$or doubl$or trebl$or tripl$) adj25 (blind$or mask$)).ti,ab. (88641)
27. placebo$.ti,ab. (99696)
28. random$.ti,ab. (359511)
29. placebos.sh. (25756)
30. research design.sh. (45986)
31. or/23–30 (823215)
32. 31 not 21 (723790)
33. 32 not 22 (382729)
34. 22 or 33 (739468)
35. 13 and 34 (329)

Source – Ovid MEDLINE(R), 1950 to February Week 2 2007

Additional search to account for alternative spelling of sitaxentan/sitaxsentan.

1. hypertension pulmonary/(16015)
2. pah.mp. (6358)
3. pulmonary hypertension.mp. (15802)
4. pulmonary arterial hypertension.mp. (1630)
5. pulmonary artery hypertension.mp. (460)
6. or/1–5 (27871)
7. sitaxsentan.mp. (48)
8. 6 and 7 (32)
9. randomized controlled trial.pt. (229481)
10. controlled clinical trial.pt. (74116)
11. randomized controlled trials.sh. (46944)
12. random allocation.sh. (56812)
13. double blind method.sh. (89516)
14. single blind method.sh. (10609)
15. or/9–14 (389441)
16. (animals not human).sh. (3990282)
17. 15 not 16 (357227)
18. clinical trial.pt. (431918)
19. exp clinical trials/(186631)
20. (clin$adj25 trial$).ti,ab. (125889)
21. ((singl$or doubl$or trebl$or tripl$) adj25 (blind$or mask$)).ti,ab. (88764)
22. placebo$.ti,ab. (99860)
23. random$.ti,ab. (360222)
24. placebos.sh. (25762)
25. research design.sh. (46062)
26. or/18–25 (824452)
27. 26 not 16 (724876)
28. 27 not 17 (383417)
29. 17 or 28 (740644)
30. 8 and 29 (23)

Source – EMBASE (Ovid), 1980 to 2007 Week 8

1. (epoprostenol or flolan or prostacyclin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (19059)

2. (iloprost or ventavis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (3222)
3. (bosentan or tracleer).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2059)
4. (sitaxentan or thelin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (20)
5. (sildenafil or revatio).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (5736)
6. or/1–5 (26908)
7. pah.mp. (7544)
8. pulmonary hypertension.mp. (18439)
9. pulmonary arterial hypertension.mp. (1394)
10. pulmonary artery hypertension.mp. (373)
11. pulmonary hypertension/(16068)
12. or/7–11 (25738)
13. 6 and 12 (2854)
14. randomized controlled trial/(114078)
15. exp clinical trial/(422654)
16. exp controlled study/(2359146)
17. double blind procedure/(62924)
18. randomization/(21582)
19. placebo/(94966)
20. single blind procedure/(6391)
21. (control$adj (trial$or stud$or evaluation$or experiment$)).mp. (2398474)
22. ((singl$or doubl$or trebl$or tripl$) adj5 (blind$or mask$)).mp. (105032)
23. (placebo$or matched communities or matched schools or matched populations). mp. (143199)
24. (comparison group$or control group$).mp. (141821)
25. (clinical trial$or random$).mp. (675397)
26. (quasiexperimental or quasi experimental or pseudo experimental).mp. (1498)
27. matched pairs.mp. (1904)
28. or/14–27 (2810149)
29. 13 and 28 (1306)
30. limit 29 to human (1158)

Source – EMBASE (Ovid), 1980 to 2007 Week 8

Additional search to account for alternative spelling of sitaxentan/sitaxsentan.

1. pah.mp. (7569)
2. pulmonary hypertension.mp. (18495)
3. pulmonary arterial hypertension.mp. (1408)
4. pulmonary artery hypertension.mp. (375)
5. pulmonary hypertension/(16121)
6. or/1–5 (25814)
7. sitaxsentan.mp. (289)
8. 6 and 7 (240)
9. randomized controlled trial/(114430)
10. exp clinical trial/(423797)
11. exp controlled study/(2365454)
12. double blind procedure/(62995)
13. randomization/(21692)
14. placebo/(95340)
15. single blind procedure/(6412)
16. (control$adj (trial$or stud$or evaluation$or experiment$)).mp. (2404868)
17. ((singl$or doubl$or trebl$or tripl$) adj5 (blind$or mask$)).mp. (105168)
18. (placebo$or matched communities or matched schools or matched populations). mp. (143619)
19. (comparison group$or control group$).mp. (142366)
20. (clinical trial$or random$).mp. (677217)
21. (quasiexperimental or quasi experimental or pseudo experimental).mp. (1502)
22. matched pairs.mp. (1910)
23. or/9–22 (2817435)
24. 8 and 23 (196)

Cochrane Library (CENTRAL), 2007 Issue 1

#1 pulmonary next arterial next hypertension 83
#2 pah 147
#3 pulmonary next hypertension 516
#4 pulmonary next artery next hypertension 15
#5 MeSH descriptor Hypertension, Pulmonary, this term only 264
#6 (#1 OR #2 OR #3 OR #4 OR #5) 714
#7 epoprostenol or prostacyclin or flolan 898
#8 iloprost or ventavis 223
#9 bosentan or tracleer 57
#10 sitaxentan or thelin or sitaxsentan 25
#11 sildenafil or revatio 398
#12 (#7 OR #8 OR #9 OR #10 OR #11) 1450
#13 (#6 AND #12) 137

Source – Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, 27 February 2007

1. pah.mp. (392)
2. pulmonary hypertension.mp. (364)
3. pulmonary arterial hypertension.mp. (109)
4. pulmonary artery hypertension.mp. (19)
5. or/1–4 (776)
6. (epoprostenol or flolan or prostacyclin).mp. (142)

7. (iloprost or ventavis).mp. (25)
8. (bosentan or tracleer).mp. (56)
9. (sitaxentan or thelin).mp. (1)
10. (sildenafil or revatio).mp. (169)
11. or/6–10 (342)
12. 5 and 11 (93)

Source – Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, 27 February 2007

Additional search to account for alternative spelling of sitaxentan/sitaxsentan.

1. pah.mp. (368)
2. pulmonary hypertension.mp. (357)
3. pulmonary arterial hypertension.mp. (99)
4. pulmonary artery hypertension.mp. (20)
5. sitaxsentan.mp. (8)
6. or/1–4 (748)
7. 5 and 6 (6)

Appendix 2.2 Economic evaluation searches

Source – Ovid MEDLINE(R), 1950 to February Week 3 2007

1. hypertension pulmonary/(16015)
2. pah.mp. (6358)
3. pulmonary hypertension.mp. (15802)
4. pulmonary arterial hypertension.mp. (1630)
5. pulmonary artery hypertension.mp. (460)
6. or/1–5 (27871)
7. (epoprostenol or flolan or prostacyclin).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (15459)
8. (iloprost or ventavis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1821)
9. (bosentan or tracleer).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1029)
10. (sitaxentan or sitaxsentan or thelin).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (55)
11. (sildenafil or revatio).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2720)
12. or/7–11 (19615)
13. 6 and 12 (1620)
14. economics/(24681)
15. exp "costs and cost analysis"/(126798)
16. cost of illness/(8780)
17. exp health care costs/(27787)
18. economic value of life/(4800)
19. exp economics medical/(11276)
20. exp economics hospital/(14542)
21. economics pharmaceutical/(1717)
22. exp "fees and charges"/(22697)
23. (econom$or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (238018)
24. (expenditure$not energy).tw. (10144)
25. (value adj1 money).tw. (10)
26. budget$.tw. (10446)
27. or/14–26 (349667)
28. 13 and 27 (38)
29. quality of life/(57413)
30. life style/(25231)
31. health status/(32068)
32. health status indicators/(10696)
33. value of life/(4800)
34. quality adjusted life.mp. (3745)
35. or/29–34 (120619)
36. 6 and 35 (116)

Source – Cochrane Library (DARE and NHS EED), 2007 Issue 1

See above Cochrane Library clinical effectiveness search strategy.

Source – HEED, February 2007

Search terms: epoprostenol or flolan or prostacyclin; iloprost or ventavis; bosentan or tracleer sitaxentan or sitaxsentan or thelin; sildenafil or revatio. References were selected when they also included the terms pulmonary artery hypertension or pulmonary hypertension.

Source – EMBASE (Ovid), 1980 to 2007 Week 9

1. (epoprostenol or flolan or prostacyclin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (19083)
2. (iloprost or ventavis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (3235)
3. (bosentan or tracleer).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2072)
4. (sitaxentan or sitaxsentan or thelin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (292)

5. (sildenafil or revatio).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (5764)
6. or/1–5 (27002)
7. pah.mp. (7569)
8. pulmonary hypertension.mp. (18495)
9. pulmonary arterial hypertension.mp. (1408)
10. pulmonary artery hypertension.mp. (375)
11. pulmonary hypertension/(16121)
12. or/7–11 (25814)
13. 6 and 12 (2890)
14. cost benefit analysis/(25543)
15. cost effectiveness analysis/(47494)
16. cost minimization analysis/(1092)
17. cost utility analysis/(1869)
18. economic evaluation/(3519)
19. (cost or costs or costed or costly or costing).tw. (143239)
20. (economic$or pharmacoeconomic$or price$or pricing).tw. (68823)
21. (technology adj assessment$).tw. (1319)
22. or/14–21 (218757)
23. 13 and 22 (69)
24. "quality of life"/or quality adjusted life year/ (74702)
25. health status/(30678)
26. health status indicator$.mp. (127)
27. or/24–26 (100428)
28. 12 and 27 (317)
29. 23 or 28 (372)

Source – CINAHL (EBSCO), 1982 to February 2007

S1 TX (epoprostenol OR flolan OR prostacyclin) AND DE Hypertension, pulmonary, drug therapy

S2 TX (iloprost OR ventavis) AND DE Hypertension, pulmonary, drug therapy

S3 TX (bosentan OR tracleer) AND DE Hypertension, pulmonary, drug therapy

S4 TX (sitaxentan OR sitaxsentan OR thelin) AND DE Hypertension, pulmonary, drug therapy

S5 TX (sildenafil OR revation) AND DE Hypertension, pulmonary, drug therapy

S6 S1 OR S2 OR S3 OR S4 OR S5

Appendix 2.3 Ongoing studies

Source – National Research Register, 2007 Issue 1

See above Cochrane Library clinical effectiveness search strategy

Sources – Current Controlled Trials and ClinicalTrials.gov

Search terms: epoprostenol or flolan or prostacyclin; iloprost or ventavis; bosentan or tracleer sitaxentan or sitaxsentan or thelin; sildenafil or revatio. References were selected when they also included the terms pulmonary artery hypertension or pulmonary hypertension.

Appendix 3

Table of excluded studies with rationale

TABLE 68 *Clinical effectiveness review: list of excluded studies and reasons for exclusion*

Study	Inclusion criteria not met/reasons for exclusion
Archer 2006[105]	Study design/narrative review
Battistini 2006[106]	Study design/narrative review
Bell 2006[107]	Study design/narrative review
Benza 2007[108]	Comparator/comparison of two doses of sitaxentan without placebo or other active control
Castro 2001[109]	Study design/Spanish commentary on Channick 2001[43]
Galiè 2004[110]	Study design/narrative review
Ghofrani 2002[111]	Study design/< 1 week duration
Ghofrani 2002[112]	Study design/< 1 week duration
Goldsmith 2004[113]	Study design/narrative review
Hughes 2006[114]	Study design/uncontrolled study
Keogh 2007[84]	Study design/uncontrolled study
McLaughlin 2005[115]	Comparator/comparison of survival data from RCT with predicted survival using mathematical equation
Oudiz 2004[116]	Intervention/treprostinil not included in this review
Ricachinevsky 2006[117]	Population/review of treatment of PAH in children
Simonneau 2002[118]	Intervention/treprostinil not included in this review
Voswinckel 2006[119]	Intervention/treprostinil not included in this review

PAH, pulmonary arterial hypertension; RCT, randomised controlled trial.

Appendix 4

Included systematic reviews

Systematic reviews included in this assessment were utilised to identify relevant RCTs and for background information. A list of these reviews is presented in *Table 69*.

TABLE 69 *List of included systematic reviews*

Study	Description
Kenyon 2003[120]	Bosentan for the treatment of PAH
Fung 2004[121]	Sildenafil for the treatment of PAH
Kanthapillai 2004[122]	Sildenafil for pulmonary hypertension (Cochrane review)
Baker 2005[123]	Inhaled iloprost in PAH
Lee 2005[124]	Sildenafil for pulmonary hypertension
Paramothayan 2005[60]	Prostacyclin for pulmonary hypertension in adults (Cochrane review)
Liu 2006[125]	Endothelin receptor antagonists for PAH (Cochrane review)
Wittbrodt 2007[126]	Sitaxentan for treatment of pulmonary hypertension

PAH, pulmonary arterial hypertension.

Appendix 5

Extracted data from included randomised controlled trials for outcomes included in meta-analysis

TABLE 70 *Extracted data for death/survival, clinical worsening, withdrawal for any reason, changes in functional class and SAEs*

	Death		Clinical worsening	
	n/N	**Life table estimates: proportion died (95% CI)**	***n/N***	**Life table estimates: proportion worsened (95% CI)**
Epoprostenol				
Rubin 1990,[39] 8 weeks				
Control	3/12	NR	NR	NR
Epoprostenol	1/11	NR	NR	NR
Barst 1996,[11] 12 weeks				
Control	8/40	0.2[a]	NR	NR
Epoprostenol	0/41	0	NR	NR
ITT population (used in analysis) assuming worsening FC for patients who died or who had transplantation:				
Control	NR	NR	NR	NR
Epoprostenol	NR	NR	NR	NR
Badesch 2000,[33] 12 weeks				
Control	5/55	NR	NR	NR
Epoprostenol	4/56	NR	NR	NR
Iloprost				
AIR-1/Olschewski 2002,[41] 12 weeks				
Placebo	4/102	NR	12/102[c]	NR
Iloprost	***1/101***	***NR***	***5/101***[c]	***NR***
PPH, all FC:				
Placebo	2/55	NR	NR	NR
Iloprost	1/53	NR	NR	NR
PPH, FC III (from industry submission):				
Placebo	NR	NR	NR	NR
Iloprost	NR	NR	NR	NR
AIR-2/Olschewski,[36] 12 weeks [data from industry submission or unpublished manuscript (academic-in-confidence)]				
Control	2[f]/33	NR	NR	NR
Iloprost	2/30	NR	NR	NR
COMBI/Hoeper 2006,[58] 12 weeks				
Ongoing bosentan	0/21	Not applicable	4/21	NR
Iloprost + ongoing bosentan	0/19	Not applicable	3/19	NR
STEP/McLaughlin 2006,[59] 12 weeks				
Placebo + ongoing bosentan	0/33	Not applicable	5/33	0.16[a]
Iloprost + ongoing bosentan	0/34	Not applicable	0/32	0

Withdrawal for any reason	Change in functional class				SAEs
n/N	***N***	**Improved**	**Unchanged**	**Worsened**	***n/N***
NR	9	2	NR	NR	NR
NR	10	10	0	0	NR
10[b]/40	31	1	27	3	NR
3[b]/41	40	16	19	5	NR
NR	40	1	27	12	NR
NR	41	16	19	6	NR
NR	55	0	NR	NR	NR
NR	56	21	NR	NR	NR
14/102	92	13	67	12[d]	25/102
4/101	***97***	***25***	***65***	***7[d]***	***28/101***
7/55	50	4	38	8[e]	NR
2/53	51	13	35	3[e]	NR
NR	36	2	25	9	NR
NR	34	7	24	3	NR
[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	2/33[g]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	7/33
[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	6/30[g]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	8[h]/30
0/21	NR	NR	NR	NR	NR
1[i]/19	NR	NR	NR	NR	NR
5/33	33	2	30	1	7/32
4/34	31	11	20	0	5/35

continued

TABLE 70 *Extracted data for death/survival, clinical worsening, withdrawal for any reason, changes in functional class and SAEs*

	Death		Clinical worsening	
	n/N	**Life table estimates: proportion died (95% CI)**	***n/N***	**Life table estimates: proportion worsened (95% CI)**
IPAH only, mixed FC:				
Placebo + ongoing bosentan	0/20	Not applicable	NR	NR
Iloprost + ongoing bosentan	0/17	Not applicable	NR	NR
Bosentan				
Channick et al., 2001,[43] 12 weeks				
Placebo	0/11	Not applicable	3/11	NR
Bosentan 125 mg b.d.	0/21	Not applicable	0/21	NR
BREATHE-1/Rubin 2002,[45] 16 weeks				
Placebo	2/69	NR	14/69	0.15[a]
Bosentan 125 mg b.d.	1/74	NR	5/74	0.06[a]
Bosentan 250 mg b.d.	0 (3?)/70	NR	4/70	0.06[a]
BREATHE-2/Humbert 2004,[56] 16 weeks				
Placebo + epoprostenol	0/11	NR	NR	NR
Bosentan + epoprostenol	2 (3?)/22	NR	NR	NR
BREATHE-5/Galiè 2006,[47] 16 weeks				
Placebo	0/17	Not applicable	NR	NR
Bosentan 125 mg b.d.	0/37	Not applicable	NR	NR
Sitaxentan				
STRIDE-1/Barst 2004,[49] 12 weeks				
Placebo	0/60	NR	3/60	Proportion with no event: [Academic-in-confidence information has been removed]
Sitaxentan 100 mg o.d.	0/55	NR	0/55	[Academic-in-confidence information has been removed]
Sitaxentan 300 mg o.d.	1/63	NR	1/63	[Academic-in-confidence information has been removed]
IPAH, mixed FC:[61]				
Placebo	NR	NR	NR	NR
Sitaxentan 100 mg and 300 mg	NR	NR	NR	NR
CTD-APAH, mixed FC:[61]				
Placebo	NR	NR	NR	NR
Sitaxentan 100 mg and 300 mg	NR	NR	NR	NR

(continued)

Withdrawal for any reason	Change in functional class				SAEs
n/N	***N***	**Improved**	**Unchanged**	**Worsened**	***n/N***
NR	20	1	NR	NR	NR
NR	16	6	NR	NR	NR
2/11	11	1	8	2	NR
0/21	21	9	12	0	NR
NR	69	21	NR	NR	NR
NR	74	} 60[j]	NR	NR	NR
NR	70		NR	NR	NR
1/11	11	5	NR	NR	NR
4/22	22	13	NR	NR	NR
2/17	17	2	14	1	3/17
2/37	37	13	23	1	5/37
5/60	60	9	47	4	9/59
0/55	55	16	39	0	3/56
7/63	63	19	43	1	10/63
NR	37	6	28	3	NR
NR	55	18	36	1	NR
NR	9	1	7	1	NR
NR	33	8	25	0	NR

continued

TABLE 70 *Extracted data for death/survival, clinical worsening, withdrawal for any reason, changes in functional class and SAEs*

	Death		Clinical worsening	
	n/N	**Life table estimates: proportion died (95% CI)**	***n/N***	**Life table estimates: proportion worsened (95% CI)**
STRIDE-2/Barst 2006,[48] 18 weeks				
Placebo	2/62	NR	10/62	NR
Bosentan 125 mg b.d.	0/60	NR	9/60	$p = 0.80$ vs placebo
Sitaxentan 50 mg o.d.	0/62	NR	6/62	$p = 0.27$ vs placebo
Sitaxentan 100 mg o.d.	0/61	NR	4/61	$p = 0.08$ vs placebo
FCIII only, mixed PAH:				
Placebo	NR	NR	NR	NR
Bosentan 125 mg b.d.	NR	NR	NR	NR
Sitaxentan 50 mg o.d.	NR	NR	NR	NR
Sitaxentan 100 mg o.d.	NR	NR	NR	NR
STRIDE-4/Barst 2007,[37] 18 weeks				
Placebo	0/34	NR	3/34	NR
Sitaxentan 50 mg o.d.	0/32	NR	1/32	[Academic-in-confidence information has been removed]
Sitaxentan 100 mg o.d.	0/32	NR	0/32	$p = 0.0898$ vs placebo

(continued)

Withdrawal for any reason	**Change in functional class**				**SAEs**
n*/*N	***N***	**Improved**	**Unchanged**	**Worsened**	***n*/*N***
11/62	[Academic-in-confidence information has been removed]	6	[Academic-in-confidence information has been removed]	8	19/62
8/60	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	5	[Academic-in-confidence information has been removed]
8/62	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	8	[Academic-in-confidence information has been removed]
4/61	[Academic-in-confidence information has been removed]	8	[Academic-in-confidence information has been removed]	1	8/61
NR	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR
NR	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR
NR	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR
NR	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR
[Academic-in-confidence information has been removed]	34	9	21	4	[Academic-in-confidence information has been removed]
[Academic-in-confidence information has been removed]	32	8	22	2	[Academic-in-confidence information has been removed]
[Academic-in-confidence information has been removed]	32	15	17	0	[Academic-in-confidence information has been removed]

continued

TABLE 70 *Extracted data for death/survival, clinical worsening, withdrawal for any reason, changes in functional class and SAEs*

	Death		Clinical worsening	
	n/N	**Life table estimates: proportion died (95% CI)**	***n/N***	**Life table estimates: proportion worsened (95% CI)**
FCIII only, mixed PAH:				
Placebo	NR	NR	NR	NR
Sitaxentan 50 mg o.d.	NR	NR	NR	NR
Sitaxentan 100 mg o.d.	NR	NR	NR	NR
Sildenafil				
SUPER-1/Galiè 2005,[53] 12 weeks				
Placebo	1/70	NR	7/70	0.100 (0.03–0.17)
Sildenafil 20 mg t.i.d.	1/69	NR	3/69	0.044 (0–0.093)
Sildenafil 40 mg t.i.d.	0/67	NR	2/67	0.030 (0–0.071)
Sildenafil 80 mg t.i.d.	2/71	NR	5/71	0.071 (0.011–0.132)
FCIII only, mixed PAH:				
Placebo	NR	NR	NR	NR
Sildenafil 20 mg t.i.d.	NR	NR	NR	NR
Sildenafil 40 mg t.i.d.	NR	NR	NR	NR
Sildenafil 80 mg t.i.d.	NR	NR	NR	NR

(continued)

Withdrawal for any reason	**Change in functional class**				**SAEs**
n*/*N	***N***	**Improved**	**Unchanged**	**Worsened**	***n*/*N***
NR	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR
NR	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR
NR	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR
[Academic-in-confidence information has been removed]	70	5	58	7	12/70
[Academic-in-confidence information has been removed]	68	19	47	2	10/69
[Academic-in-confidence information has been removed]	66	24	40	2	10/67
[Academic-in-confidence information has been removed]	69	29	38	2	9/71
NR	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR
NR	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR
NR	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR
NR	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR

continued

TABLE 70 *Extracted data for death/survival, clinical worsening, withdrawal for any reason, changes in functional class and SAEs*

	Death		Clinical worsening	
	n/N	**Life table estimates: proportion died (95% CI)**	***n/N***	**Life table estimates: proportion worsened (95% CI)**
PACES-1,[38] *16 weeks*				
Placebo + ongoing epoprostenol	7/131	NR	22/131	0.180 (0.110–0.249)
Sildenafil + ongoing epoprostenol	1/134	NR	8/134	0.062 (0.020–0.104)
FCIII only, mixed PAH:				
Placebo + ongoing epoprostenol	NR	NR	NR	NR
Sildenafil + ongoing epoprostenol	NR	NR	NR	NR
Head-to-head trial				
SERAPH/Wilkins 2005,[57] *16 weeks*				
Bosentan 125 mg b.d.	0/12	NR	NR	NR
Sildenafil 50 mg t.i.d.	1/14	NR	NR	NR

b.d., twice daily; CI, confidence interval; CTD-APAH, PAH associated with connective tissue disease; FC, functional class; IPAH, idiopathic PAH; ITT, intention to treat; NR, not reported; PAH, pulmonary arterial hypertension; PPH, primary pulmonary hypertension; o.d., once daily; SAEs, serious adverse events; t.i.d., three times daily.

a Estimated from figures.
b Including death and lung transplantation.
c Defined as 'died or deteriorated' in the study.
d Including patients who died. Additional patients ($n = 10$ for placebo; $n = 4$ for iloprost) who did not complete the study or who had missing data were not included.
e Including patients who died. Additional patients ($n = 5$ for placebo; $n = 2$ for iloprost) who did not complete the study or who had missing data were not included.
f [Academic-in-confidence information has been removed].
g From manufacturer submission. The denominators (total number of patients included in the analysis) were different from those reported in the unpublished manuscript.
h [Academic-in-confidence information has been removed].
i Stated in the paper that 'all patients finished the study'; however, one patient stopped inhaling iloprost after 6 weeks because of intractable coughing.
j 125 mg b.d. and 250 mg b.d. combined.

(continued)

Withdrawal for any reason	Change in functional class				SAEs
n*/*N	***N***	**Improved**	**Unchanged**	**Worsened**	***n*/*N***
[Academic-in-confidence information has been removed]/131	125	18	92	15	39/131
[Academic-in-confidence information has been removed]/134	132	47	76	9	29/134
NR	85	16	62	7	NR
NR	87	32	51	4	NR
0/12	NR	NR	NR	NR	NR
1/14	NR	NR	NR	NR	NR

TABLE 71 *Extracted data for 6MWD and Borg dyspnoea index*

	6MWD (metres)								
	Baseline *n*	**Mean**	**SD**	**Post-Rx *n***	**Mean**	**SD**	**Change *n***	**Mean**	**SD**
Epoprostenol									
Rubin 1990,[39] 8 weeks									
Control	9	205	NR	9	292	NR	9	79[a]	87.3[a]
Epoprostenol	10	246	NR	10	378	NR	10	131[a]	131.3[a]
Additional data from Cochrane review[60] and used in analysis:									
Control	NR	NR	NR	NR	NR	NR	11	35.70	143.94
Epoprostenol	NR	NR	NR	NR	NR	NR	10	141.20	136.29
Barst 1996,[11] 12 weeks									
Control	40	272	145.5[b]	40	257	151.8[b]	40	–15	148.7[c]
Epoprostenol	41	316	115.3[b]	41	348	108.9[b]	41	32	112.1[c]
Badesch 2000,[33] 12 weeks									
Control	55	240.0 (median)	NR	44[d]	233.6[d]	107.3[d]	55	–36.0	NR
Epoprostenol	56	271.5 (median)	NR	50[d]	317.0[d]	133.0[d]	56	63.5	NR
Iloprost									
AIR/Olschewski 2002,[41] 12 weeks									
Placebo	102	315	96	NR	NR	NR	102	–19[e]	81[b,e]
Iloprost	101	332	93	NR	NR	NR	101	17[e]	90[b,e]
AIR-2/Olschewski,[36] 12 weeks									
Control	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Iloprost	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
COMBI/Hoeper 2006,[58] 12 weeks									
Ongoing bosentan	21	296	79	21	297	94	21	1	27
Iloprost + ongoing bosentan	19	317	74	19	309	124	19	–9	100
STEP/McLaughlin 2006,[59] 12 weeks									
Placebo + ongoing bosentan	33	340	73	33	343[f]	99[f]	33	4[f]	61[f]
Iloprost + ongoing bosentan	34	331	64	32	367[f]	84[f]	32	30[f]	60[f]
Bosentan									
Channick 2001,[43] 12 weeks									
Placebo	11	355.09	81.96	11	349.64	147.12	11	–5.45	120.47
Bosentan 125 mg b.d.	21	360.29	86.05	21	430.52	66.43	21	70.24	56.09

Borg dyspnoea index								
Baseline *n*	**Mean**	**SD**	**Post-Rx *n***	**Mean**	**SD**	**Change *n***	**Mean**	**SD**
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	1.0 (median)	NR
NR	NR	NR	NR	NR	NR	NR	–2.0 (median)	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
33	3.5	2.1	33	3.6[f]	2.5[f]	33	0.0[f]	1.5[f]
32	3.9	1.7	32	3.4[f]	1.7[f]	32	–0.5[f]	1.2[f]
11	3.82	1.72	11	4.91	2.91	11	1.09	2.66
21	4.38	1.80	21	4.19	2.42	21	–0.19	1.66

continued

TABLE 71 *Extracted data for 6MWD and Borg dyspnoea index (continued)*

	6MWD (metres)								
	Baseline *n*	**Mean**	**SD**	**Post-Rx *n***	**Mean**	**SD**	**Change *n***	**Mean**	**SD**
BREATHE-1/Rubin 2002,[45] 16 weeks									
Placebo	69	344	76	NR	NR	NR	69	–8	100[b,e]
Bosentan 125 mg b.d.	74	326	73	NR	NR	NR	74	27	77[b,e]
Bosentan 250 mg b.d.	70	333	75	NR	NR	NR	70	46	59[b,e]
BREATHE-2/Humbert 2004,[56] 16 weeks									
Placebo + epoprostenol	11	NR	NR	NR	NR	NR	10	74 (median)	NR
Bosentan + epoprostenol	22	NR	NR	NR	NR	NR	19	68 (median)	NR
BREATHE-5/Galiè 2006,[47] 16 weeks									
Placebo	17	366.4	67.5	NR	NR	NR	17	–9.7	91.9[b]
Bosentan 125 mg b.d.	37	331.9	82.8	NR	NR	NR	37	43.3	49.3[b]
Sitaxentan									
STRIDE-1/Barst 2004,[49] 12 weeks									
Placebo	60	413	105	NR	NR	NR	60	–13	62.8
Sitaxentan 100 mg o.d.	55	394	114	NR	NR	NR	55	22	47.6
Sitaxentan 300 mg o.d.	63	387	110	NR	NR	NR	63	20	67.8
IPAH, mixed FC:[61]									
Placebo	NR	NR	NR	NR	NR	NR	37	–10	65
Sitaxentan 100 mg and 300 mg	NR	NR	NR	NR	NR	NR	57	24	68
CTD-APAH, mixed FC:[61]									
Placebo	NR	NR	NR	NR	NR	NR	9	–38	84
Sitaxentan 100 mg and 300 mg	NR	NR	NR	NR	NR	NR	33	20	52
STRIDE-2/Barst 2006,48 18 weeks									
Placebo	62	321	85	NR	NR	NR	[Academic-in-confidence information has been removed]	–6.5	84.4
Bosentan 125 mg b.d.	60	337	78	NR	NR	NR	[Academic-in-confidence information has been removed]	23.0	76.4
Sitaxentan 50 mg o.d.	62	328	80	NR	NR	NR	[Academic-in-confidence information has been removed]	17.8	58.3

Borg dyspnoea index								
Baseline *n*	**Mean**	**SD**	**Post-Rx *n***	**Mean**	**SD**	**Change *n***	**Mean**	**SD**
69	3.8	2.0	69	4.2	2.5[b]	69	0.3	1.7[b]
74	3.3	2.2	74	3.2	2.6[b]	74	–0.1	1.7[b]
70	3.8	1.9	70	3.3	2.5[b]	70	–0.6	1.7[b]
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	[Academic-in-confidence information has been removed]	0.19	2.15
NR	NR	NR	NR	NR	NR	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
NR	NR	NR	NR	NR	NR	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]

continued

TABLE 71 *Extracted data for 6MWD and Borg dyspnoea index (continued)*

	6MWD (metres)								
	Baseline *n*	**Mean**	**SD**	**Post-Rx *n***	**Mean**	**SD**	**Change *n***	**Mean**	**SD**
Sitaxentan 100 mg o.d.	61	360	72	NR	NR	NR	[Academic-in-confidence information has been removed]	24.9	57.5
STRIDE-4/Barst 2007,[37] 18 weeks									
Placebo	34	342	82	NR	NR	NR	34	34	88.5
Sitaxentan 50 mg o.d.	32	350	73	NR	NR	NR	32	22	48.6
Sitaxentan 100 mg o.d.	32	344	83	NR	NR	NR	32	58	63.6
Sildenafil									
SUPER-1/Galiè 2005,[53] 12 weeks									
Placebo	70	344	79	NR	NR	NR	NR	NR	NR
Sildenafil 20 mg t.i.d.	69	347	90	NR	NR	NR	NR	NR	NR
Sildenafil 40 mg t.i.d.	67	345	77	NR	NR	NR	NR	NR	NR
Sildenafil 80 mg t.i.d.	71	339	79	NR	NR	NR	NR	NR	NR
PACES-1,[38] 16 weeks									
Placebo + ongoing epoprostenol	119	NR	NR	NR	NR	NR	119	4.1	NR
Sildenafil + ongoing epoprostenol	131	NR	NR	NR	NR	NR	131	30.1	NR

6MWD, 6-minute walk distance; b.d., twice daily; CTD-APAH, PAH associated with connective tissue disease; FC, functional class; IPAH, idiopathic PAH; NR, not reported; o.d., once daily; PAH, pulmonary arterial hypertension; Rx, treatment; SD, standard deviation; t.i.d., three times daily.
a Estimated from 95% confidence intervals.
b Estimated from standard errors.
c Imputed from standard deviations of baseline and post-treatment values assuming an intercorrelation coefficient of 0.5.
d Data from Paramothayan 2005[60] (Cochrane review).
e Estimated from figures.
f Measured post inhalation (peak drug level/effect).

Borg dyspnoea index								
Baseline *n*	**Mean**	**SD**	**Post-Rx *n***	**Mean**	**SD**	**Change *n***	**Mean**	**SD**
NR	NR	NR	NR	NR	NR	[Academic-in-confidence information has been removed]	–0.01	1.91
34	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR	NR	NR	34	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
32	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR	NR	NR	32	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
32	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR	NR	NR	32	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	–1 (median)	NR
NR	NR	NR	NR	NR	NR	NR	0 (median)	NR
NR	NR	NR	NR	NR	NR	NR	–1 (median)	NR
119	3 (median)	NR	119	3 (median)	NR	NR	NR	NR
131	3 (median)	NR	131	3 (median)	NR	NR	NR	NR

TABLE 72 *Extracted data for mPAP and RAP*

	Mean pulmonary arterial pressure (mPAP) (mmHg)								
	Baseline *n*	**Mean**	**SD**	**Post-Rx *n***	**Mean**	**SD**	**Change n**	**Mean**	**SD**
Epoprostenol									
Rubin 1990,[39] 8 weeks									
Control	9	62.2	NR	9	62.2	NR	9	0[a]	13.6[a]
Epoprostenol	10	58.6	NR	10	49.3	NR	10	–8.4[a]	15.0[a]
Additional data from Cochrane review[60] and used in analysis:									
Control	NR	NR	NR	NR	NR	NR	11	0.30	13.50
Epoprostenol	NR	NR	NR	NR	NR	NR	10	–7.57	14.14
Barst 1996,[11] 12 weeks									
Control	40	59	12.6[b]	NR	NR	NR	30	1.87	8.49[b]
Epoprostenol	41	61	12.8[b]	NR	NR	NR	38	–4.82	8.14[b]
Badesch 2000,[33] 12 weeks									
Control	55	49.1	10.2	NR	NR	NR	NR	0.94	8.16[b]
Epoprostenol	56	50.9	10.6	NR	NR	NR	NR	–5.03	8.16[b]
Iloprost									
AIR-1/Olschewski 2002,[41] 12 weeks									
Placebo	101	53.8	14.1	NR	NR	NR	NR	–0.2	6.9
Iloprost (post inhalation)	100	52.8	11.5	NR	NR	NR	NR	–4.6[c]	9.3[c]
Iloprost (preinhalation)	NR	NR	NR	NR	NR	NR	NR	–0.1[d]	7.3[d]
AIR-2/Olschewski,[36] 12 weeks									
Control	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR	NR	NR	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
Iloprost	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR	NR	NR	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
COMBI/Hoeper 2006,[58] 12 weeks									
Ongoing bosentan	59	19	NR	NR	NR	NR	NR	NR	NR
Iloprost + ongoing bosentan	54	12	NR	NR	NR	NR	NR	NR	NR
STEP/McLaughlin 2006,[59] 12 weeks									
Placebo + ongoing bosentan	28	52	13	28	55[c]	16[c]	28	2[c]	6[c]
Iloprost + ongoing bosentan	29	51	11	29	46[c]	13[c]	29	–6[c]	7[c]
Bosentan									
Channick 2001,[43] 12 weeks									
Placebo	10	56	10	NR	NR	NR	10	5.1	8.9

Right atrial pressure (RAP) (mmHg)								
Baseline *n*	**Mean**	**SD**	**Post-Rx *n***	**Mean**	**SD**	**Change *n***	**Mean**	**SD**
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
40	12	6.3	NR	NR	NR	29	0.09	4.95[b]
41	13	6.4	NR	NR	NR	36	–2.17	6.54[b]
55	11.1	5.5	NR	NR	NR	NR	1.20	5.12[b]
56	13.1	5.0	NR	NR	NR	NR	–1.26	6.14[b]
NR	NR	NR	NR	NR	NR	NR	1.4	4.8
NR	NR	NR	NR	NR	NR	NR	–0.8[c]	4.6[c]
NR	NR	NR	NR	NR	NR	NR	0.5[d]	4.6[d]
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
9	5	NR	NR	NR	NR	NR	NR	NR
9	6	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
10	9.9	4.1	NR	NR	NR	10	4.9	4.7

continued

TABLE 72 *Extracted data for mPAP and RAP (continued)*

	Mean pulmonary arterial pressure (mPAP) (mmHg)								
	Baseline *n*	**Mean**	**SD**	**Post-Rx *n***	**Mean**	**SD**	**Change n**	**Mean**	**SD**
Bosentan 125 mg b.d.	20	54	13	NR	NR	NR	20	–1.6	5.4
BREATHE-1/Rubin 2002,[45] 16 weeks									
Placebo	69	53	17	NR	NR	NR	NR	NR	NR
Bosentan 125 mg b.d.	74	53	14	NR	NR	NR	NR	NR	NR
Bosentan 250 mg b.d.	70	57	17	NR	NR	NR	NR	NR	NR
BREATHE-2/Humbert 2004,[56] 16 weeks									
Placebo + epoprostenol	11	60.9	9.6[b]	11	59.2	10.6[b]	11	–2.2%	SE 3.6%
Bosentan + epoprostenol	22	59.2	18.8[b]	22	52.5	11.3[b]	22	–9.0%	SE 6.0%
BREATHE-5/Galiè 2006,[47] 16 weeks									
Placebo	17	72.1	19.4	NR	NR	NR	17	0.5	5.8[b]
Bosentan 125 mg b.d.	37	77.8	15.2	NR	NR	NR	37	–5.0	9.7[b]
Sitaxentan									
STRIDE-1/Barst 2004,[49] 12 weeks									
Placebo	60	52	16	60	53	15	60	0	8
Sitaxentan 100 mg o.d.	55	54	17	55	51	16	55	–3	8
Sitaxentan 300 mg o.d.	63	54	14	63	49	15	63	–5	11
STRIDE-2/Barst 2006,[48] 18 weeks									
Placebo	62	49	14	NR	NR	NR	NR	NR	NR
Bosentan 125 mg b.d.	60	50	15	NR	NR	NR	NR	NR	NR
Sitaxentan 50 mg o.d.	62	48	15	NR	NR	NR	NR	NR	NR
Sitaxentan 100 mg o.d.	61	45	12	NR	NR	NR	NR	NR	NR
STRIDE-4/Barst 2007,[37] 18 weeks									
Placebo	34	64	14	NR	NR	NR	NR	NR	NR
Sitaxentan 50 mg o.d.	32	56	17	NR	NR	NR	NR	NR	NR
Sitaxentan 100 mg o.d.	32	63	23	NR	NR	NR	NR	NR	NR
Sildenafil									
SUPER-1/Galiè 2005,[53] 12 weeks									
Placebo	70	56	16	NR	NR	NR	65	0.6	5.8[a]
Sildenafil 20 mg t.i.d.	69	54	13	NR	NR	NR	65	–2.1	8.8[a]
Sildenafil 40 mg t.i.d.	67	49	13	NR	NR	NR	63	–2.6	7.1[a]
Sildenafil 80 mg t.i.d.	71	52	16	NR	NR	NR	65	–4.7	8.0[a]
PACES-1,[38] 16 weeks									
Placebo + ongoing epoprostenol	NR	NR	NR	NR	NR	NR	102	0.2	NR

Right atrial pressure (RAP) (mmHg)								
Baseline *n*	**Mean**	**SD**	**Post-Rx *n***	**Mean**	**SD**	**Change *n***	**Mean**	**SD**
19	9.7	5.6	NR	NR	NR	19	–1.3	3.9
67	8.9	5.1	NR	NR	NR	NR	NR	NR
74	9.7	5.4	NR	NR	NR	NR	NR	NR
69	9.9	6.5	NR	NR	NR	NR	NR	NR
11	11.9	7.3[b]	11	12.2	6.0[b]	11	0.3	4.3[b]
22	11.9	5.2[b]	22	10.0	5.6[b]	22	–1.9	6.6[b]
17	5.0	3.7	NR	NR	NR	17	0.4	3.7[b]
37	6.1	3.4	NR	NR	NR	37	0.3	3.0[b]
60	8	5	NR	NR	NR	60	1	4
55	7	5	NR	NR	NR	55	0	4
63	9	5	NR	NR	NR	63	–1	4
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR
70	9	4	NR	NR	NR	65	0.3	4.9[a]
69	8	5	NR	NR	NR	65	–0.8	4.5[a]
67	9	6	NR	NR	NR	63	–1.1	5.3[a]
71	9	5	NR	NR	NR	65	–1.0	4.5[a]
[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR	NR	NR	NR	NR	NR

continued

TABLE 72 *Extracted data for mPAP and RAP (continued)*

	Mean pulmonary arterial pressure (mPAP) (mmHg)								
	Baseline *n*	**Mean**	**SD**	**Post-Rx *n***	**Mean**	**SD**	**Change n**	**Mean**	**SD**
Sildenafil + ongoing epoprostenol	NR	NR	NR	NR	NR	NR	117	–3.6	NR

b.d., twice daily; NR, not reported; o.d., once daily; Rx, treatment; SD, standard deviation; SE, standard error; t.i.d., three times daily.
a Estimated from 95% confidence intervals.
b Estimated from standard errors.
c Measured post inhalation (at peak drug level/effect).
d Measured preinhalation (at trough drug level/effect).

Right atrial pressure (RAP) (mmHg)								
Baseline *n*	**Mean**	**SD**	**Post-Rx *n***	**Mean**	**SD**	**Change *n***	**Mean**	**SD**
[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR	NR	NR	NR	NR	NR

TABLE 73 *Extracted data for cardiac index and PVR*

	Cardiac index (l/min/m²)								
	Baseline *n*	**Mean**	**SD**	**Post-Rx *n***	**Mean**	**SD**	**Change *n***	**Mean**	**SD**
Epoprostenol									
Rubin 1990,[39] 8 weeks									
Data from Cochrane review:[60]									
Control	NR	NR	NR	NR	NR	NR	NR	NR	NR
Epoprostenol	NR	NR	NR	NR	NR	NR	NR	NR	NR
Barst 1996,[11] 12 weeks									
Control	40	2.1	1.3[b]	NR	NR	NR	30	–0.23	0.88[b]
Epoprostenol	41	2.0	0.6[b]	NR	NR	NR	38	0.33	0.62[b]
Badesch 2000,[33] 12 weeks									
Control	55	2.2	0.7	NR	NR	NR	NR	–0.10	0.59[b]
Epoprostenol	56	1.9	0.6	NR	NR	NR	NR	0.50	0.60[b]
Iloprost									
AIR/Olschewski 2002,[41] 12 weeks									
Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
Iloprost (post inhalation)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Iloprost (preinhalation)	NR	NR	NR	NR	NR	NR	NR	NR	NR
AIR-2/Olschewski,[36] 12 weeks									
Control	NR	NR	NR	NR	NR	NR	NR	NR	NR
Iloprost	NR	NR	NR	NR	NR	NR	NR	NR	NR
COMBI/Hoeper 2006,[58] 12 weeks									
Ongoing bosentan	21	2.1	0.5	NR	NR	NR	NR	NR	NR
Iloprost + ongoing bosentan	19	2.1	0.7	NR	NR	NR	NR	NR	NR
STEP/McLaughlin 2006,[59] 12 weeks									
Placebo + ongoing bosentan	NR	NR	NR	NR	NR	NR	NR	NR	NR
Iloprost + ongoing bosentan	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bosentan									
Channick 2001,[43] 12 weeks									
Placebo	10	2.5	1.0	NR	NR	NR	10	–0.5	0.3
Bosentan 125 mg b.d.	20	2.4	0.7	NR	NR	NR	20	0.5	0.4
BREATHE-1/Rubin 2002,[45] 16 weeks									
Placebo	68	2.4	0.7	NR	NR	NR	NR	NR	NR
Bosentan 125 mg b.d.	70	2.5	0.8	NR	NR	NR	NR	NR	NR

Pulmonary vascular resistance (dyn s/cm^5)								
Baseline *n*	**Mean**	**SD**	**Post-Rx *n***	**Mean**	**SD**	**Change *n***	**Mean**	**SD**
NR	NR	NR	NR	NR	NR	11	–23.2[a]	878.4[a]
NR	NR	NR	NR	NR	NR	10	–473.6[a]	680.8[a]
40	1280[b]	504[a,b]	NR	NR	NR	17	121.6[b]	405.6[a,b]
41	1280[b]	512[a,b]	NR	NR	NR	27	–273.6[b]	299.2[a,b]
55	896[a]	424[a]	NR	NR	NR	NR	73.6[a]	332.0[a,b]
56	1136[a]	568[a]	NR	NR	NR	NR	–366.4[a]	455.2[a,b]
96	1041	493	NR	NR	NR	NR	96	322
91	1029	390	NR	NR	NR	NR	–239	279
NR	NR	NR	NR	NR	NR	NR	–9	275
[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR	NR	NR	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	NR	NR	NR	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
21	1032[a]	536[a]	NR	NR	NR	NR	NR	NR
19	1080[a]	528[a]	NR	NR	NR	NR	NR	NR
28	783	378	28	867[c]	496[c]	28	81[c]	267[c]
29	821	389	29	676[c]	404[c]	29	–164[c]	223[c]
10	942	430	NR	NR	NR	10	191	234
19	896	425	NR	NR	NR	19	–223	244
66	880	540	NR	NR	NR	NR	NR	NR
73	884	412	NR	NR	NR	NR	NR	NR

continued

TABLE 73 *Extracted data for cardiac index and PVR (continued)*

	Cardiac index (l/min/m²)								
	Baseline *n*	**Mean**	**SD**	**Post-Rx *n***	**Mean**	**SD**	**Change *n***	**Mean**	**SD**
Bosentan 250 mg b.d.	70	2.2	0.8	NR	NR	NR	NR	NR	NR
BREATHE-2/Humbert 2004,[56] 16 weeks									
Placebo + epoprostenol	11	1.7	0.7[b]	11	2.3	0.7[b]	11	37.9%	SE 13.3%
Bosentan + epoprostenol	22	1.7	0.5[b]	22	2.5	0.5[b]	22	48.7%	SE 11.0%
BREATHE-5/Galiè 2006,[47] 16 weeks									
Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bosentan 125 mg b.d.	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sitaxentan									
STRIDE-1/Barst 2004,[49] 12 weeks									
Placebo	60	2.4	0.8	60	2.4	0.9	60	0.0	0.5
Sitaxentan 100 mg o.d.	55	2.4	0.8	55	2.7	0.8	55	0.3	0.6
Sitaxentan 300 mg o.d.	63	2.3	0.7	63	2.7	0.9	63	0.4	0.6
STRIDE-2/Barst 2006,[48] 18 weeks									
Placebo	62	2.4	0.7	NR	NR	NR	NR	NR	NR
Bosentan 125 mg b.d.	60	2.4	0.6	NR	NR	NR	NR	NR	NR
Sitaxentan 50 mg o.d.	62	2.7	1.0	NR	NR	NR	NR	NR	NR
Sitaxentan 100 mg o.d.	61	2.4	0.6	NR	NR	NR	NR	NR	NR
STRIDE-4/Barst 2007,[37] 18 weeks									
Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sitaxentan 50 mg o.d.	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sitaxentan 100 mg o.d.	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sildenafil									
SUPER-1/Galiè 2005,[53] 12 weeks									
Placebo	70	2.2	0.6	NR	NR	NR	65	–0.02	0.62[e]
Sildenafil 20 mg t.i.d.	69	2.4	0.7	NR	NR	NR	65	0.21	0.70[e]
Sildenafil 40 mg t.i.d.	67	2.3	0.7	NR	NR	NR	63	0.24	0.75[e]
Sildenafil 80 mg t.i.d.	71	2.5	0.8	NR	NR	NR	65	0.37	0.72[e]
PACES-1,[38] 16 weeks									
Placebo + ongoing epoprostenol	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sildenafil + ongoing epoprostenol	NR	NR	NR	NR	NR	NR	NR	NR	NR

b.d., twice daily; NR, not reported; o.d., once daily; Rx, treatment; SD, standard deviation; t.i.d., three times daily.
a Converted from mmHg/l/min (Wood unit).
b Estimated from standard errors.
c Measured post inhalation (at peak drug level/effect).
d Pulmonary vascular resistance index (dyn s/cm^5).
e Estimated from confidence intervals.

Pulmonary vascular resistance (dyn s/cm^5)								
Baseline *n*	**Mean**	**SD**	**Post-Rx *n***	**Mean**	**SD**	**Change *n***	**Mean**	**SD**
62	1167	875	NR	NR	NR	NR	NR	NR
10	1426	443[b]	10	1050	487[b]	10	–25.7%	SE 7.2%
20	1511	577[b]	20	947	465[b]	20	–35.2%	SE 5.4%
17	2870.0[d]	1209.3[d]	NR	NR	NR	17	155.1[d]	552.5[b,d]
37	3425.1[d]	1410.5[d]	NR	NR	NR	37	–316.9[d]	841.3[b,d]
60	911	504 (484 in text)	60	960	535	60	49	244
55	1026 (1025 in text)	694	55	805	553	55	–221	442
63	946	484	63	753	524	63	–194	330
62	880[a]	640[a]	NR	NR	NR	NR	NR	NR
60	880[a]	400[a]	NR	NR	NR	NR	NR	NR
62	800[a]	560[a]	NR	NR	NR	NR	NR	NR
61	800[a]	560[a]	NR	NR	NR	NR	NR	NR
34	1200[a]	800[a]	NR	NR	NR	NR	NR	NR
32	1120[a]	800[a]	NR	NR	NR	NR	NR	NR
32	1129[a]	640[a]	NR	NR	NR	NR	NR	NR
70	1051	512	NR	NR	NR	65	49	425.7[e]
69	987	464	NR	NR	NR	65	–122	390.8[e]
67	869	438	NR	NR	NR	63	–143	301.7[e]
71	918	601	NR	NR	NR	65	–261	427.8[e]
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR

Appendix 6

Ongoing trials of the technologies in pulmonary arterial hypertension patients

A number of ongoing studies were identified. These are tabulated in *Table 74*.

TABLE 74 *Ongoing studies*

Clinical trial identifier; location (centres)	PICO	(Expected) enrolment	Study design	Time frame	Status	Sponsor	Comments
NCT00004754; centres not stated	P: severe PAH, able to self-administer medication; I: epoprostenol; C: not stated; O: safety, economic resource consumption	Not stated	Open-label	Start: August 1993	Completed	National Center for Research Resources, Baylor College of Medicine	Unclear if published increasing dose until target is reached or at least one dose-limiting effect occurs
NCT00250640; multicentre (international)	P: NYHA FCIII familial or IPAH, no previous active treatment within 6 weeks of study inclusion; I: inhaled iloprost; C: none; O: continued effectiveness	54	Prospective, observational	Start: April 2005; follow-up: up to 4 years	Recruiting	Schering AG, Germany	
NCT00086463; multicentre (USA)	P: PAH, NYHA FCIII–FCIV, receiving conventional therapy and bosentan; I: inhaled iloprost at frequency of six to nine inhalations per day added to bosentan; C: placebo added to bosentan; O: safety and efficacy	60	Double-blind RCT	Start: June 2004; follow-up:12 weeks	Completed		Combination therapy (possibly included trial – McLaughlin 2006)[59]
NCT00302211; multicentre (USA)	P: IPAH or FPAH, age 12–80 years, on sildenafil; I: inhaled iloprost added to sildenafil; C: placebo added to sildenafil; O: 6MWT, safety and effectiveness	180	Double-blind RCT	Start: March 2006	Recruiting	CoTherix	Combination therapy; 'VISION' trial
NCT00266162; multicentre (Germany)	P: PAH secondary to Eisenmenger syndrome, age ≥ 18 years; I: bosentan; C: none; O: 6MWD, haemodynamic outcomes, NYHA FC, increase in pulmonary reagibility, normalisation of vasoactive mediators	60	Open-label, prospective	Start: August 2004; expected completion: November 2007	No longer recruiting	Competence Network for Congenital Heart Defects, German Federal Ministry of Education and Research, Actelion	

Clinical trial identifier; location (centres)	PICO	(Expected) enrolment	Study design	Time frame	Status	Sponsor	Comments
NCT00091715; multicentre (international)	P: PAH, NYHA FCII, age ≥ 12 years; I: bosentan; C: placebo; O: exercise capacity, cardiac haemodynamics	170	Double-blind RCT	Start: September 2004; completion: December 2006	Completed	Actelion	EARLY study
NCT00303459; multicentre (international)	P: symptomatic PAH, WHO FCI, age ≥ 12 years, on sildenafil; I: bosentan added to sildenafil; C: placebo added to sildenafil; O: morbidity/mortality events, 6MWT, WHO FC, Borg dyspnoea index, EQ-5D, patient global self-assessment, time to hospitalisation or worsening or complication of PAH or initiation of prostanoids, atrial septostomy, lung transplantation or death from baseline until end of study, time to death of all causes from baseline until end of study	600	Double-blind RCT	Start: April 2006; expected completion: June 2010; follow-up: 16 weeks	Recruiting	Actelion	Combination therapy
NCT00352482; single-centre (Los Angeles, USA)	P: idiopathic pulmonary fibrosis and pulmonary hypertension; age ≥ 19 years; I: sildenafil (50 mg); C: placebo; O: 6MWD, haemodynamic parameters	20	Double-blind, cross-over RCT	Start: November 2004; follow-up: 3 weeks	Recruiting	National Heart, Lung, and Blood Institute	
NCT00323297; multicentre (international)	P: PAH, age ≥ 18 years, on bosentan; I: sildenafil added to bosentan; C: placebo added to bosentan; O: 6MWT, safety, clinical worsening, Borg dyspnoea score, FC, pharmacokinetic outcomes	106	Double-blind RCT + open-label extension	Start: September 2006; follow-up: 12 weeks (extension: 12 months)	Recruiting	Pfizer	Combination therapy

6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; EQ-5D, EuroQol 5 dimensions; IPAH, idiopathic pulmonary arterial hypertension; FC, functional class; FPAH, familial pulmonary arterial hypertension; NYHA, New York Heart, Association; PICO, patient problem, intervention, comparison and outcome; RCT, randomised controlled trial; WHO, World Health Organization.

Appendix 7

Long-term follow-up studies

Long-term follow-up studies on the technologies in this assessment were identified from the manufacturer submissions for the purpose of providing further information, in particular for the independent economic evaluation (see Chapter 4). The identified studies are documented below and in *Table 75*. The key requirement was for data to be provided by FC for the outcomes of change (or no change) in FC and/or survival. Studies containing such data are indicated and further details provided in *Table 76*.

Studies were included based on their duration and number of patients enrolled. Data stratified by NYHA/WHO FC were extracted on change in NYHA/WHO FC and survival. As a rule summary data were used, but for STRIDE-1X and STRIDE-2X it was necessary to use individual patient data.

Supportive care/ standard treatment

One study of patients treated only with supportive care was identified.[5] No information applicable to the economic model was found as data on deterioration in FC were not presented. Although data on survival were provided they were also not stratified by FC and were therefore not very useful.

Epoprostenol

In total, six long-term studies were identified for epoprostenol. Four of these stratified data in some way by FC for the outcomes of change in FC and survival. These were the studies by Barst *et al*.,[127] McLaughlin *et al*.,[65] Sitbon *et al*.[66] and Kuhn *et al*.[128] Barst *et al*.[127] used a prospective design and all the other studies were retrospective.

Iloprost

Four long-term studies were identified. Only one of these, that by Hoeper *et al*.,[129] provided any data stratified by FC and this was for survival. It was an open-label, prospective study of 24 patients.

Bosentan

For bosentan a total of nine studies were identified, three of which[93,98,130] were used to obtain data for the model. Also, data from STRIDE-2X,[100] which compared sitaxentan and bosentan, were included for the long-term analysis of bosentan. Although Keogh *et al*.[84] provided data on deaths stratified by FC, the numbers were given for the end of study, without specifying the length of follow-up. It is worth mentioning that the study by Sitbon *et al*.[98] is an analysis of an IPAH subgroup of patients from the same population that was analysed in the study by Sitbon *et al*.[130]

Sitaxentan

For sitaxentan two long-term extensions of RCTs were identified: STRIDE-1X[99] and STRIDE-2X.[100] An article[131] describing the Canadian subpopulation of the STRIDE-1X trial was also found. Both STRIDE-1X and STRIDE-2X contained data stratified by FC.

Sildenafil

The manufacturer submission for sildenafil mentioned two long-term studies on treatment of PAH with sildenafil: SUPER-2[96] and PACES-2.[132] Both studies were described as ongoing and no data stratified by FC were provided.

TABLE 75 *Long-term studies on new drugs for PAH supplied in industry submissions*

Name of study	Duration/follow-up; number of participants	Type of PAH	Functional class (FC)	Design
Conventional treatment				
D'Alonzo 1991[5]	Up to 5 years; 194 patients	IPAH	I, II, III, IV (% not stated)	Registry with prospective follow-up
Epoprostenol				
Barst 1994[127]	3 years; 18 patients	IPAH	II (6%), III (72%), IV (22%)	Open-label multicentre extension to Rubin 1990;[39] matched with historic control subjects for survival
Shapiro 1997[133]	330–700 days; 69 patients (18 followed up > 330 days)	IPAH	III, IV (% not stated)	Open-label, prospective
McLaughlin 1998[134]	2 years (16.7±5.2 months); 27 patients	IPAH	III (63%), IV (37%)*	Open-label, retrospective
McLaughlin 2002[65]	5 years (36.3 months); 162 patients	IPAH	III (46%), IV (54%)	Open-label, retrospective
Sitbon 2002[66]	5 years (26±21 months); 313 patients (178 epoprostenol, 135 control)	IPAH	Epoprostenol: III (67%), IV (33%)	Open-label, retrospective
Kuhn 2003[128]	3 years; 91 patients	IPAH, scleroderma, CHD, HIV, systemic lupus erythematous, portopulmonary, pulmonary veno-occlusive disease	III (52%), IV (48%)	Retrospective cohort
Iloprost				
Hoeper 2000[129]	1 year; 24 patients	IPAH	III (83%), IV (17%)	Open-label, prospective
Opitz 2005[135]	5 years (median 535 ±61 days); 76 patients	IPAH	II, III, IV	Prospective
AIR follow-up, study report 303045[136]	Up to 5 years; 71 patients		III, IV (no % given)	Open-label extension of AIR
AIR-2; Olschewski,[36] Nikkho 2001,[137] Nikkho 2003,[138] Olschewski 2003,[139] Olschewski 2005[140]	2 years; 52 patients	IPAH, secondary	II (33.3%), III (47.6%), IV (19%)*	Prospective, open-label, active controlled
Bosentan				
Sitbon 2003[141]	1 year; 29 patients	IPAH, scleroderma	–	Open-label extension to Channick 2001[43]

FC assessed (FC specific)	Survival assessed (FC specific)	6MWT assessed	Data on adverse events	Comments
No	Yes*	No	No	*Median survival for FCIII and FCIV; D'Alonzo equation
No	Yes	Yes	Yes	Time to transplantation
No	Yes (no)	No	No	Mainly haemodynamic variables
Yes (no)	No	No	Yes	Treadmill exercise *Unclear if the % applies to 27 included patients or 38 treated
Yes (yes)	Yes (yes)	No	Yes	Treadmill exercise
Yes (no)	Yes (yes)	Yes	Yes	Control used for survival only, FC not stated
Yes (yes)	Yes (yes)*	Yes	No	*1 year
No	Yes (yes)	Yes	Yes	
No	Yes (no)	No	No	Cardiopulmonary exercise test
Yes (no)	Yes (no)	–	Yes	Based on submission; data not stratified by FC
Yes [Academic-in-confidence information has been removed]	Yes [Academic-in-confidence information has been removed]	Yes	Yes	[Academic-in-confidence information has been removed] *At baseline of RCT
Yes	–	Yes	-	No article

continued

TABLE 75 *Long-term studies on new drugs for PAH supplied in industry submissions (continued)*

Name of study	Duration/follow-up; number of participants	Type of PAH	Functional class (FC)	Design
McLaughlin 2005[115]	2.1±0.5 years; 169 patients	IPAH	I (1%), II (8%), III (82%), IV (9%)	Prospective extension of two RCTs: BREATHE-1[45] and Channick 2001[43]
Sitbon 2005[98] (bosentan vs epoprostenol)	3 years; 485 patients (139 bosentan, 346 epoprostenol)	IPAH	III (100%)	Prospective extension of two RCTs, BREATHE-1[45] and Channick 2001,[43] matched with historic control subjects
Denton 2006[44]	2 years (1.8±0.2); 64 patients	CTD	III (95.5%)*, IV (4.5%)*	Prospective extension of two RCTs: BREATHE-1[45] and Channick 2001;[43] subgroup
Gatzoulis 2006[142]	6–10 months (6-month results reported); 37 patients	Eisenmenger syndrome	II (30%), III (70%)	Open-label extension of BREATHE-5[47]
Provencher 2006[104]	1 year; 103 patients	IPAH	III (88%), IV (12%)	Retrospective single centre
Williams 2006[93]	2 years; 92 patients (45 bosentan, 47 control)	Systemic sclerosis	Bosentan: III (58%), IV (42%); control: III (77%), IV (23%)	Prospective experimental, historic control subjects
Koegh 2007[84]	Follow-up: up to 21 months; 177 patients	IPAH, CTD	III, IV (% not stated)	Multicentre, prospective, open-label study
Sitbon 2007[130]	[Academic-in-confidence information has been removed]; [Academic-in-confidence information has been removed]	IPAH, CTD	[Academic-in-confidence information has been removed]	Prospective extension of two RCTs: BREATHE-1[45] and Channick 2001[43]
Denton 2007[143]	48 weeks; 53 patients	CTD	III (100%)	Open-label prospective
Sitaxentan				
STRIDE-1X[99]	58 weeks; [Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	Randomised, double-blind prospective extension of STRIDE-1[49] (two doses)
STRIDE-1X; Langleben 2004[131]	1 year; 11 (10) patients	IPAH, CTD, CHD	II (10%), III (90%)*	Open-label prospective extension of STRIDE-1[49] (Canadian)

FC assessed (FC specific)	Survival assessed (FC specific)	6MWT assessed	Data on adverse events	Comments
No	Yes (no)	No	Yes	
No	Yes (yes)	No	Yes	Includes subgroup survival analysis for 83 patients plus 83 matched patients from both cohorts
Yes	Yes (no)	Yes	No	Data on time to clinical worsening *Data on beginning of RCTs, two did not enter extensions
Yes (yes)	Yes	Yes	Yes	Based on industry submission and conference abstract;
Yes (yes)*	Yes (no)	Yes	Yes	*4 months
Yes (yes)	Yes (no)	No	No	
Yes (no)	Yes (yes)	No	Yes	QoL; FC and survival data provided for end of study – patients followed up for different periods
[Academic-in-confidence information has been removed]	Yes [Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	
Yes	Yes	No	Yes	QoL data, time to clinical worsening
Yes (yes)	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]
Yes (yes)	Yes (yes)	Yes	Yes	One patient discontinued because of deterioration at 7 months not included later *For 10 patients

TABLE 75 *Long-term studies on new drugs for PAH supplied in industry submissions (continued)*

Name of study	Duration/follow-up; number of participants	Type of PAH	Functional class (FC)	Design
Stride-2X[100]				
(sitaxentan vs bosentan)	1 year [Commercial-in-confidence information removed]	[Commercial-in-confidence information removed]	[Commercial-in-confidence information removed]	Prospective, randomised, multi-centre, open label extension study of STRIDE-2
Sildenafil				
SUPER-2[96]				
	Ongoing (design: 3 years or proven ineffectiveness/unsafe): 259 patients	IPAH, CTD	I (0.04%) II (39%) III (58%) IV (3%)[a]	Prospective extension of SUPER-1
PACES-2[144]				
	Ongoing (design: 3 years): 242 patients	IPAH, CTD	(I–IV); mostly II and III	Open-label prospective extension of PACES-1

6MWT, 6-minute walk test; CHD, congenital heart disease; CTD, connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; QoL, quality of life; RCT(s), randomised controlled trial(s).
a RCT baseline.

FC assessed (FC specific)	Survival assessed (FC specific)	6MWT assessed	Data on adverse events	Comments
Yes (yes)	Yes (yes)	[Commercial-in-confidence information removed]	Yes	[Commercial-in-confidence information removed]
Yes (no)	Yes (no)	Yes	Yes	Based on manufacturer submission:data for 1-year survival; QOL
Yes	Yes	Yes	Yes	Based on sildenafil industry submission; QOL

TABLE 76 *Characteristics of long-term studies with data on change in FC and/or survival stratified by FC*

Study name/key paper (protocol number); location/ centres	Duration/follow-up; design (retrospective or prospective); number of patients included	Intervention (and comparator if applicable)	Type of PAH
D'Alonzo 1991;[5] 32 clinical centres in USA	Up to 5 years; registry with prospective follow-up; 194 patients	Long-term drug therapy in 19% at study entry and 83% on hospital discharge; therapy included vasodilators, digitalis, diuretics, anticoagulants, oxygen and other drugs	IPAH (100%)
Barst 1994;[127] four referral centres	Up to 70 months; open-label, multicentre, uncontrolled; 18 patients	Epoprostenol started at 2 ng/kg/min and increased by 2 ng/kg/min every 10–15 minutes; dose increased no further when one or more of the following occurred: (1) > 40% decrease in systemic arterial pressure, (2) > 40% increase in heart rate, (3) nausea, vomiting, headache; afterwards dose decreased to one not causing adverse effects Background: warfarin; five patients oral vasodilator therapy	IPAH (100%)
McLaughlin 2002;[65] Rush Heart Institute, Centre for Pulmonary Heart Disease database	Mean follow-up 36.3 ± 27.1 months; retrospective database analysis; 162 patients	Epoprostenol started at 2 ng/kg/min and gradually increased to maximum tolerated dose; additionally increased on outpatient basis, depending on symptoms of PAH and side effects of epoprostenol; from 1998 doses readjusted based on cardiac index Background (according to patient state and needs): warfarin, diuretics, digoxin, continuous nasal oxygen	IPAH (100%)
Sitbon 2002;[66] Clamart, France	5 years (26 ± 21 months); retrospective; 178 epoprostenol patients, 135 historic control subjects matched for NYHA FC for survival analysis – not FC stratified	Epoprostenol started at 1 ng/kg/min and increased every 12 hours by 1 ng/kg/min up to 10 ng/kg/min; dose adjustments made systematically to reach mean level of 14 ± 4 ng/kg/min at 3 months Background (according to patient state and needs): warfarin, diuretics, digoxin, continuous nasal oxygen	IPAH (100%)

Functional class	Age (years), mean (SD, range); % female	Baseline exercise capacity and haemodynamic measures, mean (SD)	Comments (inclusion criteria)
I, II, III, IV (% not stated)	No data on age; 56%	No data	Inclusion: PPH; criteria described in Rich 1987[4]
II (6%), III (72%), IV (22%)	35.9 (13.4); 67%	6MWT: 264 (160) metres; mPAP: 60.9 (15) mmHg; PVR: no data	Inclusion: PPH diagnosis based on NIH registry criteria Exclusion: patients with associated conditions such as portal hypertension, HIV, collagen vascular diseases, pulmonary vasculitides
III 46%, IV 54%	42.2; 75%	Mean treadmill exercise time: 192±183 seconds (127 patients); mPAP: 61 (13) mmHg; PVR: 17.5 (8.1) Wood units	Inclusion: FCIII or FCIV; treated with calcium channel blockers previously and failed to improve or with limited response (predicting failure of calcium channel blocker therapy)
III 67%, IV 33%	43 (13); 76%	6MWT: 240 (146) metres; mPAP: 67 (14) mmHg; PVR: no data	Inclusion: age > 15 years, PPH diagnosis based on NIH registry criteria Exclusion: (1) CTD, CHD, portal hypertension, HIV; (2) distal chronic thromboembolic pulmonary hypertension, (3) chronic pulmonary disease; (4) acute pulmonary vasodilator response that predicted response to calcium channel blockers

continued

TABLE 76 *Characteristics of long-term studies with data on change in FC and/or survival stratified by FC*

Study name/key paper (protocol number); location/ centres	Duration/follow-up; design (retrospective or prospective); number of patients included	Intervention (and comparator if applicable)	Type of PAH
Kuhn 2003;[128] one centre; Vanderbilt University Medical Center, USA	Follow-up: up to 3 years; 1 year for FC; retrospective cohort study; 91 patients	Epoprostenol on discharge from hospital at 4–6 ng/kg/min as limited by side effects with a goal of 20 ng/kg/min at 4–6 months; regimen did not change significantly during study period; mean dose at 1 year was 23 (18) ng/kg/min Background: anticoagulants (84%), calcium channel blockers (25%), digoxin (23%), diuretics (78%), additional vasoactive medications (31%)	IPAH (54.5%), scleroderma (21%), CHD (12%), systemic lupus erythematous (5.5%), HIV (2%), portopulmonary (3%), pulmonary veno-occlusive disease (2%)
Hoeper 2000;[129] one centre; Hannover, Germany	12 months; open-label, prospective; 24 patients	Iloprost daily dose was 100 μg; subsequently increased to 150 μg in patients whose exercise capacity did not increase after 3 months Background: anticoagulants; some were receiving diuretics, digitalis, calcium channel blockers	IPAH (100%)
Sitbon 2005;[98] multicentre, international; records from referral centres: Clamart, France; Chicago; Denver; New York; San Diego	36 months; prospective extension of two RCTs: BREATHE-1[45] and Channick 2001[43] (subgroup); matched with historic control subjects; 485 patients (139 bosentan, 346 control)	Intervention: bosentan as first-line treatment; control: epoprostenol	IPAH (100%)

(continued)

Functional class	Age (years), mean (SD, range); % female	Baseline exercise capacity and haemodynamic measures, mean (SD)	Comments (inclusion criteria)
III (52%), III (48%);	43 (15); 70%	6MWD: 296 (111) metres*; haemodynamics reported by aetiology for 57 patients	Inclusion: IPAH, scleroderma, systemic lupus erythematous; patients with scleroderma were eligible if they did not have significant restrictive lung disease *Data for 25 patients
III (83%), IV (17%)	38 (12, 22–65); 63%	6MWT: 278 (96) metres; mPAP: 59 (10) mmHg; PVR: 1205 (467) dyn s/cm^5 (preinhalation data)	Inclusion: PPH according to NIH Registry criteria; FCIII or FCIV; non-responders to conventional treatment Exclusion: secondary pulmonary hypertension; severe right heart failure who were receiving catecholamines at time of presentation, lost to follow-up
III (100%)	Experimental: 46 (16, 13–80); 80% Control: 41 (14, 10–75); 74%	Experimental: 6MWT: 351 (80) metres; mPAP: 56 (15) mmHg; PVR: 12 (6) Wood units Control: 6MWT: 335 (106) metres; mPAP: 66 (18); PVR: 18 (10) Wood units	Inclusion, bosentan: age at least 12 years; symptomatic FCIII IPAH; primary or secondary to CTD; resting mPAP > 25 mmHg; PVR > 3 Wood units; pulmonary capillary wedge pressure < 15 mmHg; 6MWT 150–450 metres Inclusion, epoprostenol: FCIII IPAH at start of epoprostenol; more than zero survival time; known survival status; started epoprostenol on or after January 1995

continued

TABLE 76 *Characteristics of long-term studies with data on change in FC and/or survival stratified by FC*

Study name/key paper (protocol number); location/ centres	Duration/follow-up; design (retrospective or prospective); number of patients included	Intervention (and comparator if applicable)	Type of PAH
Williams 2006;[93] Royal Free Hospital, London	Up to 6 years; data for 2 years; prospective experimental, historic control subjects; 92 patients (45 bosentan, 47 control: 27 prostanoids)	Intervention: bosentan 62.5 mg twice a day for 4 weeks, increased to 125 mg twice a day; deterioration: prostanoids (combination or on their own) Control: intravenous iloprost (predominant) or epoprostenol, inhaled iloprost, treprostinil Basic treatment: diuretics (loop diuretics and spironolactone), digoxin, oxygen (at least 16 hours in every 24 hours) if resting oxygen saturation < 90%, warfarin, calcium channel blockers (nifedipine, diltiazem, almodipine) for Raynaud's phenomenon – continued, high-dose calcium channel blockers rarely used and withdrawn after 6 months	Secondary to systemic sclerosis (100%)
Sitbon 2007;[130] multicentre, international	[Academic-in-confidence information has been removed]; prospective extension of two RCTs: BREATHE-1[45] and Channick 2001;[43] [Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
STRIDE-1X (FPH01-X);[99] [Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]
STRIDE-2X (FPH02-X);[100] [Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]

6MWT, 6-minute walk test; CHD, congenital heart disease; CTD, connective tissue disease; FC, functional class; IPAH, idiopathic pulmonary arterial hypertension; NYHA, New York Heart Association; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PPH, primary pulmonary hypertension; PVR, pulmonary vascular resistance; RCT(s), randomised controlled trial(s); SD, standard deviation.

(continued)

Functional class	Age (years), mean (SD, range); % female	Baseline exercise capacity and haemodynamic measures, mean (SD)	Comments (inclusion criteria)
Experimental: III (58%), IV (42%) Control: III (77%), IV (23%) (11)	Experimental: 60 (11.3); 84% Control: 58 (11.1); 85%	Experimental: 6MWT: median 207 (range 0–538) metres; mPAP: 40 (11.8) mmHg; PVR: 613 (345) dyn s/cm^5 Control: 6MWT: median 179 (range 0–471) metres*; mPAP: 40 (11.4) mmHg; PVR: 613 (345) dyn s/cm^5	Inclusion: mPAP > 25 mmHg; pulmonary capillary wedge pressure < 15 mmHg; PVR > 240 dyn s/cm^5; FCIII or FCIV, conventional treatment; 6MWT < 450 metres Exclusion: FCI or FCII; interstitial pulmonary fibrosis resulting in total lung capacity of < 60% and either mPAP < 35 mmHg or oxygen saturation at rest on air of < 85% or both; substitutes for 6MWT < 150 metres: cardiac index < 2.1 l/min/m^2, right arterial pressure > 11 mmHg, mixed venous oxygen saturation < 63% *Data on 30 patients of whom majority in FCIV
[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]	[Academic-in-confidence information has been removed]
[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]
[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]

Appendix 8

Review of economic evaluations

TABLE 77 *Drummond adapted criteria (after Drummond and Jefferson[69])*

	Highland 2003[72]	**Einarson 2005[70]**	**Narine 2005[71]**	**Wlodarczyk 2006[73]**
1. Was a well-defined question posed in an answerable form?	Yes	Yes	Yes	Yes
2. Was a comprehensive description of the competing alternatives given?	Yes	Yes	Yes	Yes
3. Was there evidence that the programmes effectiveness was established?	Yes	Yes	Yes	Yes
4. Were all of the important and relevant costs and consequences for each alternative identified?	Yes	Yes (costs)	Yes (costs)	Yes
5. Were costs and consequences measured accurately in appropriate physical units?	Yes	Yes (costs)	Yes (costs)	Yes
6. Were costs and consequences valued credibly?	Yes	Yes (costs)	Yes (costs)	Yes
7. Were costs and consequences adjusted for differential timing?	Yes	Yes (costs)	Yes (costs)	Yes
8. Was an incremental analysis of costs and consequences of alternatives performed?	Yes	No	No	Yes
9. Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Yes (costs)	Yes (costs)	Yes
10. Did the presentation and discussion of study results include all issues of concern to users?	Yes	No	No	Yes

TABLE 78 *Consensus on Health Economic Criteria list (after Evers* et al.*[68])*

	Highland 2003[72]	**Einarson 2005[70]**	**Narine 2005[71]**	**Wlodarczyk 2006[73]**
1. Is the study population clearly described?	Yes	Yes	Yes	Yes
2. Are competing alternatives clearly described?	Yes	Yes	Yes	Yes
3. Is a well-defined research question posed in answerable form?	Yes	Yes	Yes	Yes
4. Is the economic study design appropriate to the stated objective?	Yes	Yes	Yes	Yes
5. Is the chosen time horizon appropriate to include relevant costs and consequences?	Yes	Yes	Yes	Yes
6. Is the actual perspective chosen appropriate?	Yes	Yes	Yes	Yes
7. Are all important and relevant costs for each alternative identified?	Yes	Yes	Yes	Yes
8. Are all costs measured appropriately in physical units?	Yes	Yes	Yes	Yes
9. Are costs valued appropriately?	Yes	Yes	Yes	Yes
10. Are all important and relevant outcomes for each alternative identified?	Yes	Yes	Yes	Yes
11. Are all outcomes measured appropriately?	Unclear	Not applicable	Not applicable	Yes
12. Are outcomes valued appropriately?	No	Not applicable	Not applicable	Yes
13. Is an incremental analysis of costs and outcomes of alternatives performed?	Yes	Not applicable	Not applicable	Yes
14. Are all future costs and outcomes discounted appropriately?	Yes	Yes (costs)	Yes (costs)	Yes
15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Yes	Yes	Yes	Yes
16. Do the conclusions follow from the data reported?	Yes	Yes	Yes	Yes
17. Does the study discuss the generalisability of the results to other settings and patient/client groups?	Yes	No	No	Yes
18. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	No	No	No	No
19. Are ethical and distributional issues discussed appropriately?	Yes	No	No	Yes

Appendix 9

Mortality parameters for the model

Other-cause mortality

This was based on general population mortality assuming a starting age of 50 years and a ratio of women to men of 1.5:1. Annual survival figures were based on actuarial data (www.gad.gov.uk; accessed 1 August 2007). Linear interpolation was used to estimate the survival probability at the end of each cycle. This was converted to a conditional probability of dying in each cycle. These were entered as constants.

Mortality due to pulmonary arterial hypertension

This was assumed to be an independent competing risk, dependent on FC and treatment but not age (such data that were available were consistent with this assumption). The per-cycle mortality probabilities were entered as samples from beta distributions. The explanation here gives the calculations used for epoprostenol in FCIII. The same method was used for other treatments. It was assumed that there was no additional mortality in FCII.

Overall survival at 3 years was given as 0.75 (95% CI 0.71–0.79). Taking the central estimate of 0.75, this was compared with a general population mortality of 0.9901 to give a PAH-related survival of $0.75/0.9901 = 0.7575$. This is the PAH-related survival over 13 cycles of the model (13×12 weeks equals 3 years). Survival in one cycle was found by solving the equation $x^{13} = 0.7575$ to give $x = 0.979$, or a probability of PAH-related mortality in one cycle of 0.021. Similar calculations give a 95% CI of 0.017–0.025. These numbers fit to a beta distribution with $n = 5000$ and $r = 105$.

Applying the same method to all of the other treatments gave the following result:

Treatment	FC	Time	Survival (95% CI)	Per cycle mortality (95% CI)	Beta distribution
Epoprostenol, iloprost	III	3 years	0.75 (0.71–0.79)	0.021 (0.017–0.025)	$n = 5000$, $r = 105$
Epoprostenol	IV	3 years	0.47 (0.39–0.55)	0.056 (0.044–0.069)	$n = 1250$, $r = 70$
Bosentan	III	3 years	0.87 (0.81–0.92)	0.010 (0.006–0.015)	$n = 1600$, $r = 16$
Sitaxentan, sildenafil	III	1 year	0.95 (0.90–0.98)	0.011 (0.004–0.023)	$n = 450$, $r = 5$

CI, confidence interval; FC, functional class.

Mortality when on supportive care

In the absence of better data we have used the odds ratios for deterioration from FCIII to FCIV to give us the effect of treatment on reducing mortality. Again, using epoprostenol in FCIII as the example, the odds ratio of 0.4 in favour of epoprostenol gives us per-cycle mortality on supportive care of 0.051 (95% CI 0.041–0.069). Beta distributions were fitted to the correct mean and width of confidence interval. In this case this gives $n = 950$ and $r = 48$.

As with transitions for supportive care we have used a single figure for oral therapies, but separate figures for epoprostenol and iloprost. The figures used are shown in the following table:

Treatments	FC	Mortality on treatment (95% CI)	Odds ratio	Mortality on supportive care (95% CI)	Beta distribution
Epoprostenol	III	0.021 (0.017–0.025)	0.4	0.051 (0.041–0.069)	$n = 950$, $r = 48$
Epoprostenol	IV	0.056 (0.044–0.069)	0.4	0.129 (0.103–0.156)	$n = 600$, $r = 77.5$
Iloprost	III	0.021 (0.017–0.025)	0.29	0.069 (0.056–0.093)	$n = 700$, $r = 48$
Oral therapies	III	0.011 (0.004–0.023)	0.18	0.058 (0.006–0.116)	$n = 66$, $r = 3.84$

CI, confidence interval; FC, functional class.

Appendix 10

Resource use information provided by Schering Health Care

New York Heart Association (NYHA) functional class II

TABLE 79 *NHS contacts and personal and social services – New York Heart Association (NYHA) functional class II*

NHS contacts	Mean number per year	SD	Frequency per 3 months	% patients	Mean cost	Total cost per 3 months
Physician at specialist PAH centre	2.800	0.8	0.7	100%	£51.1	£138.4
Specialist nurse at PAH centre	2.750	2.8	0.7	100%	£19.9	
Physician at non-specialist centre	2.500	1.1	0.6	100%	£45.6	
Nurse at non-specialist centre	1.000	1.7	0.3	100%	£5.5	
GP	2.600	1.6	0.7	100%	£16.3	
A&E	0.002	0.0	0.0	100%	£0.0	
Personal and social services	**Mean days per week**	**SD**	**Frequency per 3 months**	**% patients**	**Mean cost**	**Total cost per 3 months**
Residential care	1.750	3.5	21.0	0%	£0.0	£16.0
Day care	1.250	2.5	15.0	2%	£5.6	
Home care	0.500	1.0	6.0	10%	£10.3	

GP, general practice; PAH, pulmonary arterial hypertension; SD, standard deviation.

TABLE 80 *Hospitalisations – New York Heart Association (NYHA) functional class II*

	Mean number per year	SD	Average LOS	SD	% patients	Total cost per 3 months
Overall hospitalisation	0.8	0.4	6.5	6.3	18%	£62
General ward					96%	£46
ICU					3%	£9
CCU					1%	£3
A&E					50%	£4

CCU, critical care unit; ICU, intensive care unit; LOS, length of stay in days; SD, standard deviation.

New York Heart Association (NYHA) functional class III

TABLE 81 *NHS contacts and personal and social services – New York Heart Association (NYHA) functional class III*

NHS contacts	Mean number per year	SD	Frequency per 3 months	% patients	Mean cost	Total cost per 3 months
Physician at specialist PAH centre	4.200	1.1	1.1	100%	£76.6	£224.6
Specialist nurse at PAH centre	5.500	4.4	1.4	100%	£39.9	
Physician at non-specialist centre	2.300	1.1	0.6	100%	£42.0	
Nurse at non-specialist centre	0.800	1.8	0.2	100%	£4.4	
GP	3.800	1.6	1.0	100%	£23.8	
A&E	0.730	0.6	1.2	100%	£38.0	
Personal and social services	**Mean days per week**	**SD**	**Frequency per 3 months**	**% patients**	**Mean cost**	**Total cost per 3 months**
Residential care	3.500	4.0	42.0	6%	£50.5	£178.8
Day care	3.750	2.5	45.0	8%	£67.4	
Home care, hospice	1.400	0.9	16.8	28%	£60.8	

GP, general practice; PAH, pulmonary arterial hypertension; SD, standard deviation.

TABLE 82 *Hospitalisations – New York Heart Association (NYHA) functional class III*

	Mean number per year	SD	Average LOS	SD	% patients	Total cost per 3 months
Overall hospitalisation	1.40	0.22	7.60	5.19	38%	£280
General ward					97%	£199
ICU					4%	£53
CCU					1%	£13
A&E					43%	£14

CCU, critical care unit; ICU, intensive care unit; LOS, length of stay in days; SD, standard deviation.

New York Heart Association (NYHA) functional class IV

TABLE 83 *NHS contacts and personal and social services – New York Heart Association (NYHA) functional class IV*

NHS contacts	Mean number per year	SD	Frequency per 3 months	% patient	Mean cost	Total cost per 3 months
Physician at specialist PAH centre	7.100	2.9	1.8	100%	£129.6	£290.4
Specialist nurse at PAH centre	8.750	2.8	2.2	100%	£63.4	
Physician at non-specialist centre	1.900	1.5	0.5	100%	£34.7	
Nurse at non-specialist centre	0.800	1.1	0.2	100%	£4.4	
GP	5.900	1.2	1.5	100%	£36.9	
A&E	2.600	1.2	0.7	100%	£21.5	
Personal and social services	**Mean days per week**	**SD**	**Frequency per 3 months**	**% patient**	**Mean cost**	**Total cost per 3 months**
Residential care	7.000	0.0	84.0	13%	£529.6	£2313.4
Day care	5.667	1.2	68.0	25%	£321.4	
Home care	4.600	2.5	55.2	61%	£580.4	
Hospice	5.000	3.5	60.0	18%	£882	

GP, general practice; PAH, pulmonary arterial hypertension; SD, standard deviation.

TABLE 84 *Hospitalisations – New York Heart Association (NYHA) functional class IV*

	Mean number per year	SD	Average LOS	SD	% patients	Total cost per 3 months
Overall hospitalisation	2.6	1.2	9.5	4.1	70%	£1963
General ward					86%	£755
ICU					16%	£909
CCU					4%	£227
A&E					50%	£71

CCU, critical care unit; ICU, intensive care unit; LOS, length of stay in days; SD, standard deviation.

Appendix 11

Effects of single parameter values on model outputs

The graphs shown in *Figures 17–71* were obtained as follows. The results from the 10,000 replications of the model used for the reference case PSA were sorted in order according to the value of one of the model parameters. These sorted results were then divided into decile groups. For each group the mean cost and QALY difference, and corresponding ICER, were calculated. These results are plotted on the various graphs shown. To assist visual comparison the same scales are used throughout each section of this appendix.

When the parameter in question makes a clear difference to the outcome, the points lie close to a smooth curve. When the parameter makes little or no difference, the randomness in the selection of other parameters becomes more apparent. As the purpose of this analysis is to determine whether or not a particular parameter is important to the outcome of the model, no attempt has been made to remove this randomness; to do so would require unfeasibly large numbers of runs of the model.

In some cases negative ICERs are shown. These invariably result from points in the south-east quadrant of the cost-effectiveness plane, where the treatment option dominates the comparator. Although the numerical value of a negative ICER is never relevant to a decision, the values are shown on the graph to preserve the smoothness of the curves. The ICER graph is omitted in cases in which all ICERs are negative.

Appendix 11.1 Epoprostenol starting in functional class III

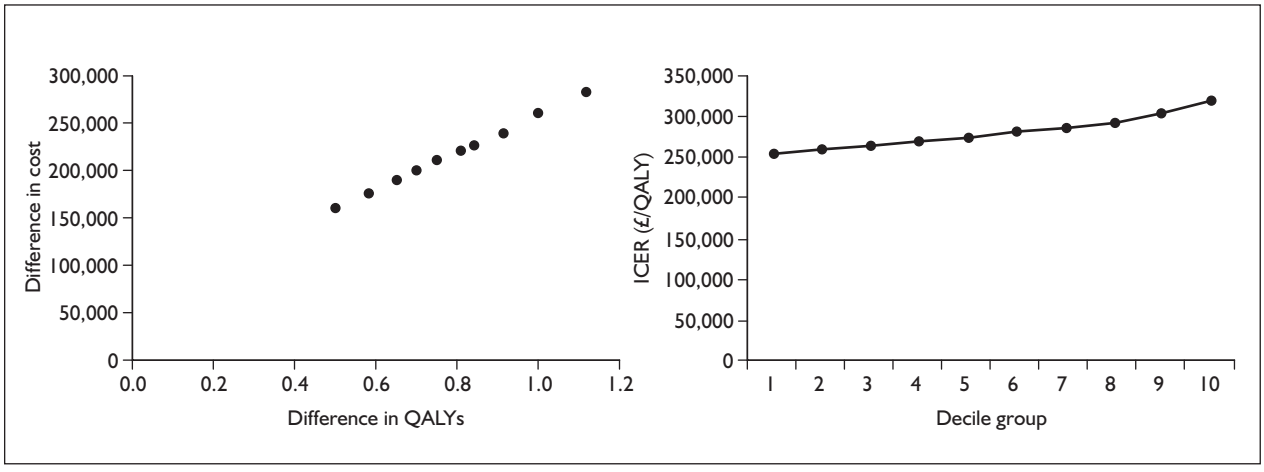

FIGURE 17 *Epoprostenol functional class III variation by odds ratio of improvement from functional class III to functional class II. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

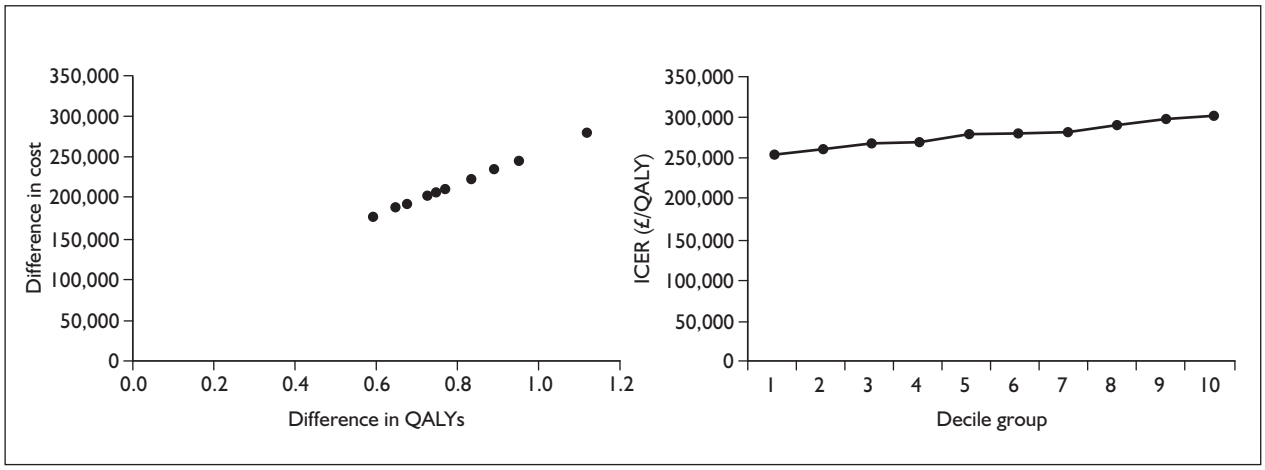

FIGURE 18 *Epoprostenol functional class III variation by odds ratio of deterioration from functional class II to functional class III. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

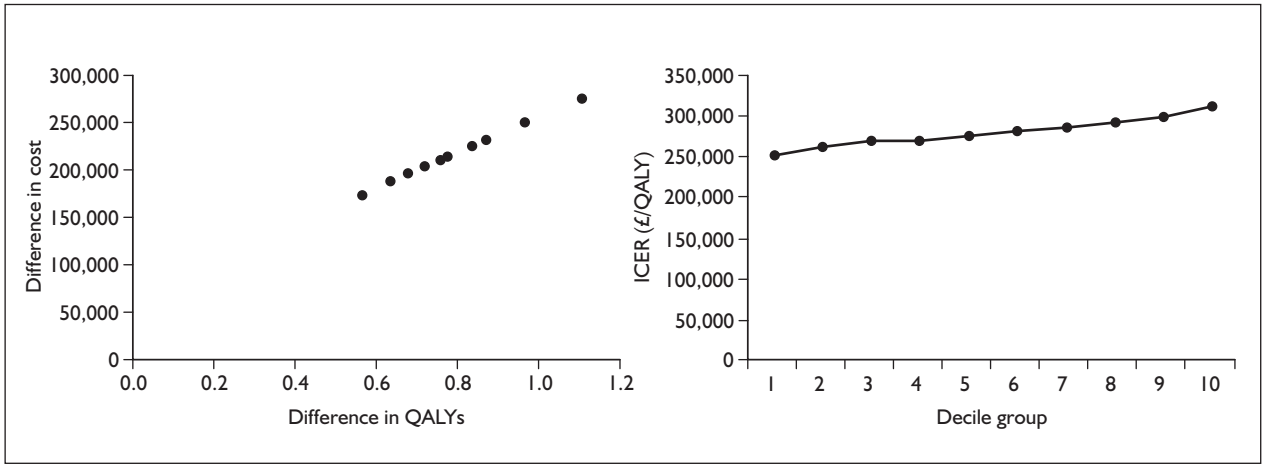

FIGURE 19 *Epoprostenol functional class III variation by odds ratio of deterioration from functional class III to functional class IV. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

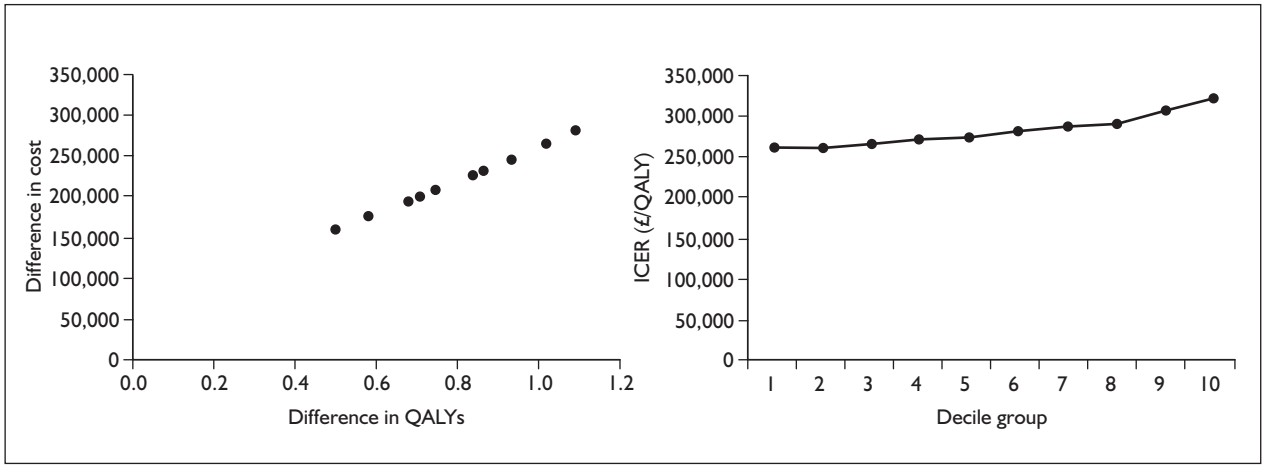

FIGURE 20 *Epoprostenol functional class III variation by probability of improvement from functional class III to functional class II on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

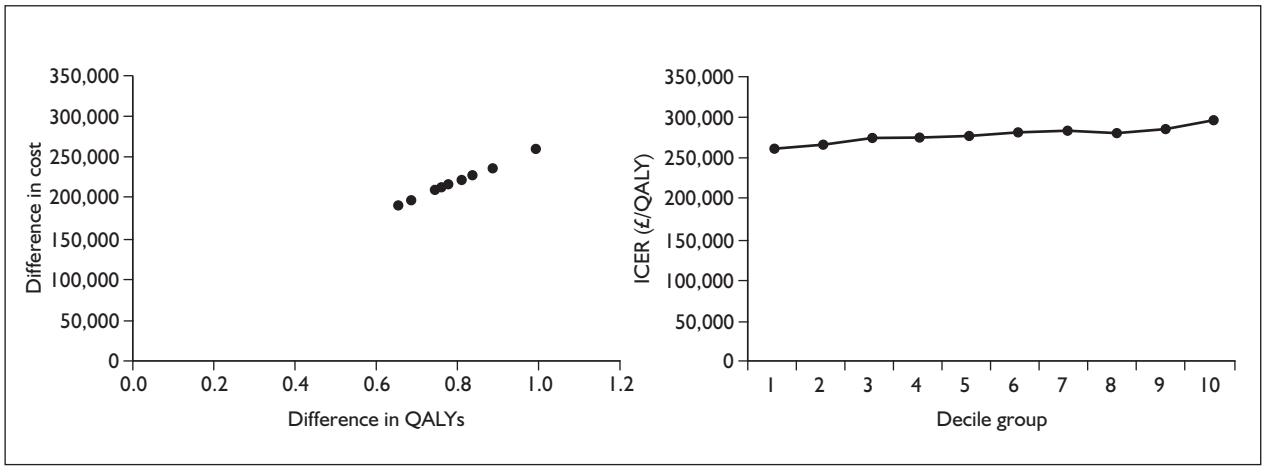

FIGURE 21 *Epoprostenol functional class III variation by probability of deterioration from functional class II to functional class III on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

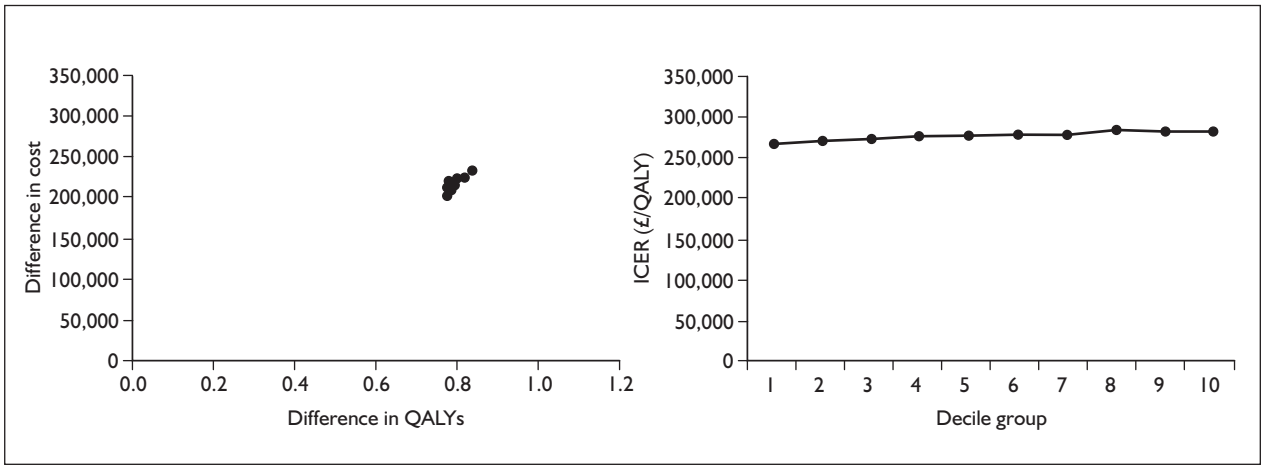

FIGURE 22 *Epoprostenol functional class III variation by probability of deterioration from functional class III to functional class IV in the first cycle on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

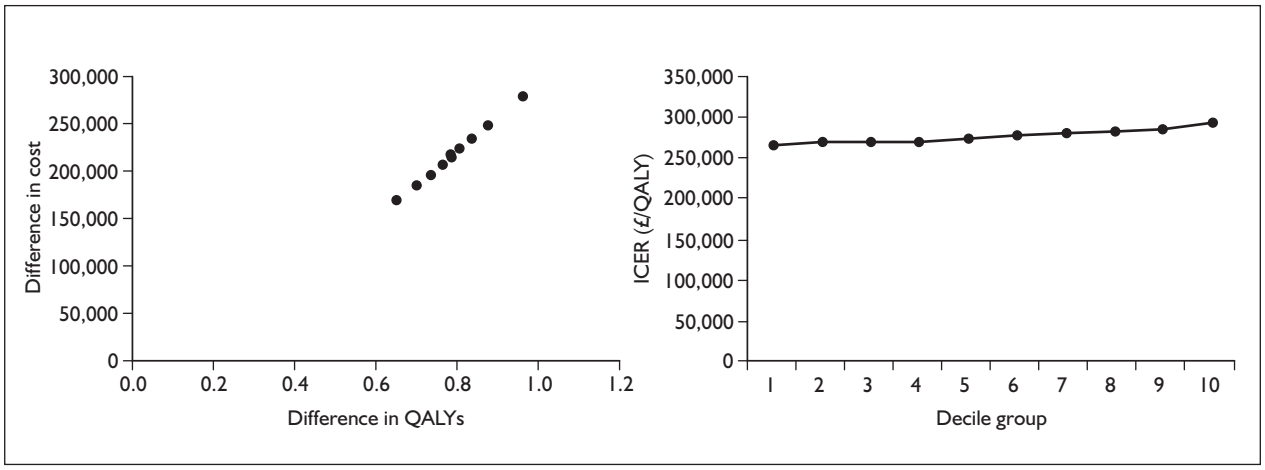

FIGURE 23 *Epoprostenol functional class III variation by probability of deterioration from functional class III to functional class IV after the first cycle on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

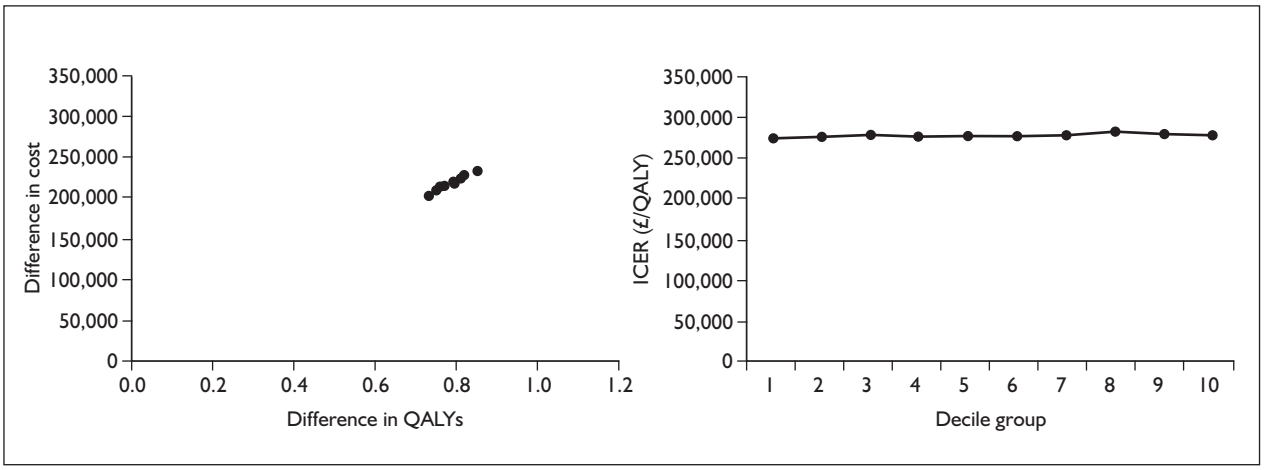

FIGURE 24 *Epoprostenol functional class III variation by mortality in functional class III on treatment. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

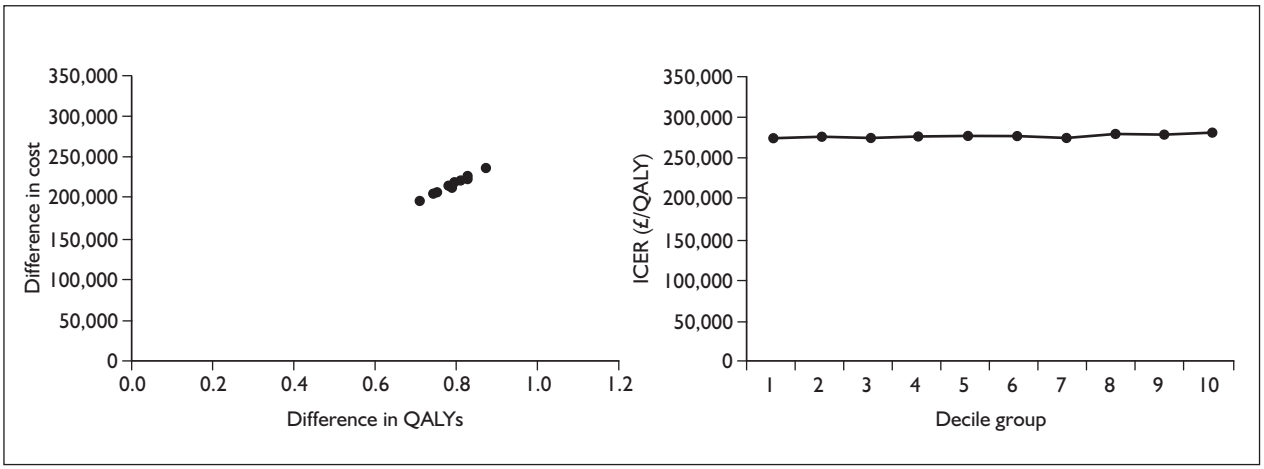

FIGURE 25 *Epoprostenol functional class III variation by mortality in functional class III on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

Appendix 11.2 Epoprostenol starting in functional class IV

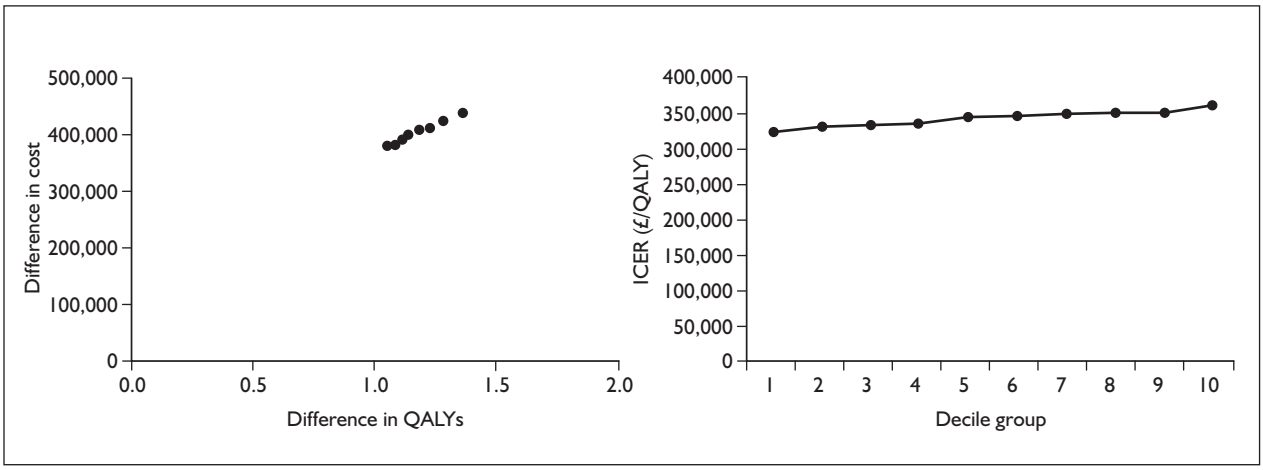

FIGURE 26 *Epoprostenol functional class IV variation by odds ratio of improvement from functional class IV to functional class III. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

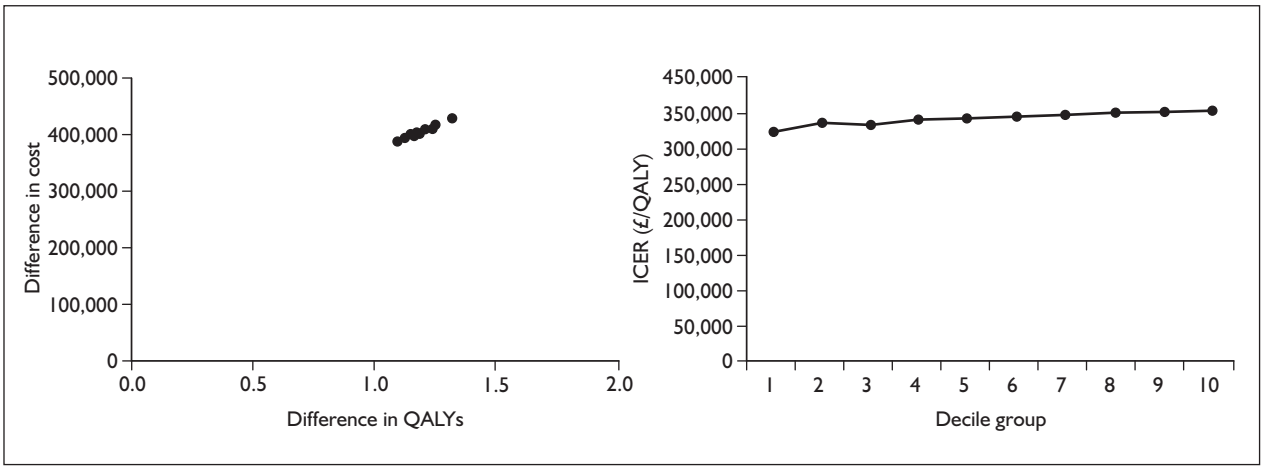

FIGURE 27 *Epoprostenol functional class IV variation by odds ratio of deterioration from functional class III to functional class IV. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

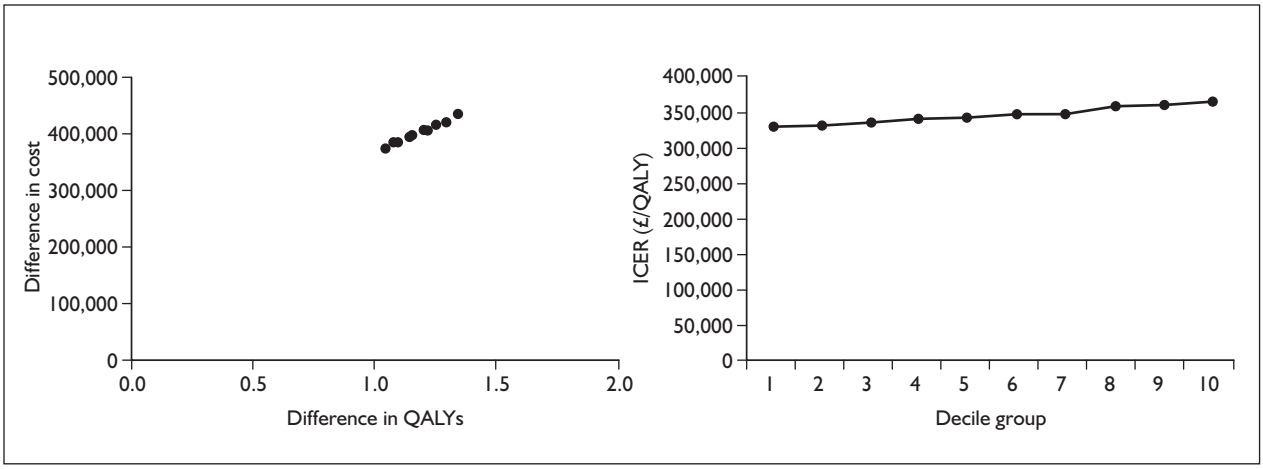

FIGURE 28 *Epoprostenol functional class IV variation by probability of improvement from functional class IV to functional class III on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

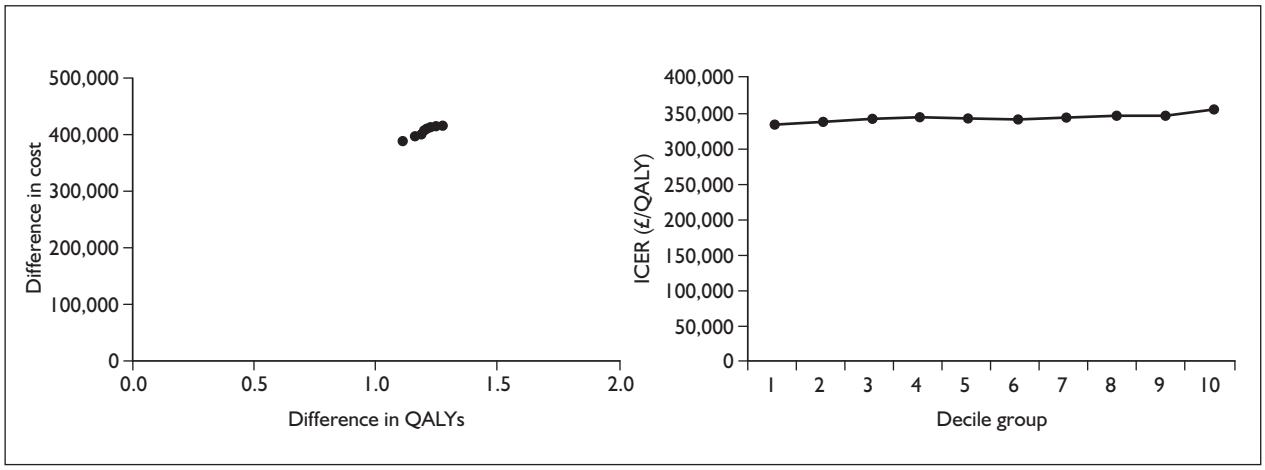

FIGURE 29 *Epoprostenol functional class IV variation by probability of deterioration from functional class III to functional class IV on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

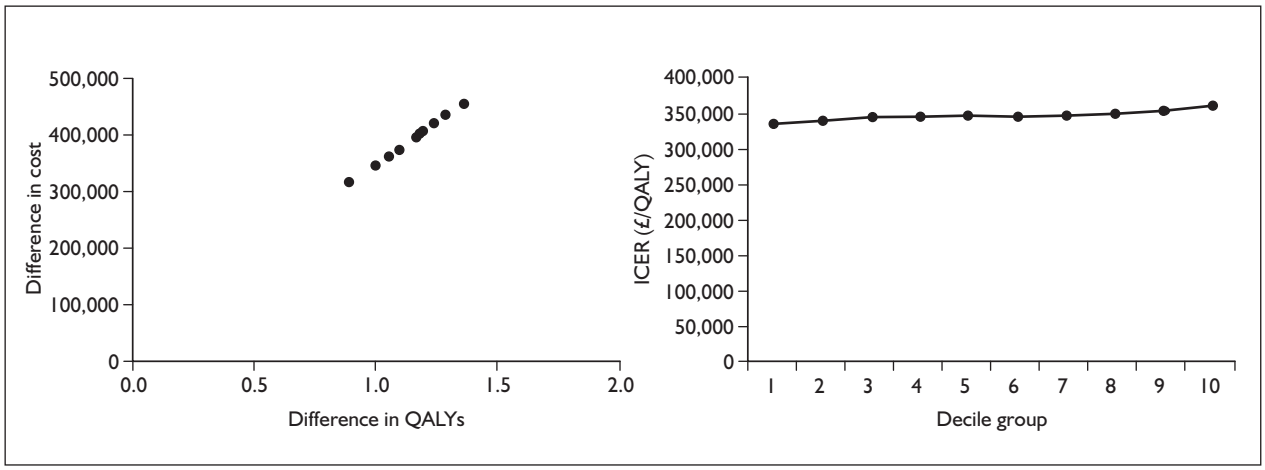

FIGURE 30 *Epoprostenol functional class IV variation by mortality in functional class IV on treatment. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

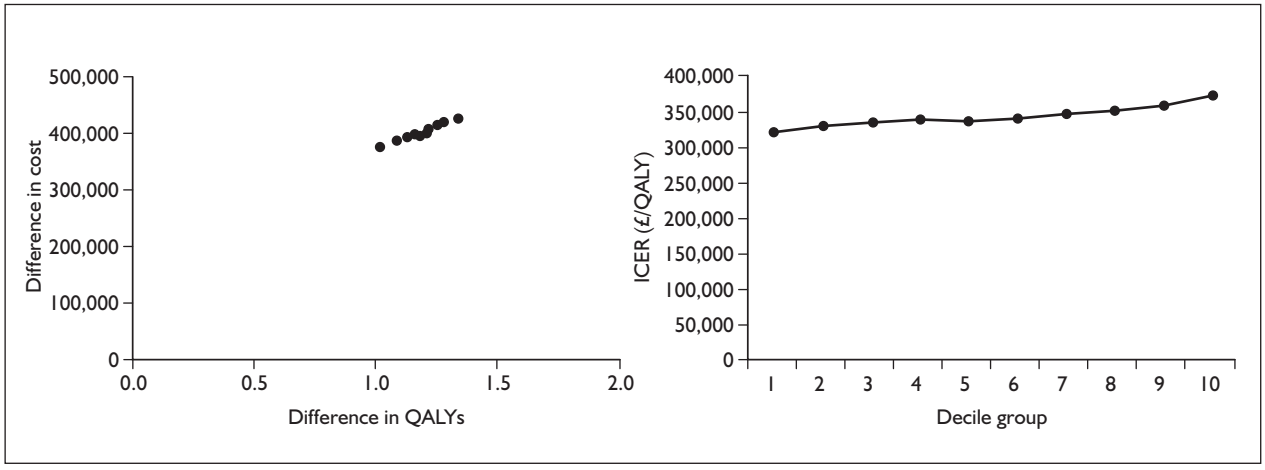

FIGURE 31 *Epoprostenol functional class IV variation by mortality in functional class IV on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

Appendix 11.3 Iloprost

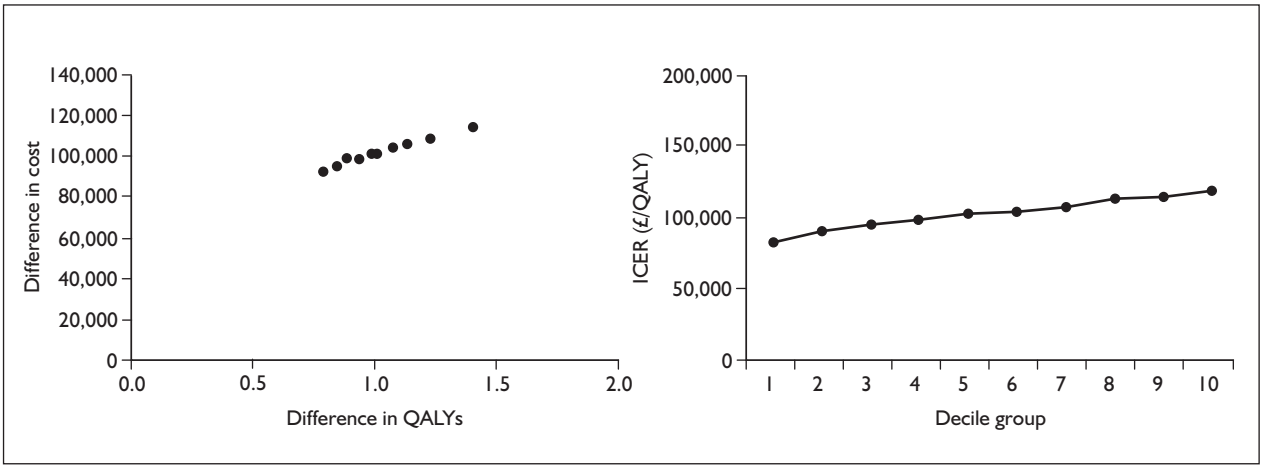

FIGURE 32 *Iloprost variation by odds ratio of improvement from functional class III to functional class II. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

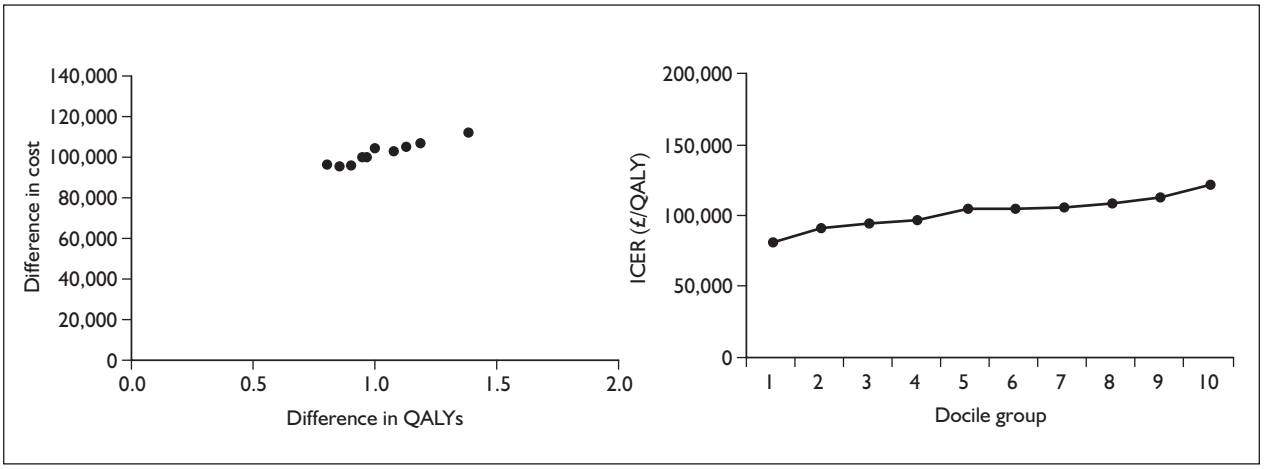

FIGURE 33 *Iloprost variation by odds ratio of deterioration from functional class II to functional class III. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

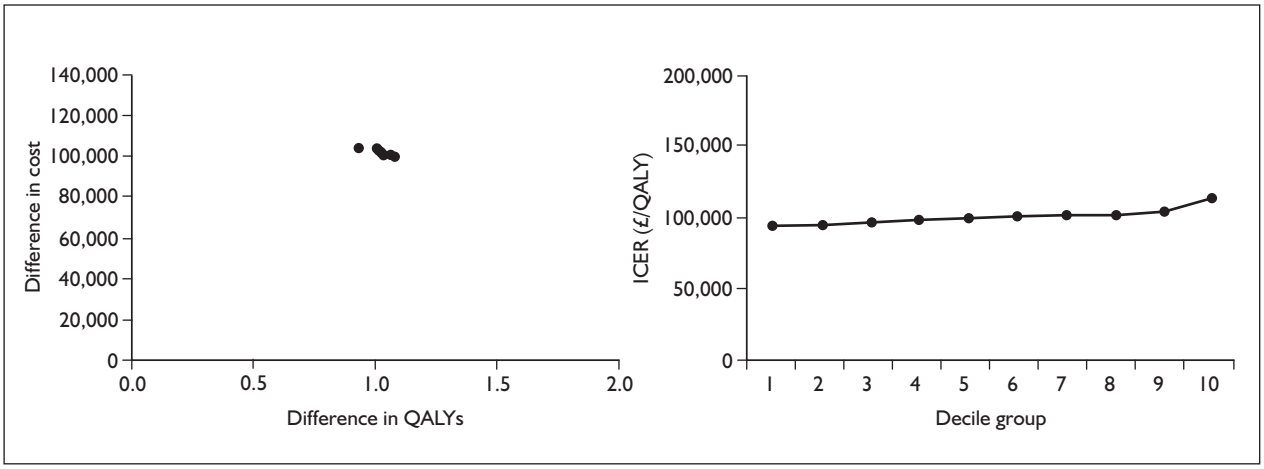

FIGURE 34 *Iloprost variation by odds ratio of deterioration from functional class III to functional class IV in the first cycle. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

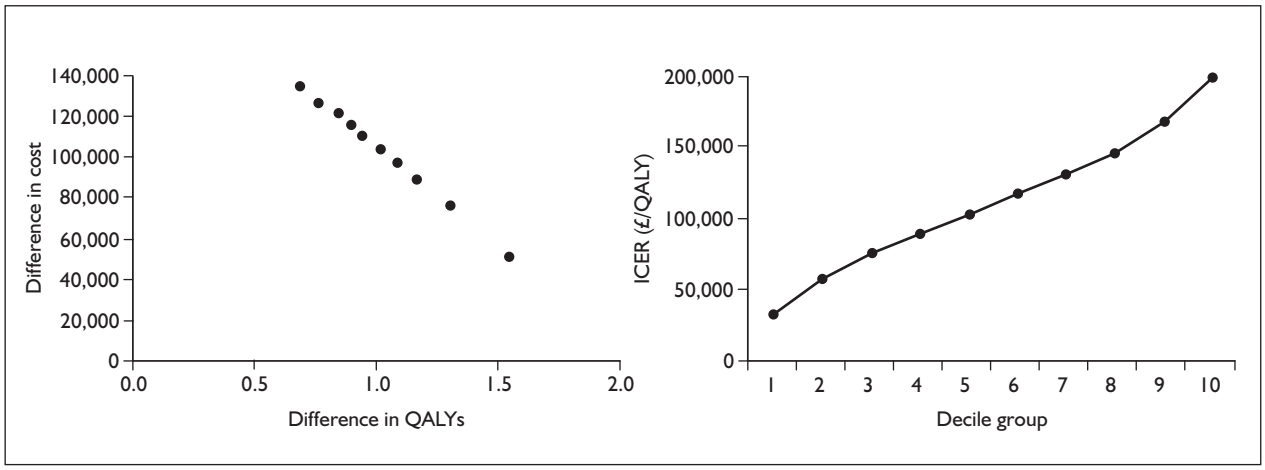

FIGURE 35 *Iloprost variation by odds ratio of deterioration from functional class III to functional class IV after the first cycle. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

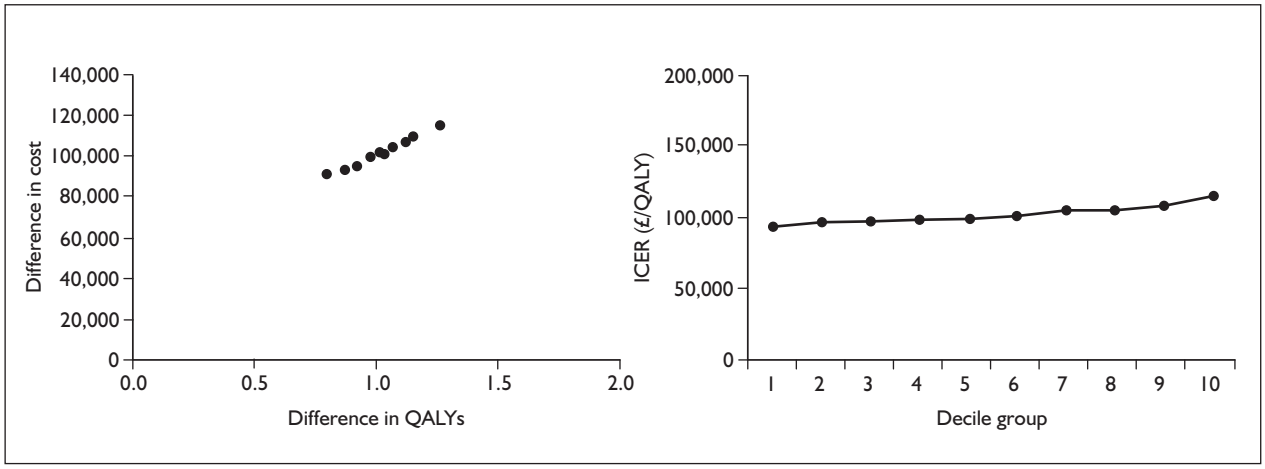

FIGURE 36 *Iloprost variation by probability of improvement from functional class III to functional class II on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

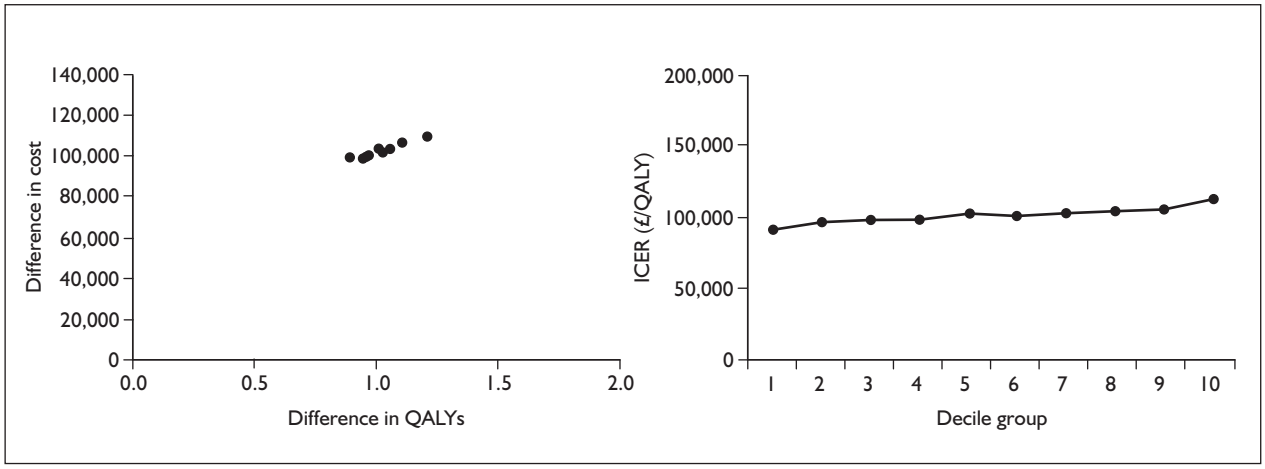

FIGURE 37 *Iloprost variation by probability of deterioration from functional class II to functional class III on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

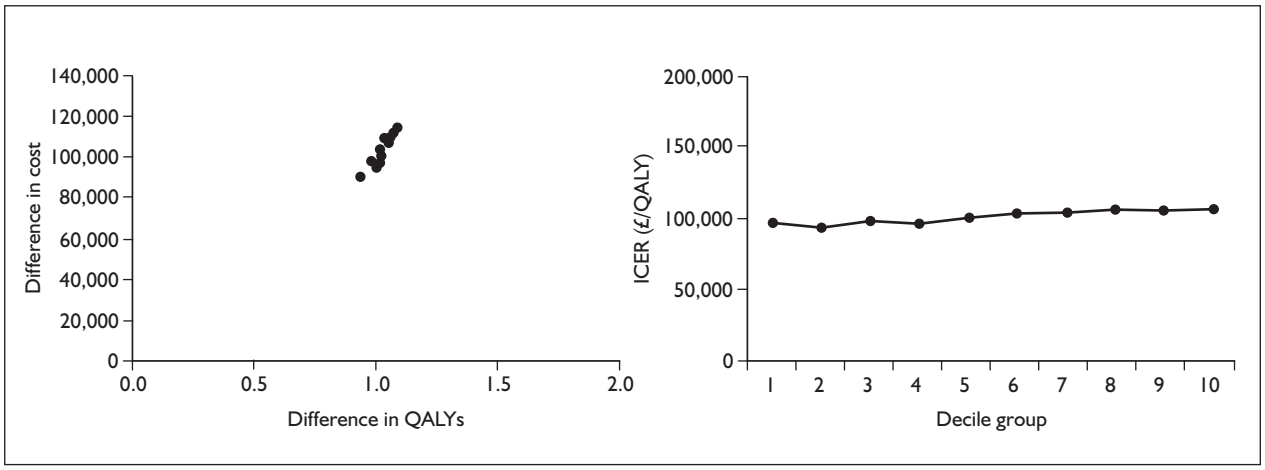

FIGURE 38 *Iloprost variation by probability of deterioration from functional class III to functional class IV in the first cycle on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

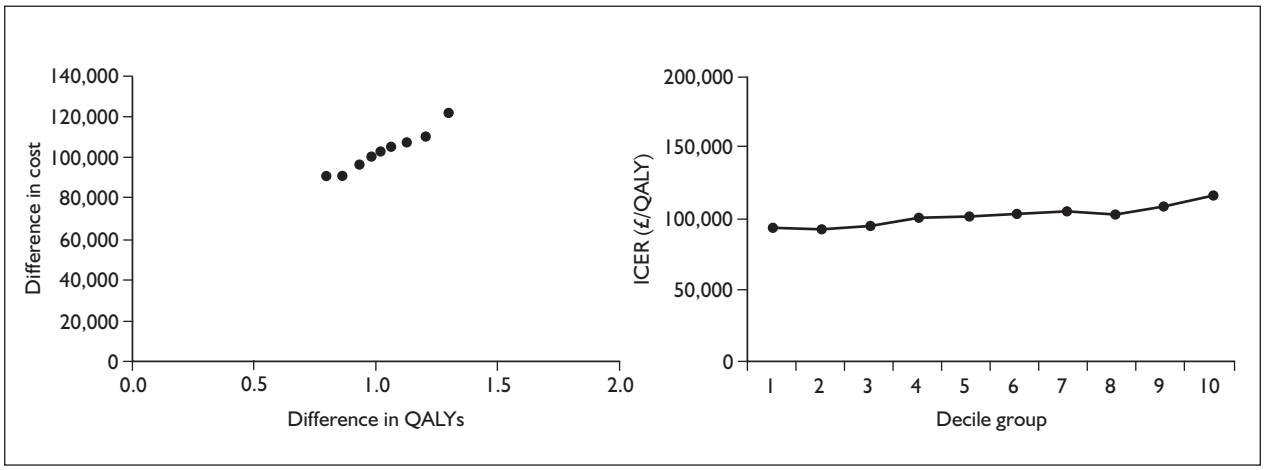

FIGURE 39 *Iloprost variation by probability of deterioration from functional class III to functional class IV after the first cycle on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

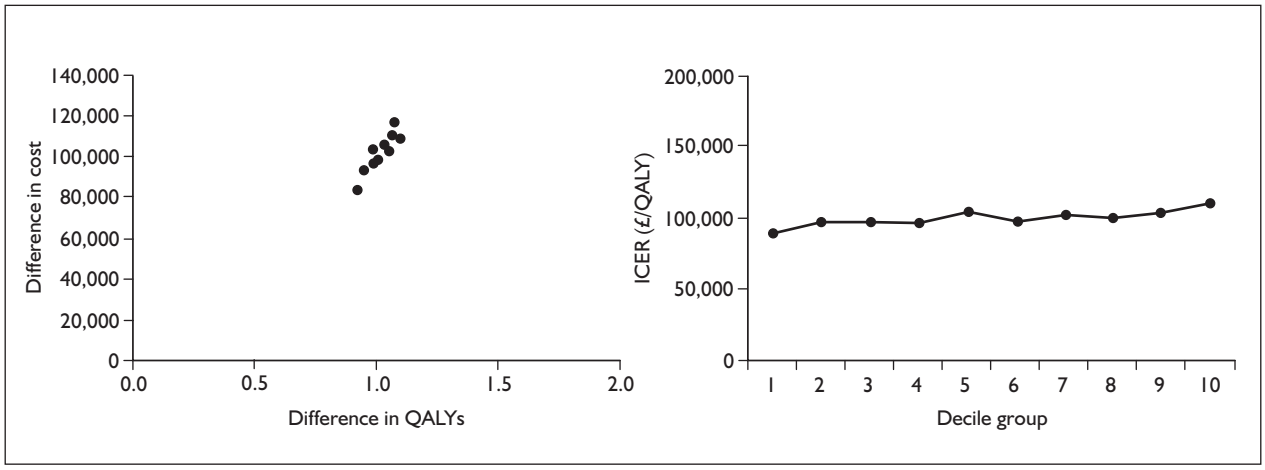

FIGURE 40 *Iloprost variation by mortality in functional class III on treatment. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

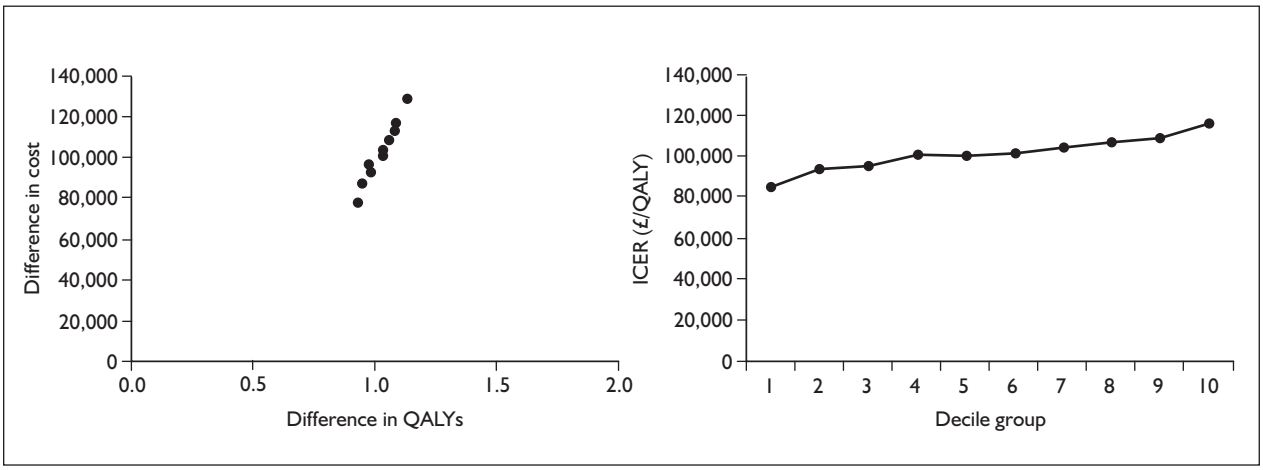

FIGURE 41 *Iloprost variation by mortality in functional class III on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

Appendix 11.4 Bosentan

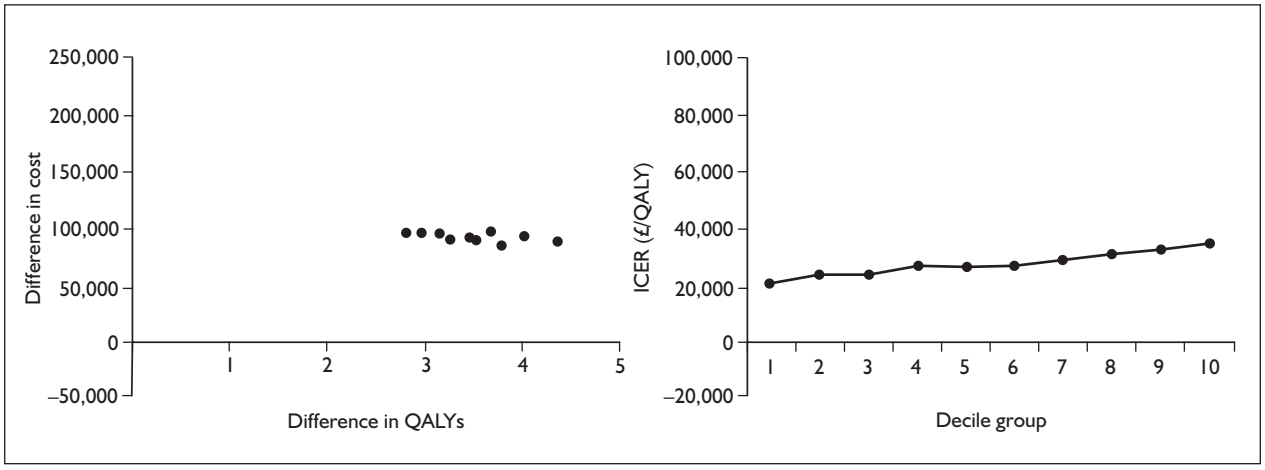

FIGURE 42 *Bosentan variation by odds ratio of improvement from functional class III to functional class II. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

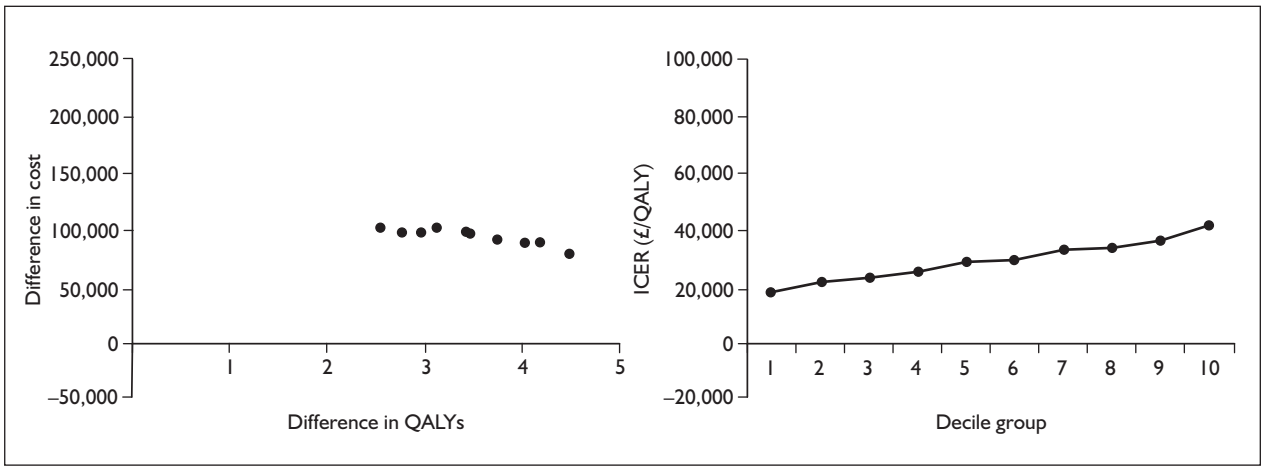

FIGURE 43 *Bosentan variation by odds ratio of deterioration from functional class II to functional class III. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

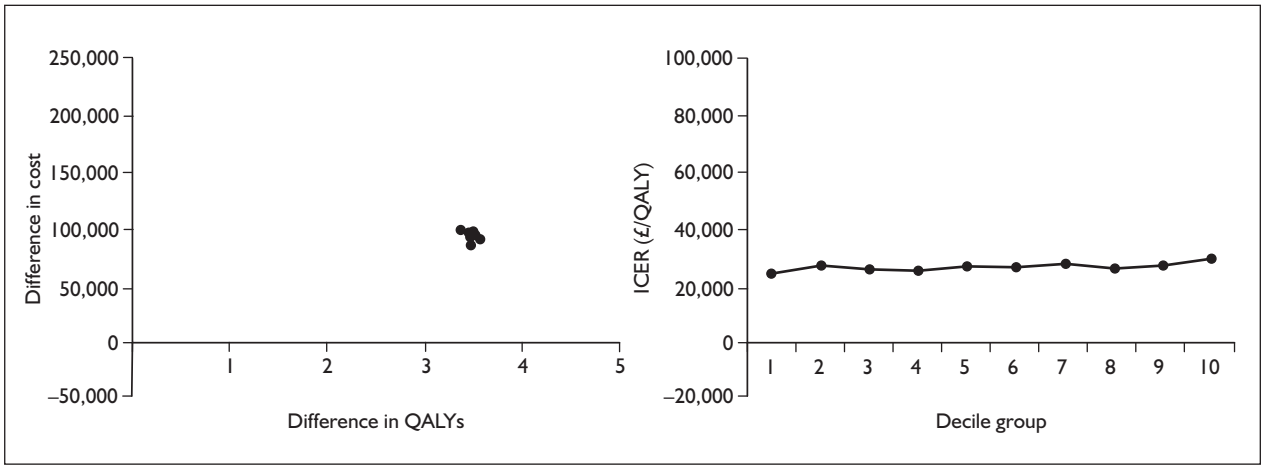

FIGURE 44 *Bosentan variation by odds ratio of deterioration from functional class III to functional class IV in the first cycle. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

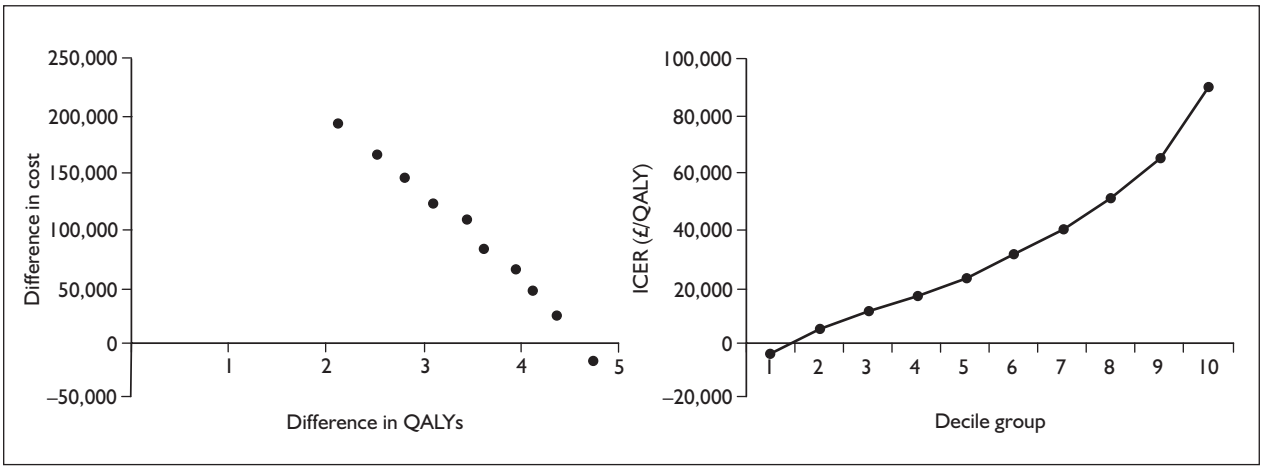

FIGURE 45 *Bosentan variation by odds ratio of deterioration from functional class III to functional class IV after the first cycle. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

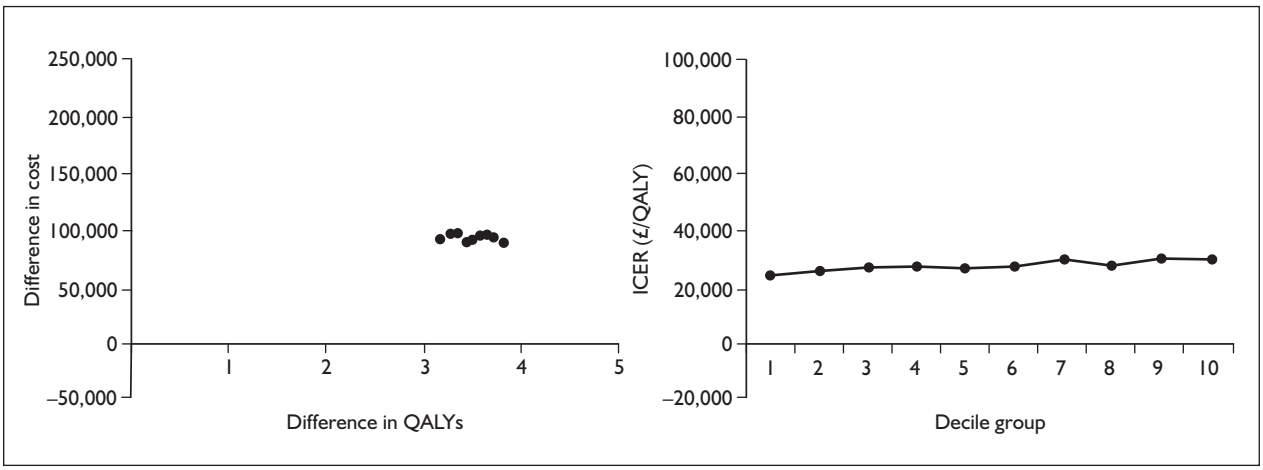

FIGURE 46 *Bosentan variation by probability of improvement from functional class III to functional class II on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

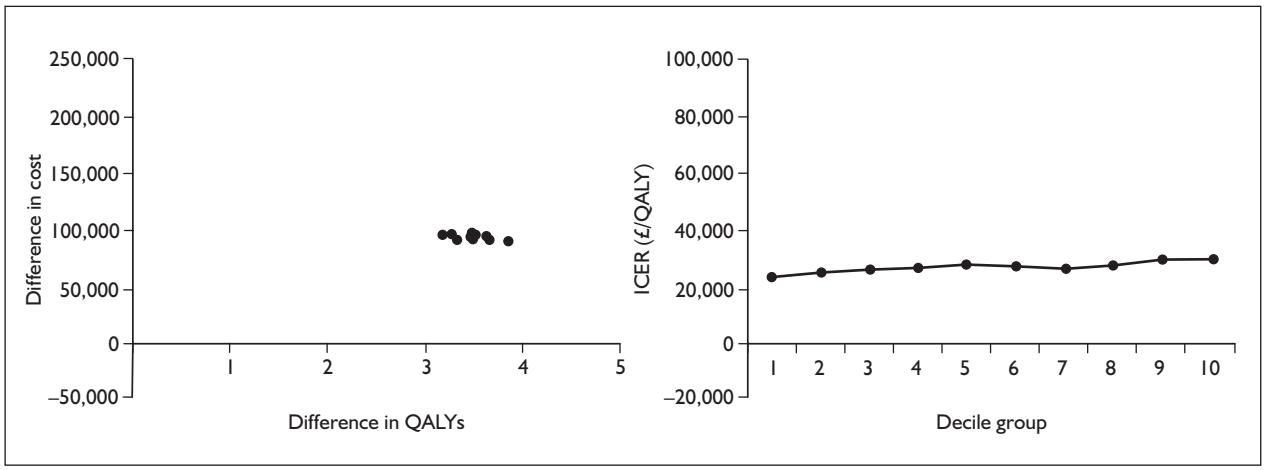

FIGURE 47 *Bosentan variation by probability of deterioration from functional class II to functional class III on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

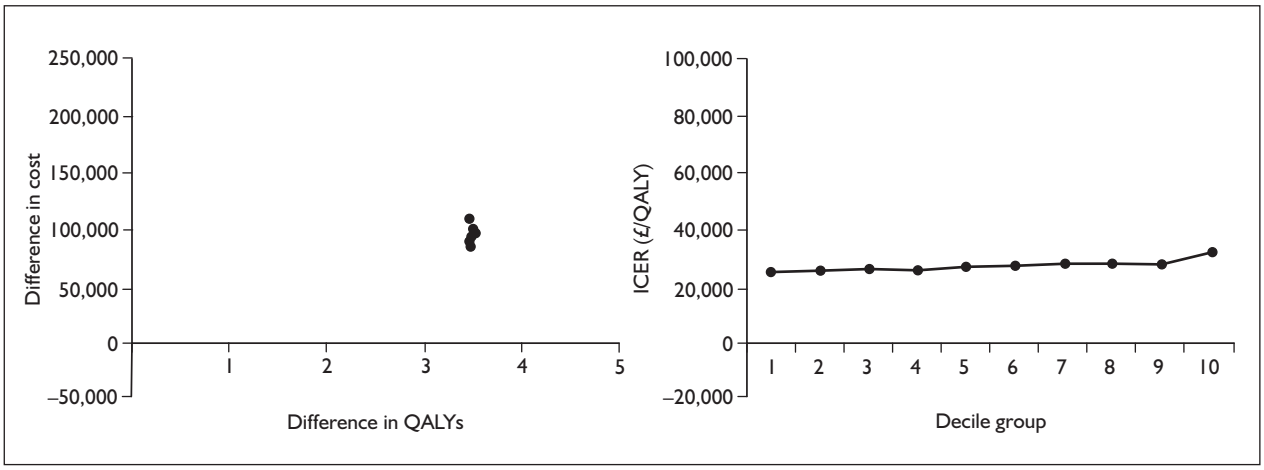

FIGURE 48 *Bosentan variation by probability of deterioration from functional class III to functional class IV in the first cycle on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

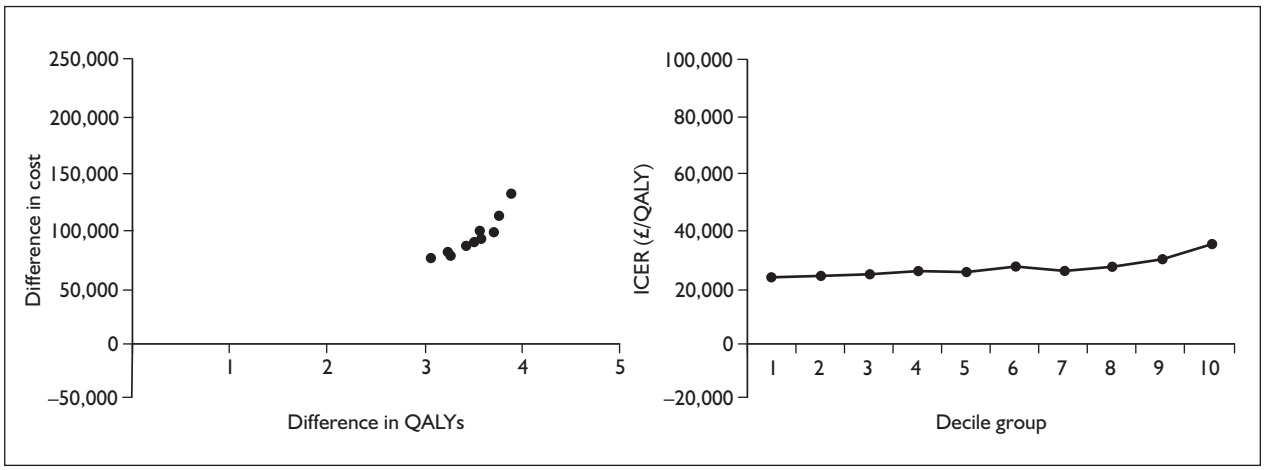

FIGURE 49 *Bosentan variation by probability of deterioration from functional class III to functional class IV after the first cycle on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

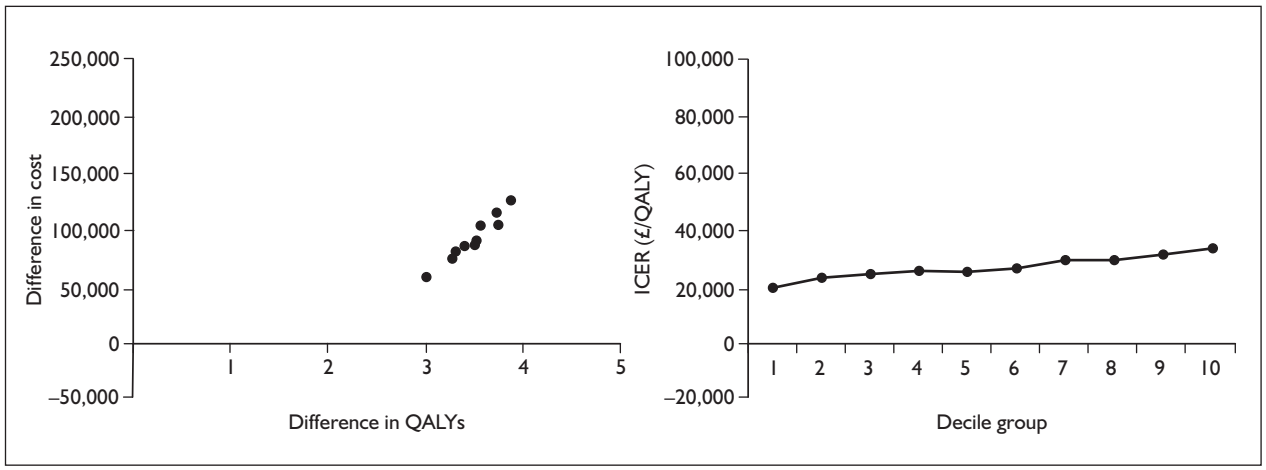

FIGURE 50 *Bosentan variation by mortality in functional class III on treatment. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

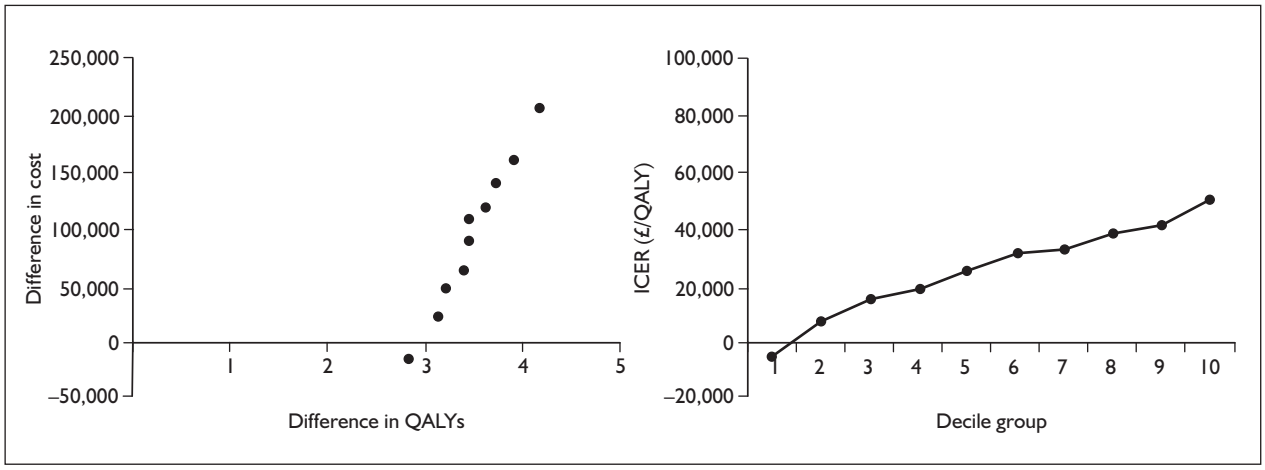

FIGURE 51 *Bosentan variation by mortality in functional class III on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

Appendix 11.5 Sitaxentan

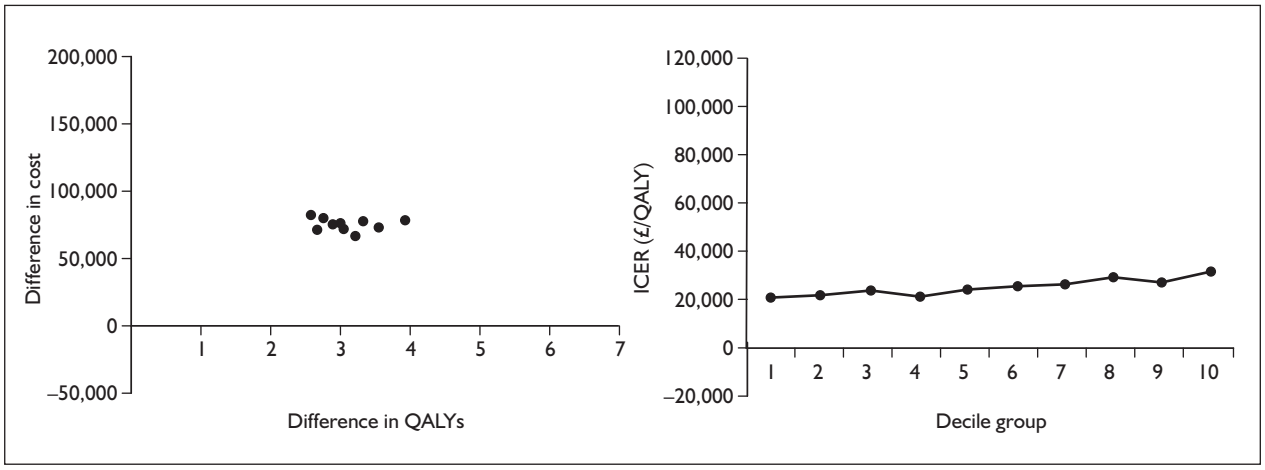

FIGURE 52 *Sitaxentan variation by odds ratio of improvement from functional class III to functional class II. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

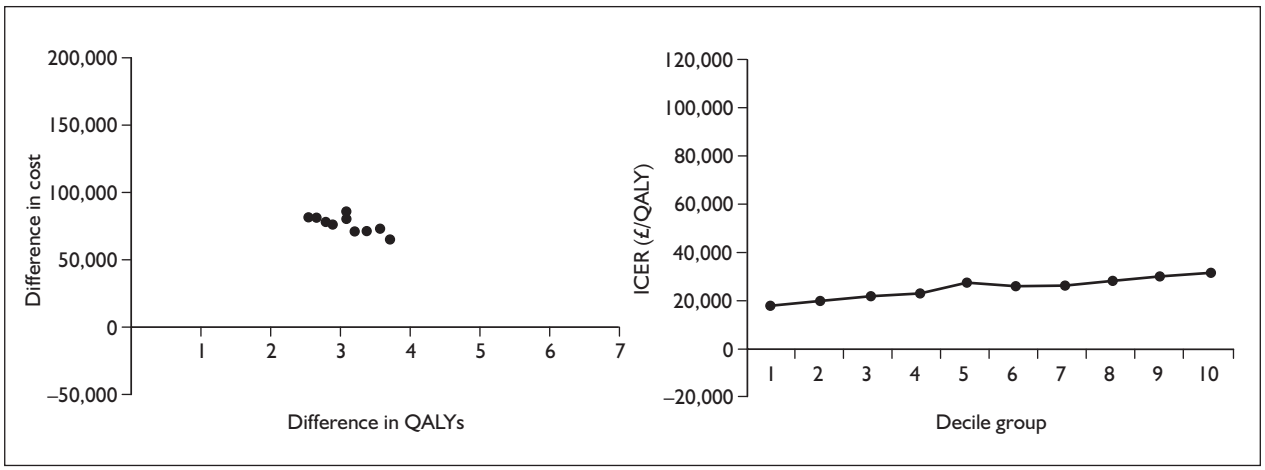

FIGURE 53 *Sitaxentan variation by odds ratio of deterioration from functional class II to functional class III. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

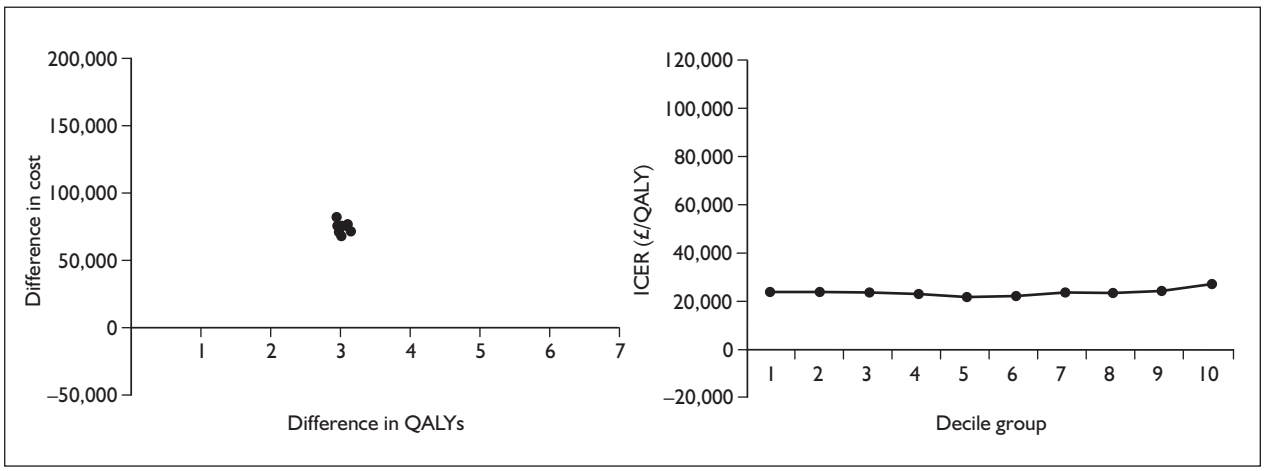

FIGURE 54 *Sitaxentan variation by odds ratio of deterioration from functional class III to functional class IV in the first cycle. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

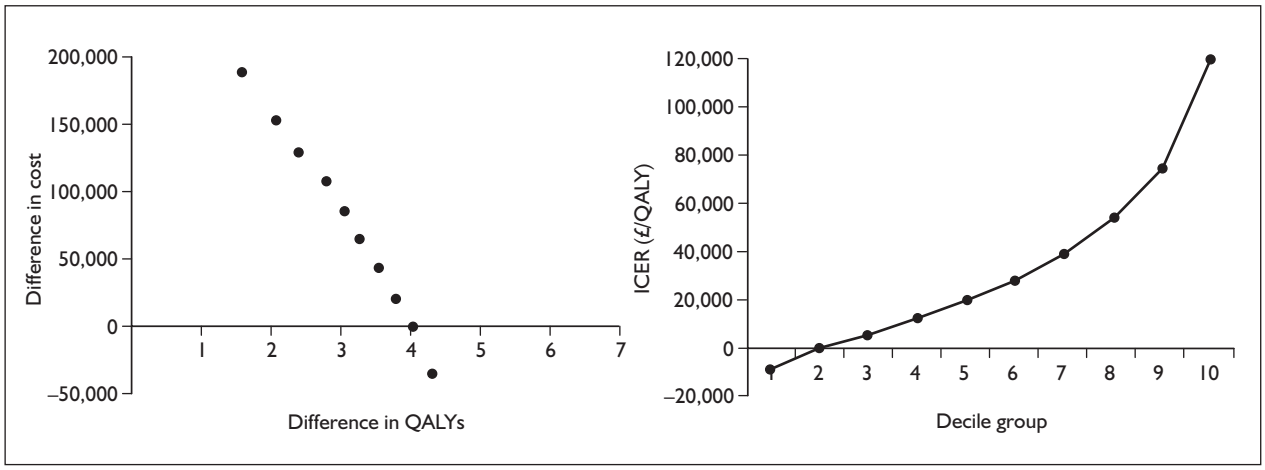

FIGURE 55 *Sitaxentan variation by odds ratio of deterioration from functional class III to functional class IV after the first cycle. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

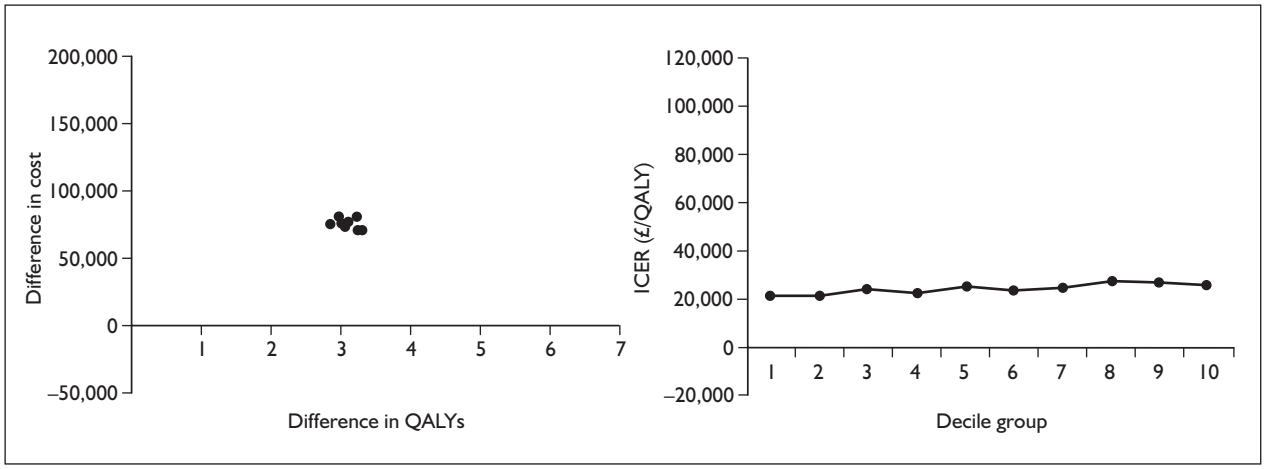

FIGURE 56 *Sitaxentan variation by probability of improvement from functional class III to functional class II on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

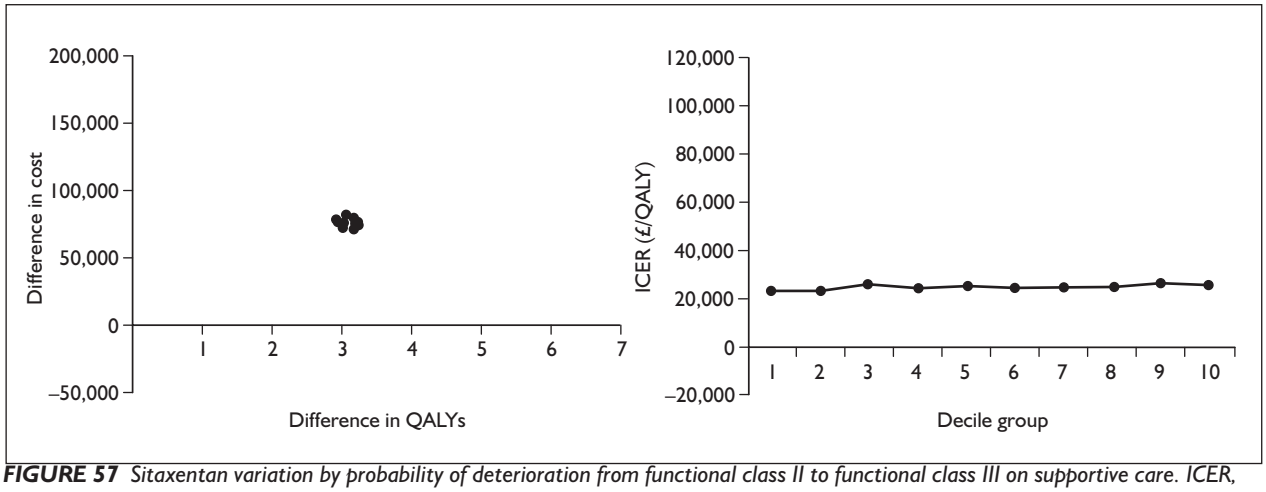

FIGURE 57 *Sitaxentan variation by probability of deterioration from functional class II to functional class III on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

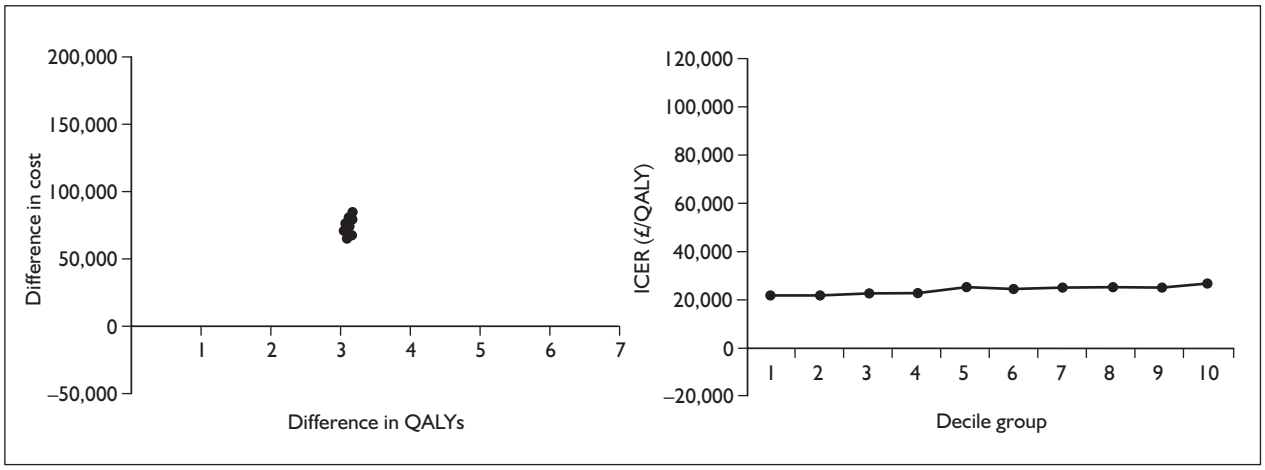

FIGURE 58 *Sitaxentan variation by probability of deterioration from functional class III to functional class IV in the first cycle on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

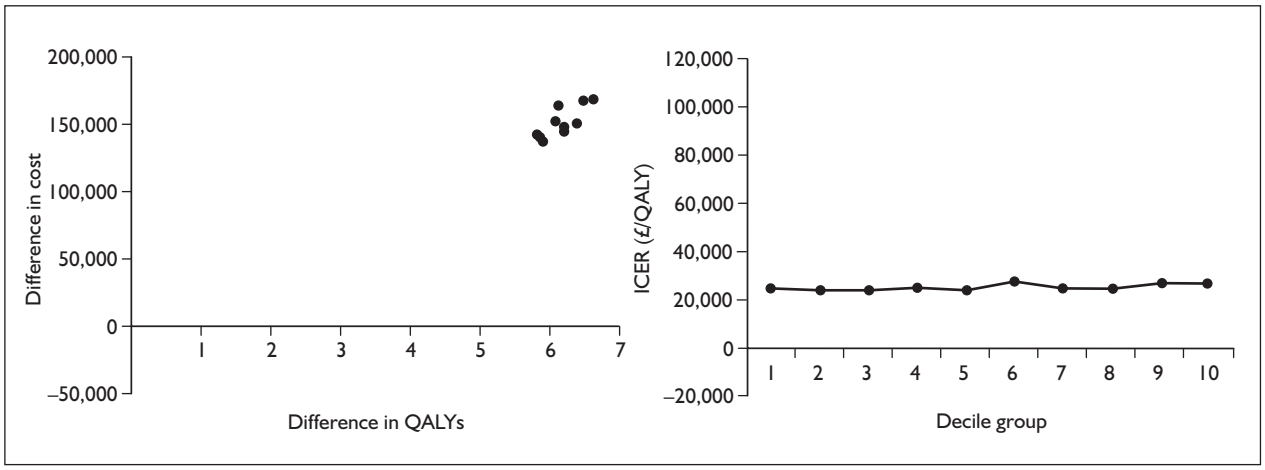

FIGURE 59 *Sitaxentan variation by probability of deterioration from functional class III to functional class IV after the first cycle on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

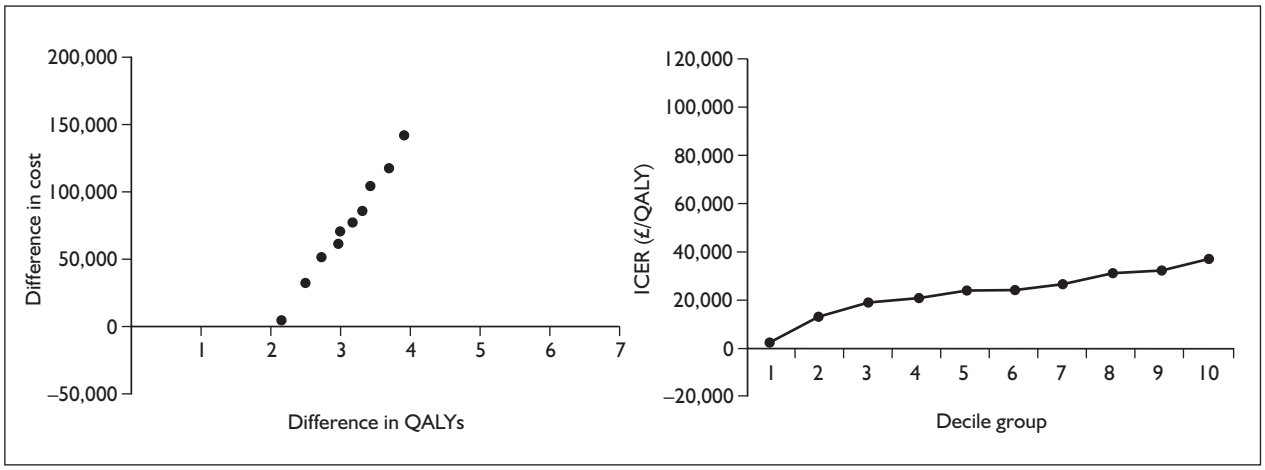

FIGURE 60 *Sitaxentan variation by mortality in functional class III on treatment. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

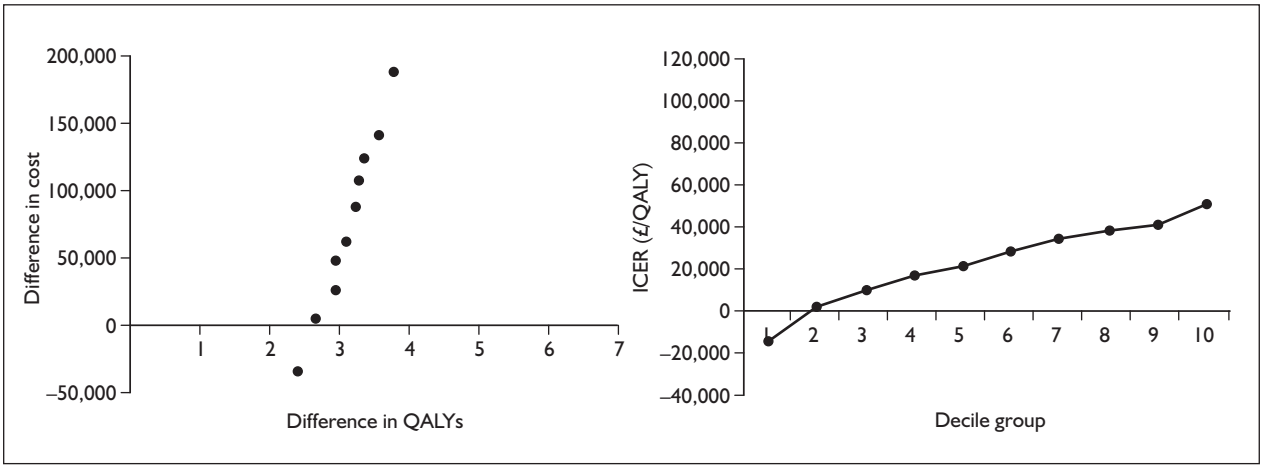

FIGURE 61 *Sitaxentan variation by mortality in functional class III on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

Appendix 11.6 Sildenafil

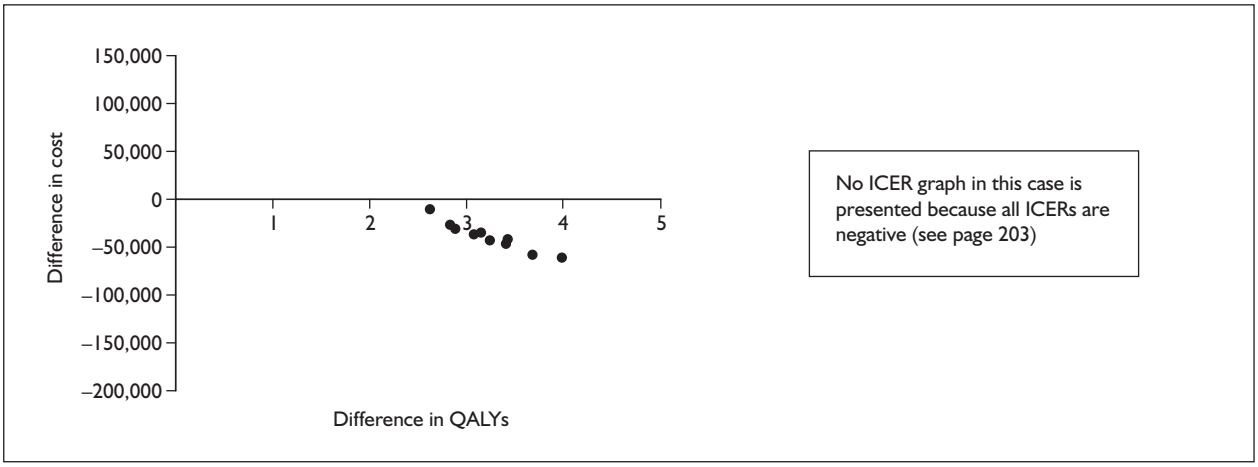

FIGURE 62 *Sildenafil variation by odds ratio of improvement from functional class III to functional class II. QALYs, quality-adjusted life-years.*

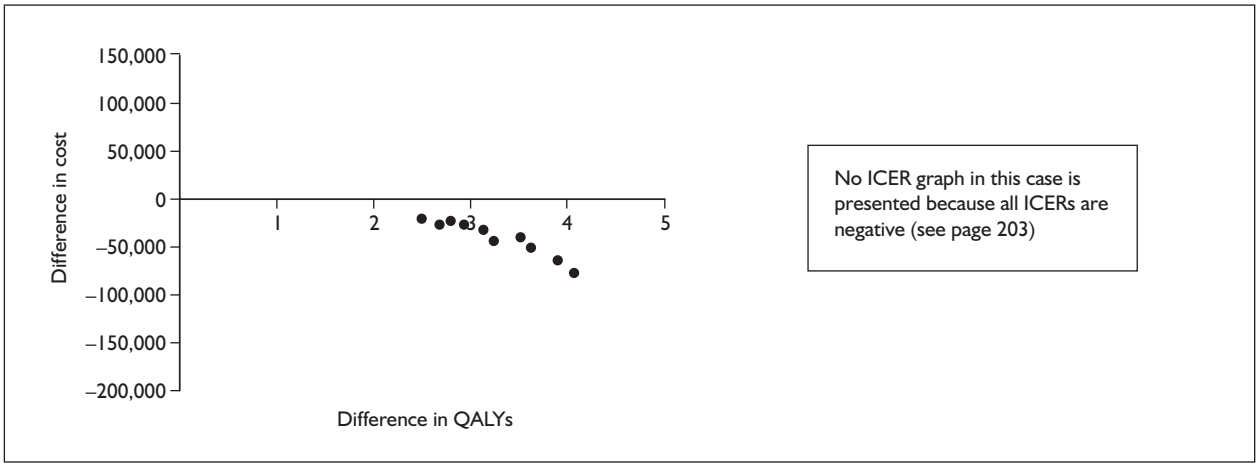

FIGURE 63 *Sildenafil variation by odds ratio of deterioration from functional class II to functional class III. QALYs, quality-adjusted life-years.*

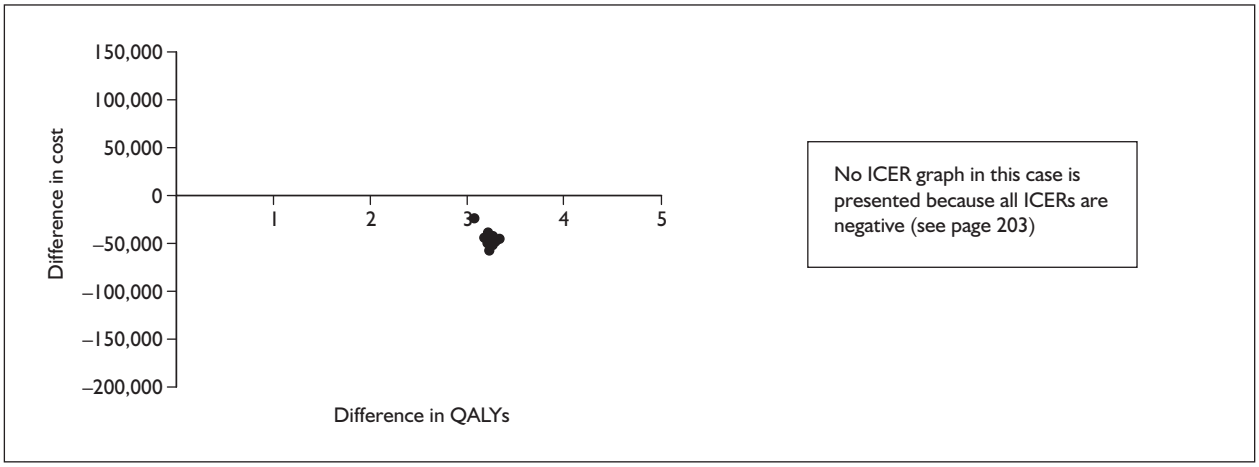

FIGURE 64 *Sildenafil variation by odds ratio of deterioration from functional class III to functional class IV in the first cycle. QALYs, quality-adjusted life-years.*

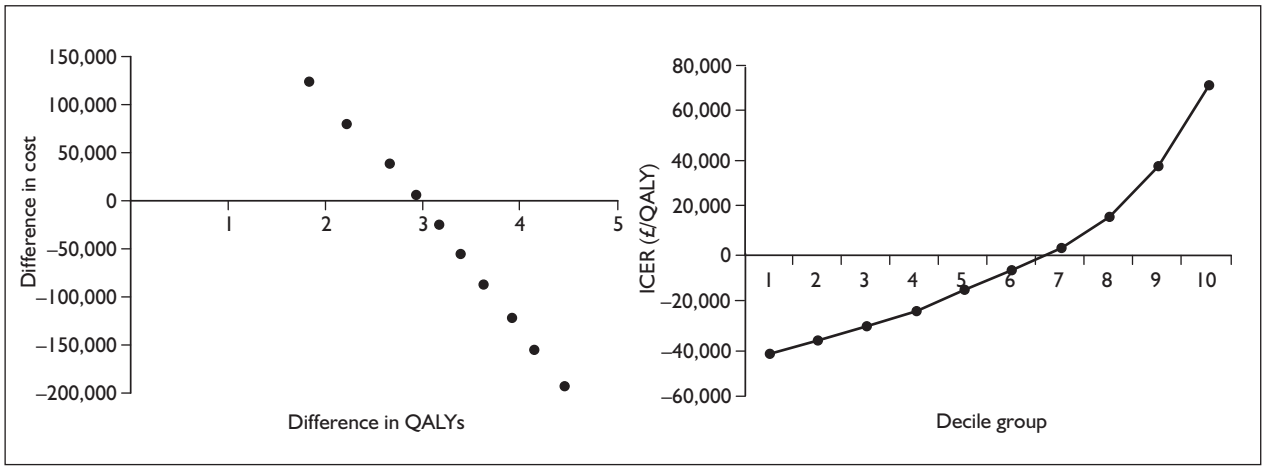

FIGURE 65 *Sildenafil variation by odds ratio of deterioration from functional class III to functional class IV after the first cycle. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

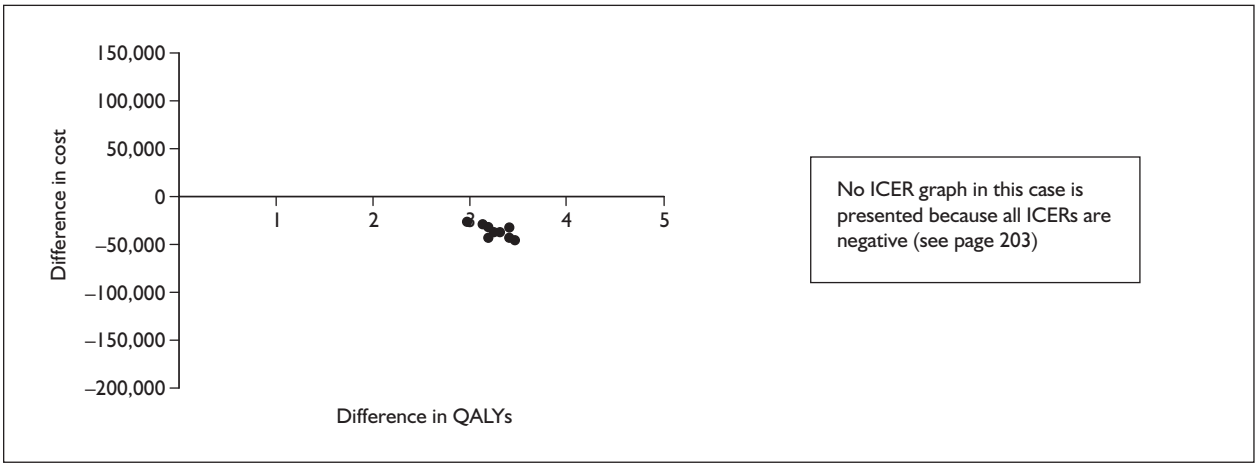

FIGURE 66 *Sildenafil variation by probability of improvement from functional class III to functional class II on supportive care. QALYs, quality-adjusted life-years.*

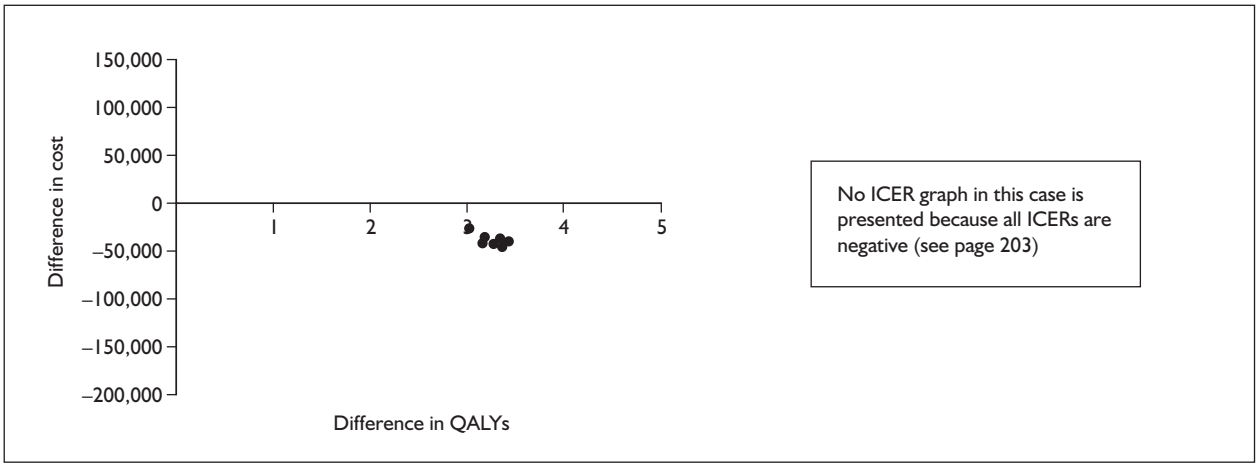

FIGURE 67 *Sildenafil variation by probability of deterioration from functional class II to functional class III on supportive care. QALYs , quality-adjusted life-years.*

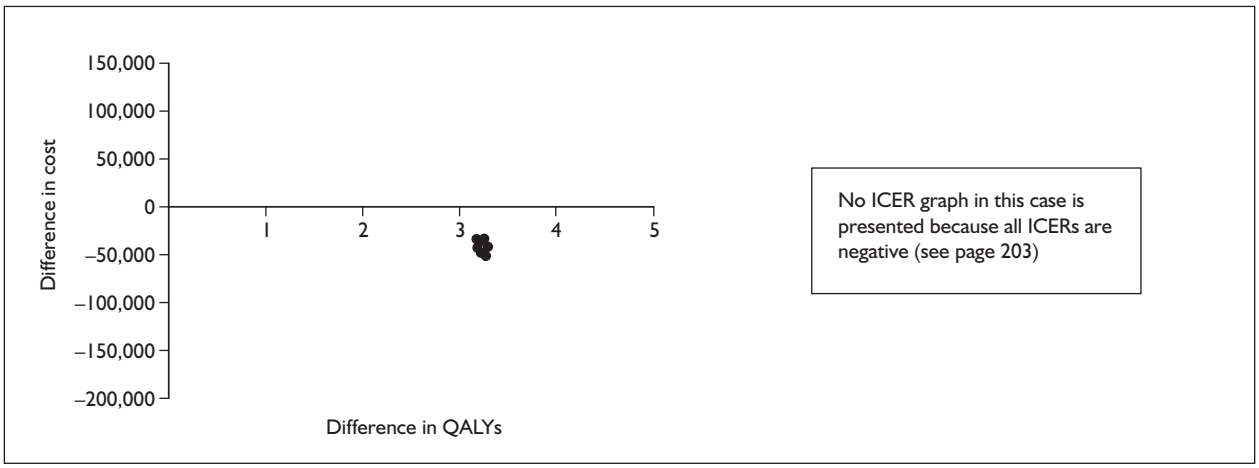

FIGURE 68 *Sildenafil variation by probability of deterioration from functional class III to functional class IV in the first cycle on supportive care. QALYs, quality-adjusted life-years.*

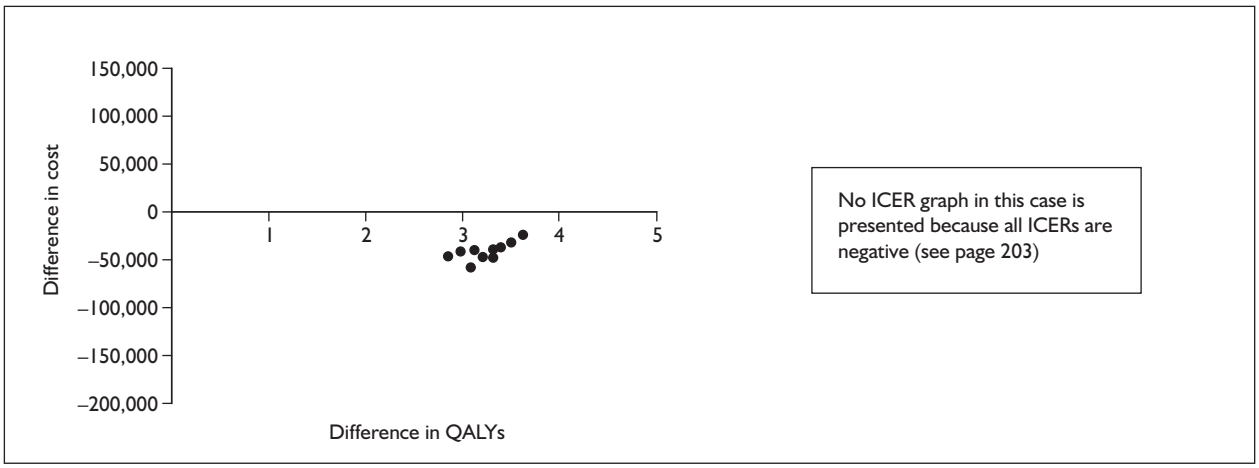

FIGURE 69 *Sildenafil variation by probability of deterioration from functional class III to functional class IV after the first cycle on supportive care. QALYs, quality-adjusted life-years.*

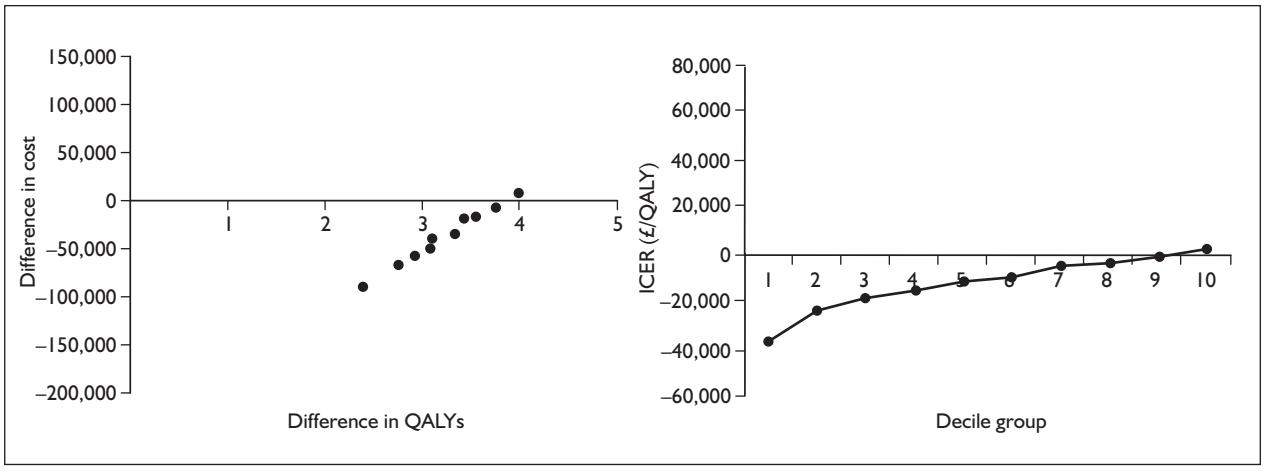

FIGURE 70 *Sildenafil variation by mortality in functional class III on treatment. ICER, incremental cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

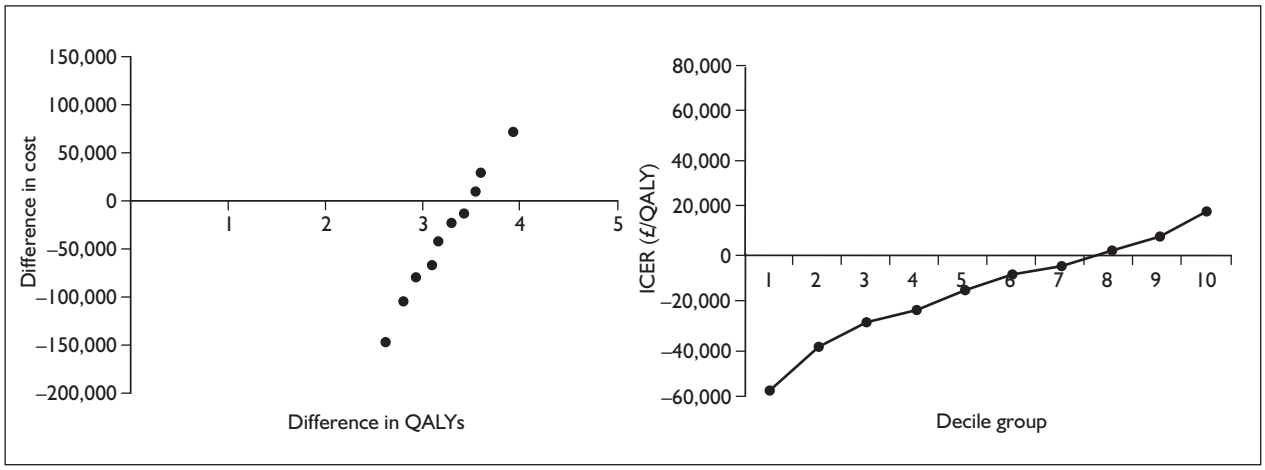

FIGURE 71 *Sildenafil variation by mortality in functional class III on supportive care. ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).*

Appendix 12

Non-reference case model runs

The following tables and cost-effectiveness acceptability curves are for the non-reference case analyses conducted to consider alternative time horizons, pricing and health state utility value sets. The analyses are presented therapy-by-therapy.

Appendix 12.1 Epoprostenol with supportive care versus supportive care alone, functional class III

Alternative time horizon

Time horizon of 20 years

TABLE 85 *Epoprostenol versus supportive care, functional class III: time horizon of 20 years*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	477,000		2.049		
Epoprostenol	693,000	216,000	2.828	0.779	277,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

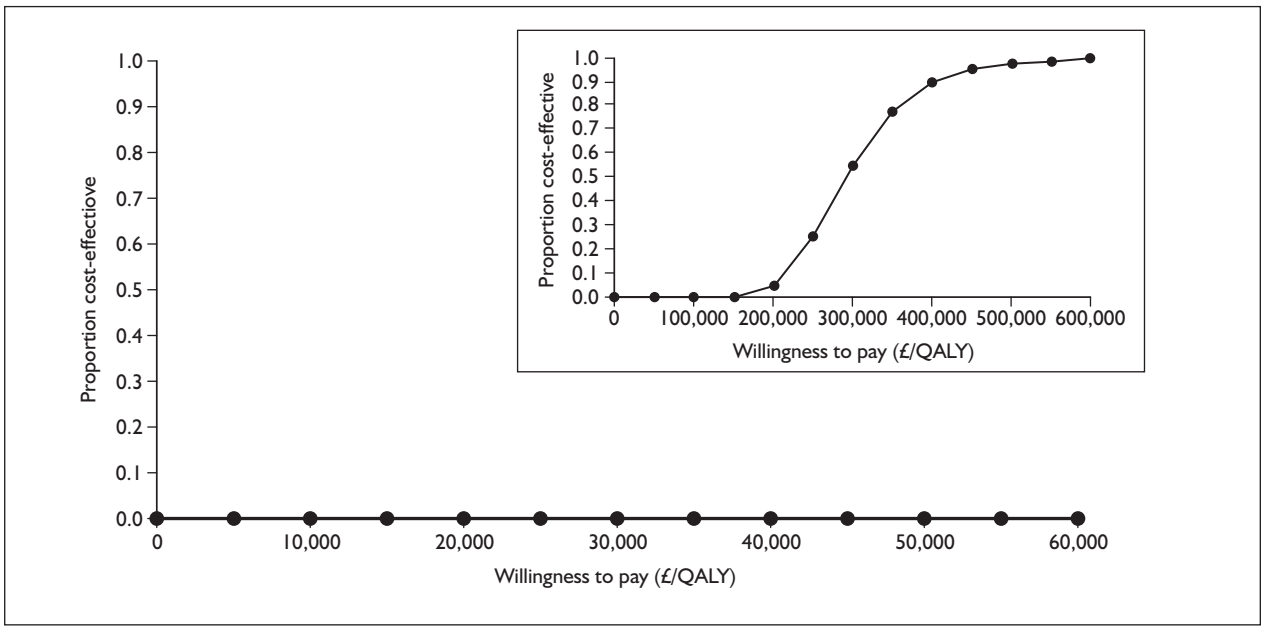

FIGURE 72 *Cost-effectiveness acceptability curve for epoprostenol versus supportive care, functional class III: time horizon of 20 years. QALY, quality-adjusted life-year.*

Time horizon of 10 years

TABLE 86 *Epoprostenol versus supportive care, functional class III: time horizon of 10 years*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	443,000		1.936		
Epoprostenol	632,000	189,000	2.619	0.683	277,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

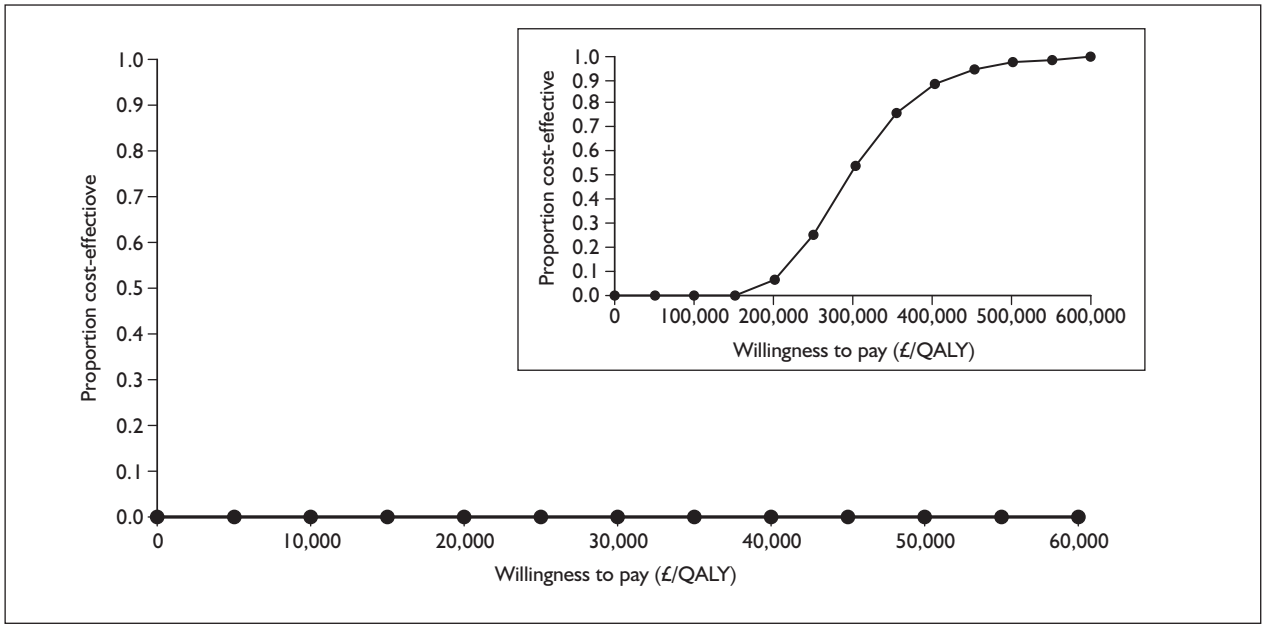

FIGURE 73 *Cost-effectiveness acceptability curve for epoprostenol versus supportive care, functional class III: time horizon of 10 years. QALY, quality-adjusted life-year.*

Alternative prices

Alternative price for epoprostenol

TABLE 87 *Epoprostenol versus supportive care, functional class III: alternative price for epoprostenol*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	217,000		2.056		
Epoprostenol	301,000	83,000	2.843	0.787	106,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

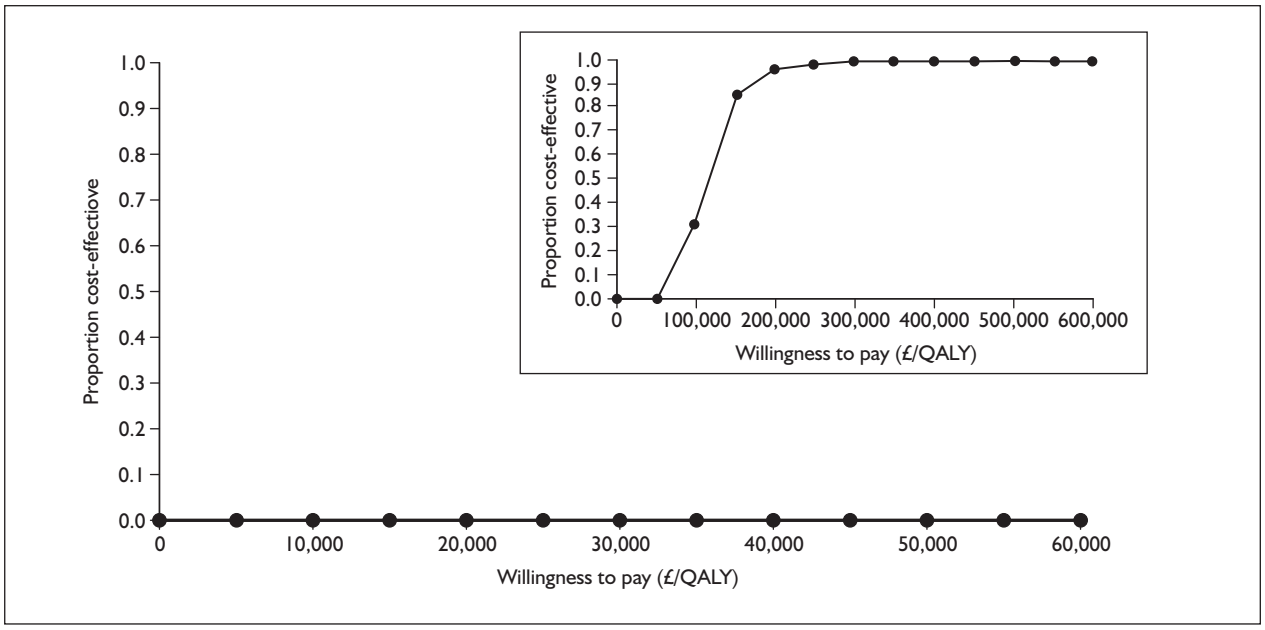

FIGURE 74 *Cost-effectiveness acceptability curve for epoprostenol versus supportive care, functional class III: alternative price for epoprostenol. QALY, quality-adjusted life-year.*

Alternative health state utility values
Utilities from Meads et al.[94]

TABLE 88 *Epoprostenol versus supportive care, functional class III: alternative health state utility values (Meads* et al.*)*[94]

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	479,000		[Commercial-in-confidence information has been removed]		
Epoprostenol	697,000	218,000	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

FIGURE 75 *Cost-effectiveness acceptability curve for epoprostenol versus supportive care, functional class III: alternative health state utility values (Meads* et al.*).*[94] *[Commercial-in-confidence information has been removed].*

Utilities from Kirsch,[76] 2-year time trade-off

TABLE 89 *Epoprostenol versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 2-year time trade-off)*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	478,000		1.590		
Epoprostenol	696,000	218,000	2.422	0.831	262,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

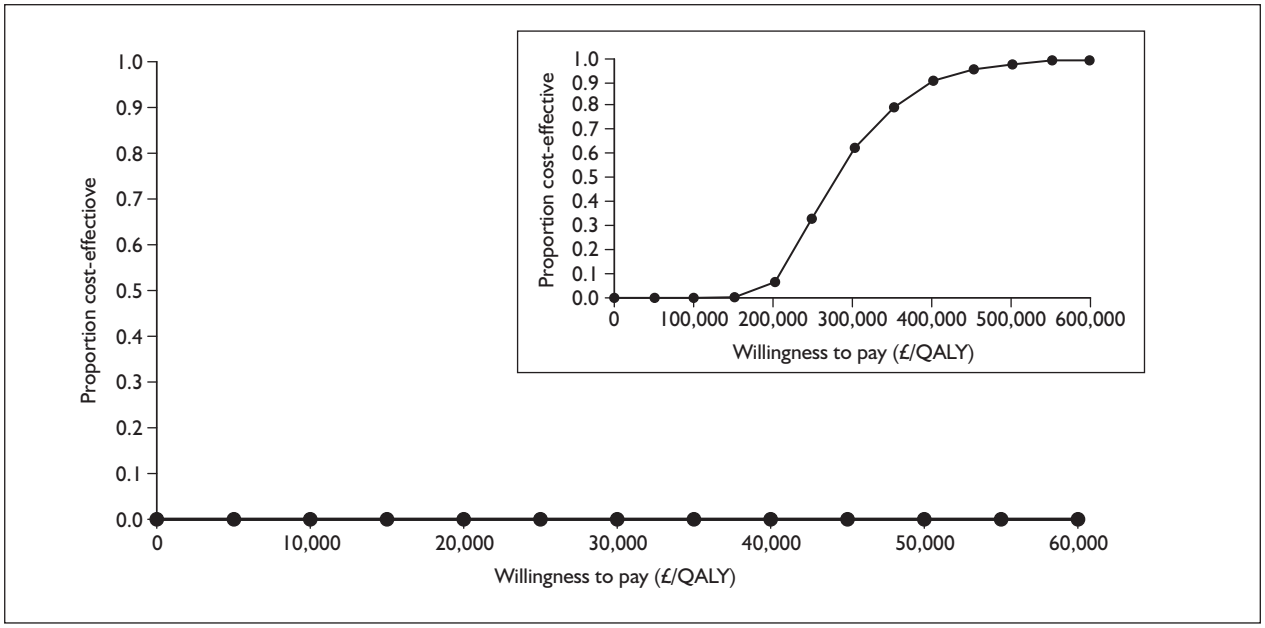

FIGURE 76 *Cost-effectiveness acceptability curve for epoprostenol versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 2-year time trade-off). QALY, quality-adjusted life-year.*

Utilities from Kirsch,[76] 10-year time trade-off

TABLE 90 *Epoprostenol versus supportive care, functional class III: alternative health state utility values (Kirsch[76], 10-year time trade-off)*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	478,000		1.303		
Epoprostenol	696,000	218,000	2.102	0.799	272,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

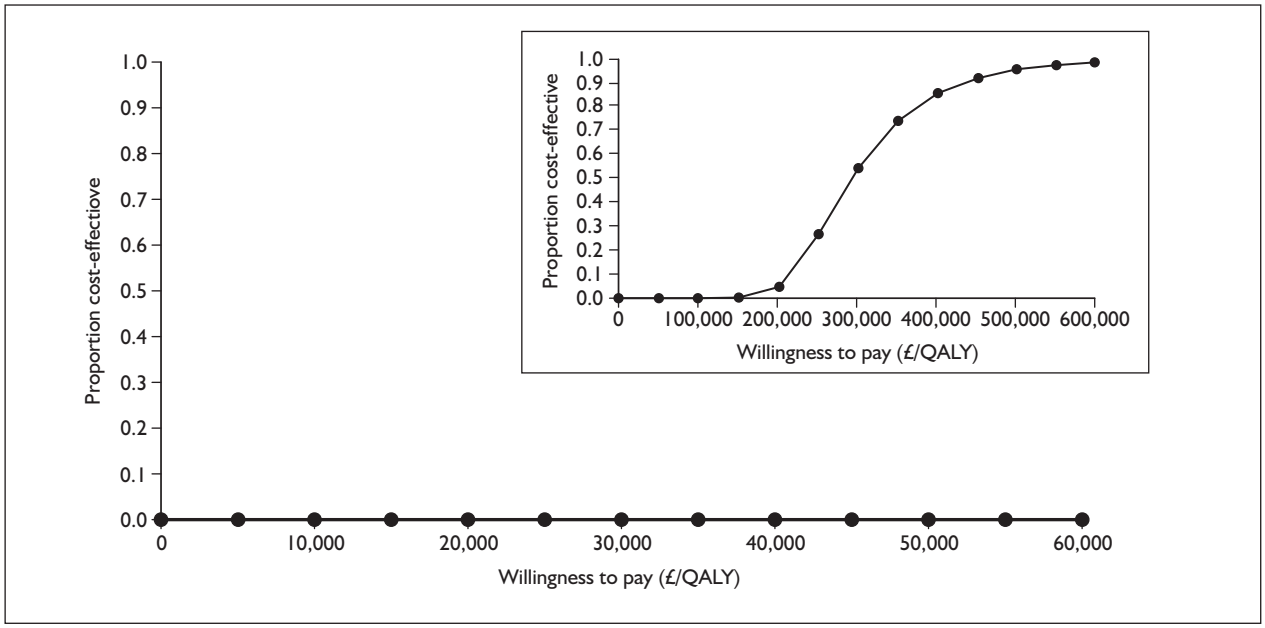

FIGURE 77 *Cost-effectiveness acceptability curve for epoprostenol versus supportive care, functional class III: alternative health state utility values (Kirsch[76], 10-year time trade-off). QALY, quality-adjusted life-year.*

Utilities from Olschewski et al.[41]

TABLE 91 *Epoprostenol versus supportive care, functional class III: alternative health state utility values (Olschewski* et al.*)*[41]

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	479,000		1.853		
Epoprostenol	697,000	218,000	2.706	0.853	256,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

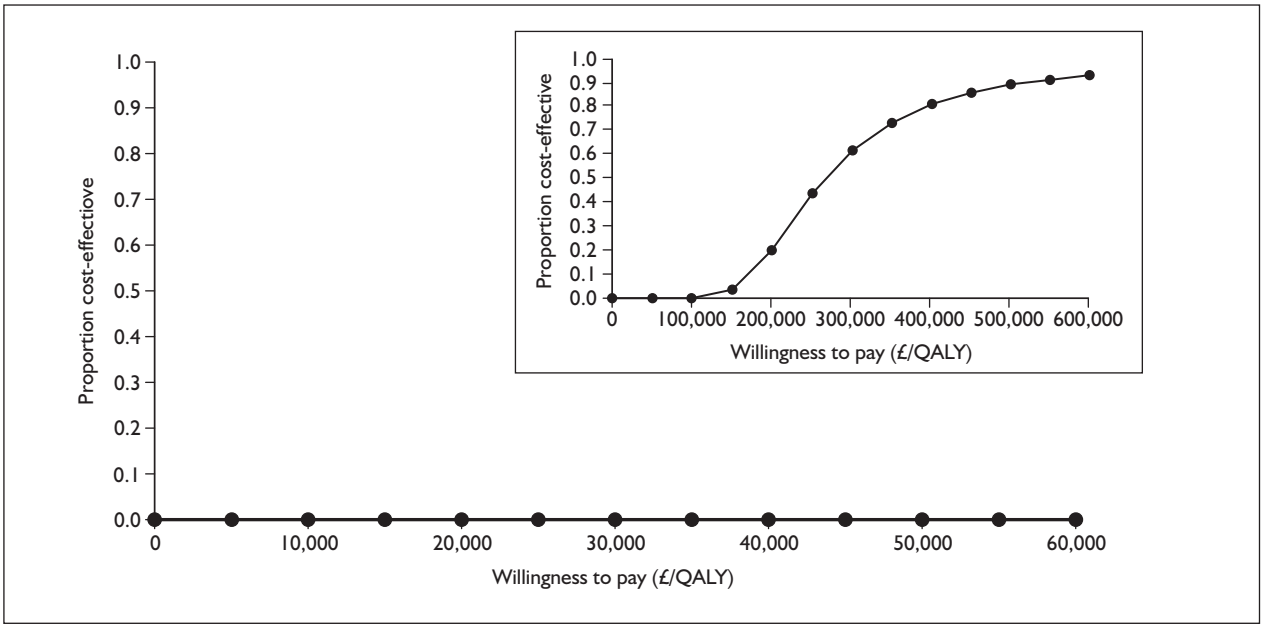

FIGURE 78 *Cost-effectiveness acceptability curve for epoprostenol versus supportive care, functional class III: alternative health state utility values (Olschewski* et al.*).*[41] *QALY, quality-adjusted life-year.*

Appendix 12.2 Epoprostenol with supportive care versus supportive care alone, functional class IV

Alternative time horizon

Time horizon of 20 years

TABLE 92 *Epoprostenol versus supportive care, functional class IV: time horizon of 20 years*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	128,000		0.829		
Epoprostenol	529,000	401,000	1.996	1.167	344,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

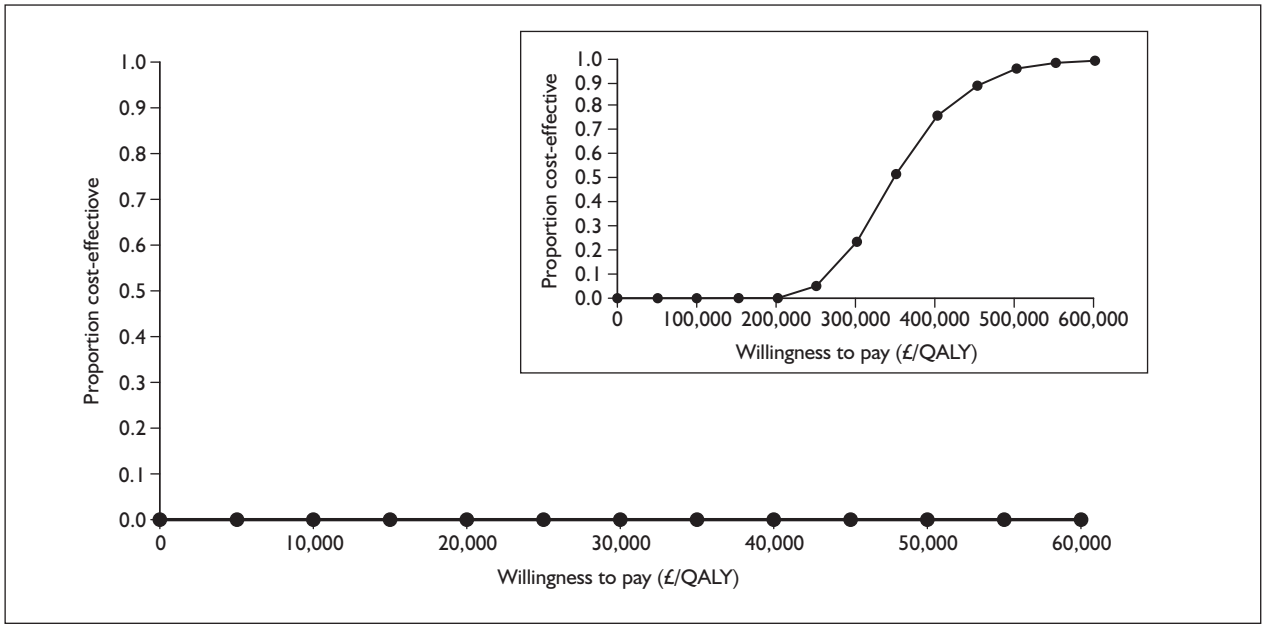

FIGURE 79 *Cost-effectiveness acceptability curve for epoprostenol versus supportive care, functional class IV: time horizon of 20 years. QALY, quality-adjusted life-year.*

Time horizon of 10 years

TABLE 93 *Epoprostenol versus supportive care, functional class IV: time horizon of 10 years*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	127,000		0.827		
Epoprostenol	495,000	368,000	1.885	1.058	348,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

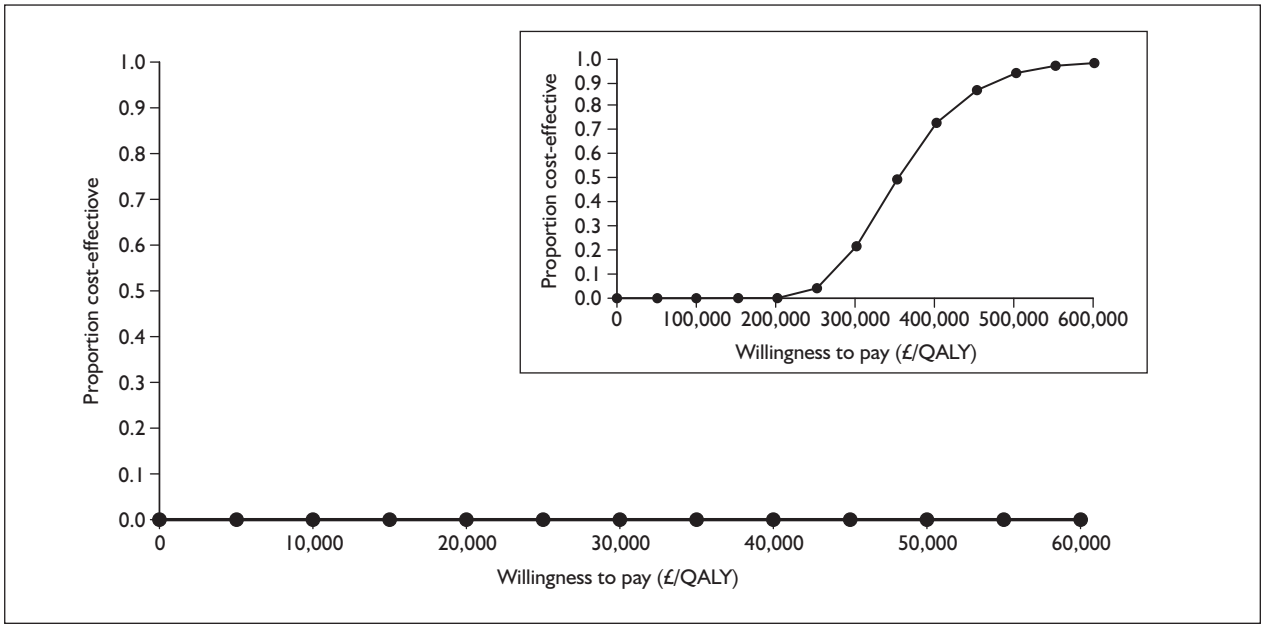

FIGURE 80 *Cost-effectiveness acceptability curve for epoprostenol versus supportive care, functional class IV: time horizon of 10 years. QALY, quality-adjusted life-year.*

Alternative prices

Alternative price for epoprostenol

TABLE 94 *Epoprostenol versus supportive care, functional class IV: alternative price for epoprostenol*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	128,000		0.829		
Epoprostenol	240,000	113,000	2.003	1.174	96,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

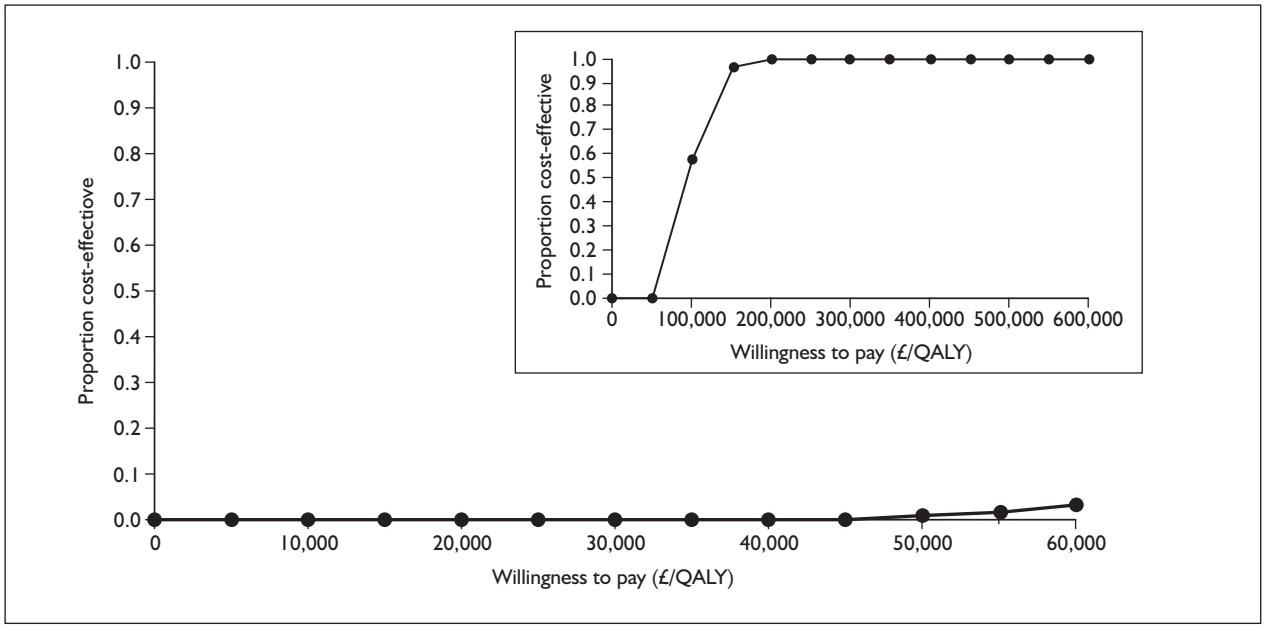

FIGURE 81 *Cost-effectiveness acceptability curve for epoprostenol versus supportive care, functional class IV: alternative price for epoprostenol. QALY, quality-adjusted life-year.*

Alternative health state utility values
Utilities from Meads et al.[94]

TABLE 95 *Epoprostenol versus supportive care, functional class IV: alternative health state utility values (Meads* et al.*)*[94]

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	128,000		[Commercial-in-confidence information has been removed]		
Epoprostenol	531,000	403,000	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

FIGURE 82 *Cost-effectiveness acceptability curve for epoprostenol versus supportive care, functional class IV: alternative health state utility values (Meads* et al.*).*[94] *[Commercial-in-confidence information has been removed].*

Utilities from Kirsch,[76] 2-year time trade-off

TABLE 96 *Epoprostenol versus supportive care, functional class IV: alternative health state utility values (Kirsch,[76] 2-year time trade-off)*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	128,000		0.590		
Epoprostenol	530,000	402,000	1.485	0.895	449,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

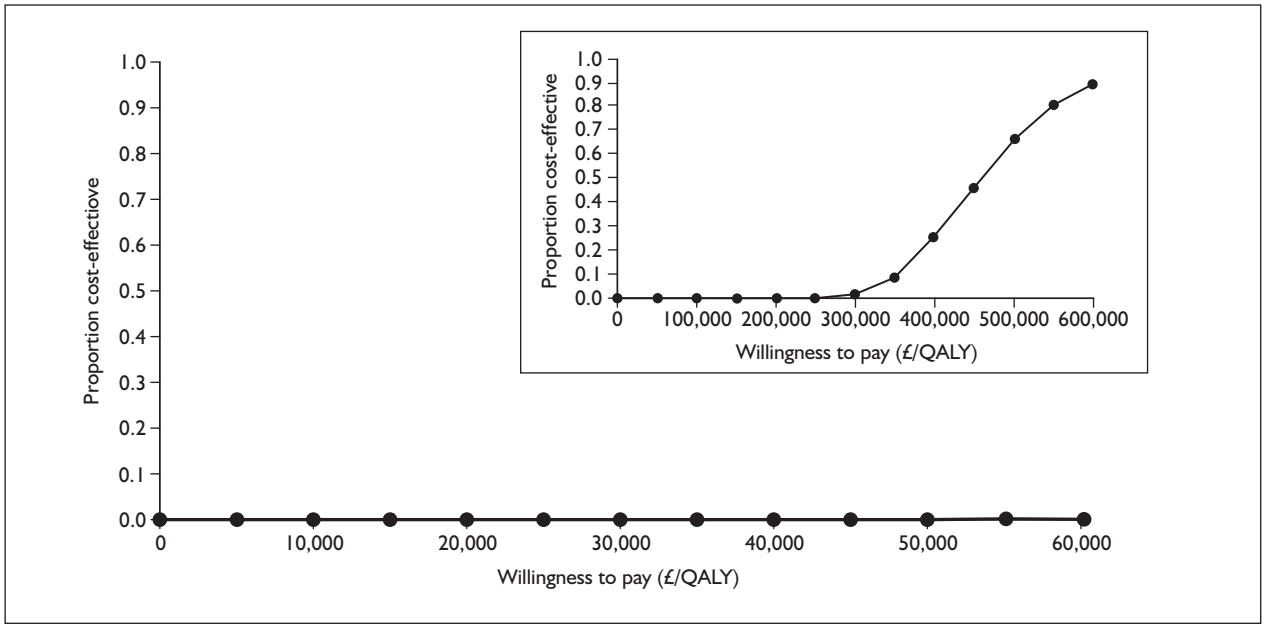

FIGURE 83 *Cost-effectiveness acceptability curve for epoprostenol versus supportive care, functional class IV: alternative health state utility values (Kirsch,[76] 2-year time trade-off). QALY, quality-adjusted life-year.*

Utilities from Kirsch,[76] 10-year time trade-off

TABLE 97 *Epoprostenol versus supportive care, functional class IV: alternative health state utility values (Kirsch,[76] 10-year time trade-off)*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	128,000		0.451		
Epoprostenol	530,000	402,000	1.177	0.726	554,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

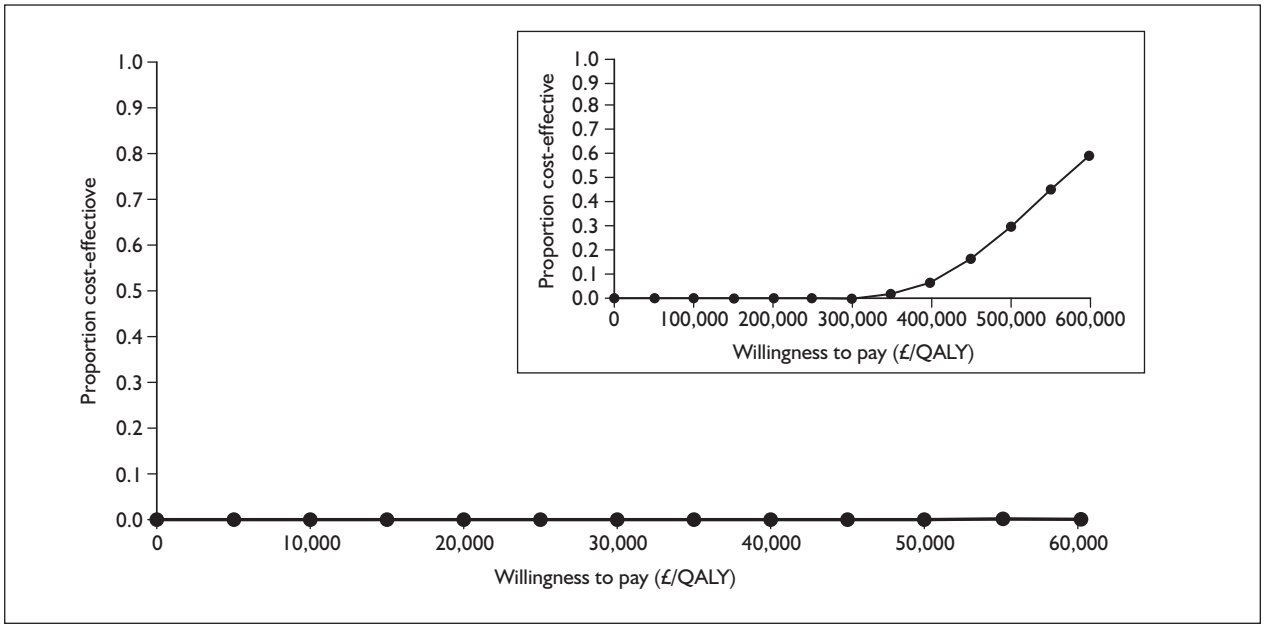

FIGURE 84 *Cost-effectiveness acceptability curve for epoprostenol versus supportive care, functional class IV: alternative health state utility values (Kirsch,[76] 10-year time trade-off). QALY, quality-adjusted life-year.*

Utilities from Olschewski et al.[41]

TABLE 98 *Epoprostenol versus supportive care, functional class IV: alternative health state utility values (Olschewski* et al.*)*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	128,000		0.705		
Epoprostenol	531,000	403,000	1.754	1.049	384,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

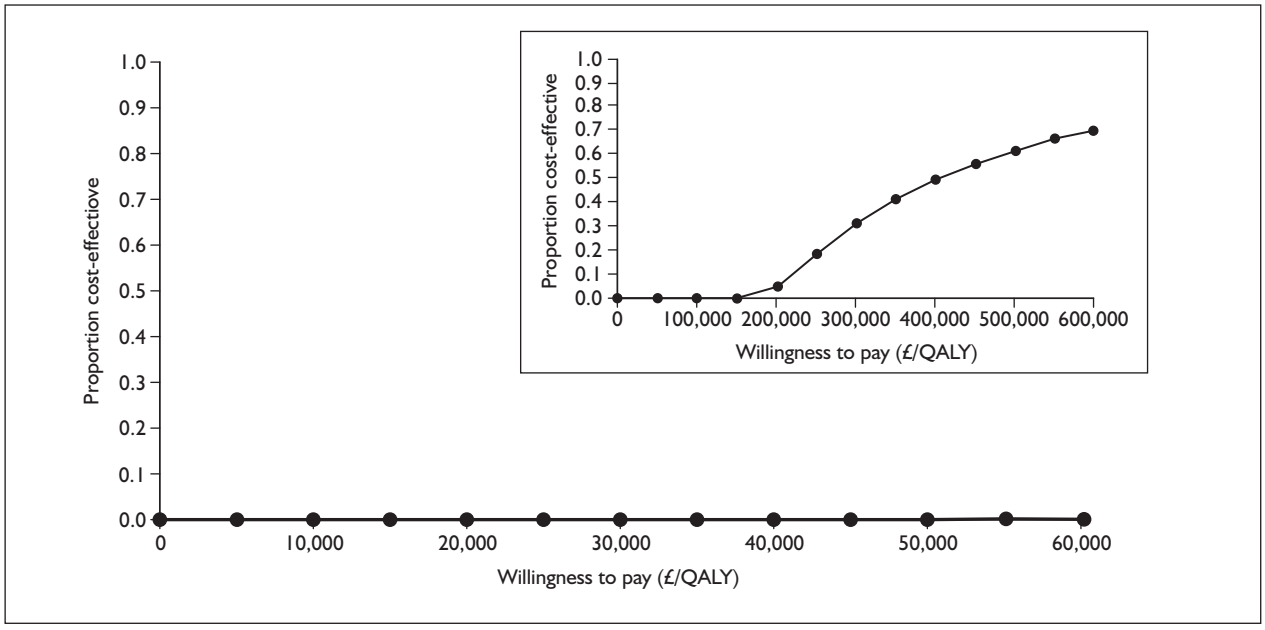

FIGURE 85 *Cost-effectiveness acceptability curve for epoprostenol versus supportive care, functional class IV: alternative health state utility values (Olschewski).*[41] *QALY, quality-adjusted life-year.*

Appendix 12.3 Iloprost with supportive care versus supportive care alone, functional class III

Alternative time horizon

Time horizon of 20 years

TABLE 99 *Iloprost versus supportive care, functional class III: time horizon of 20 years*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	432,000		1.952		
Iloprost	531,000	99,000	2.951	0.999	99,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

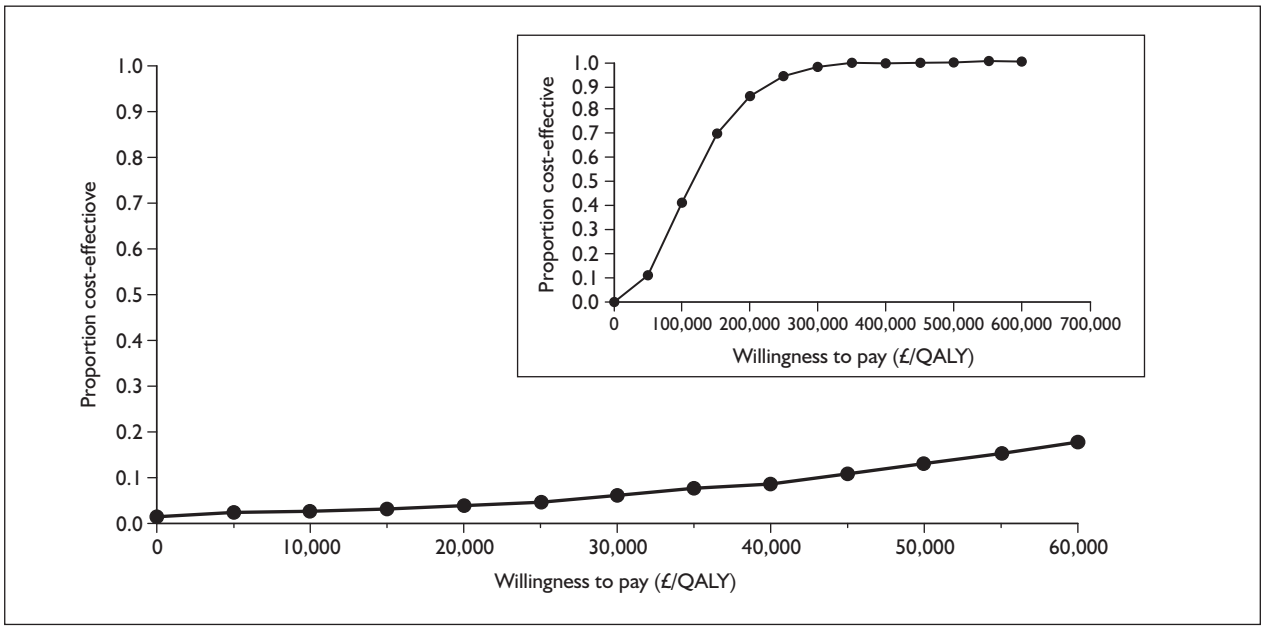

FIGURE 86 *Cost-effectiveness acceptability curve for iloprost versus supportive care, functional class III: time horizon of 20 years. QALY, quality-adjusted life-year.*

Time horizon of 10 years

TABLE 100 *Iloprost versus supportive care, functional class III: time horizon of 10 years*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	400,000		1.846		
Iloprost	469,000	68,000	2.690	0.844	81,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

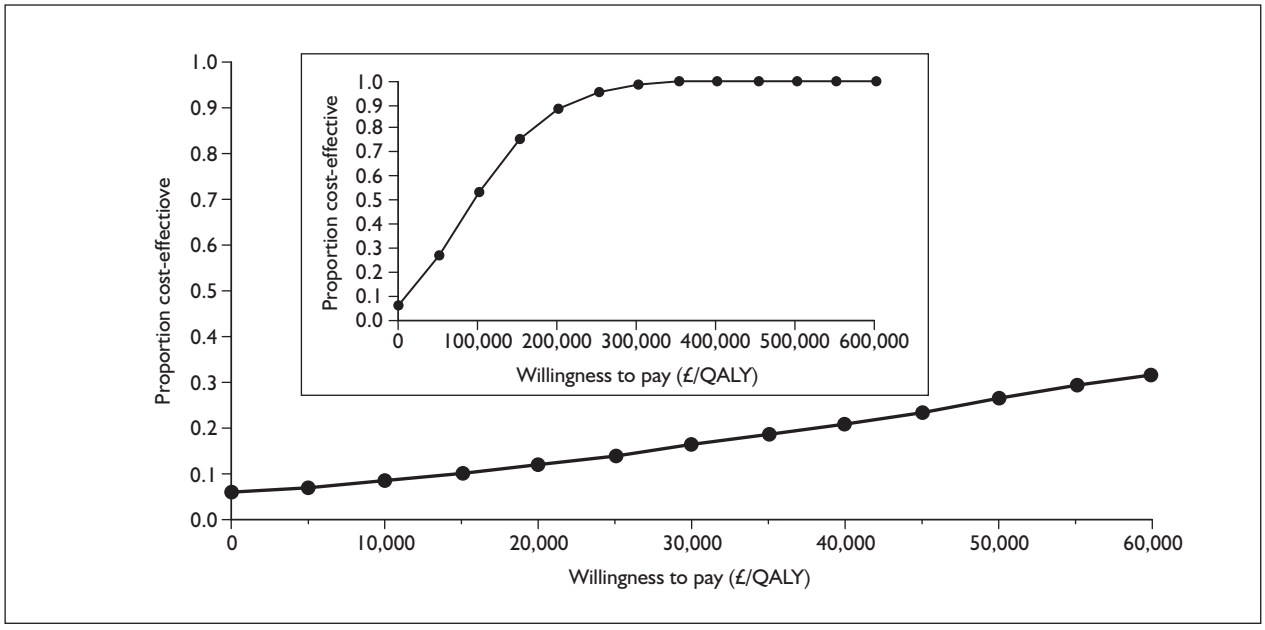

FIGURE 87 *Cost-effectiveness acceptability curve for iloprost versus supportive care, functional class III: time horizon of 10 years. QALY, quality-adjusted life-year.*

Alternative prices

Alternative price for epoprostenol

TABLE 101 *Iloprost versus supportive care, functional class III: alternative price for epoprostenol*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	197,000		1.958		
Iloprost	299,000	102,000	2.975	1.017	101,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

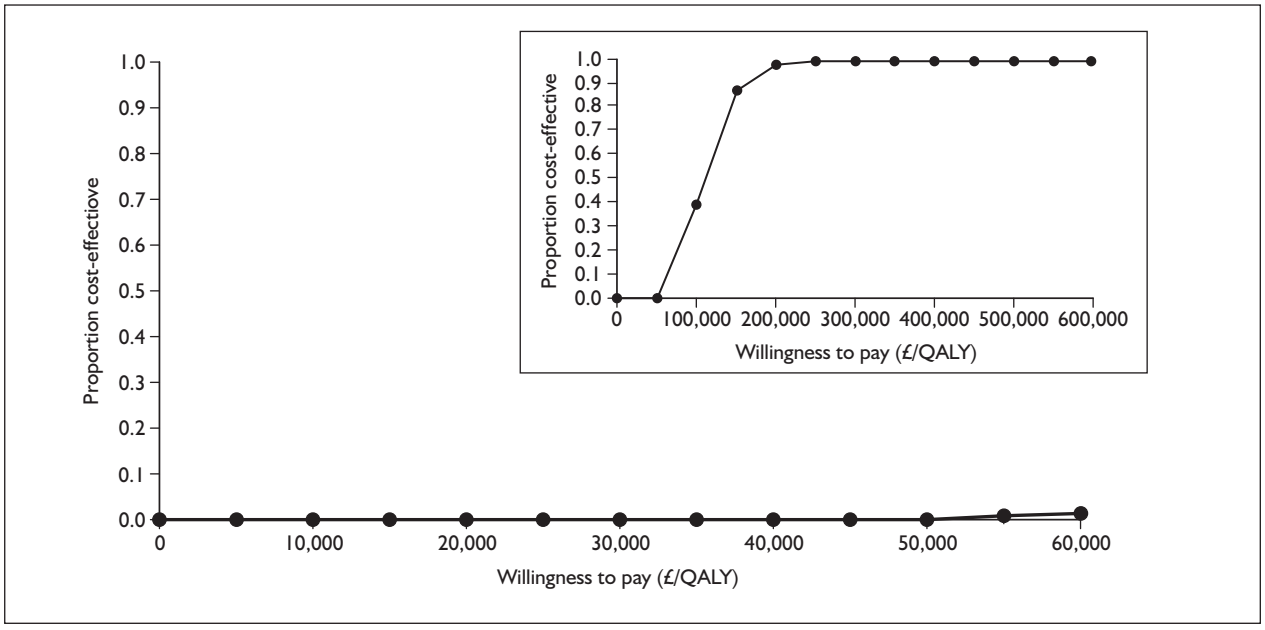

FIGURE 88 *Cost-effectiveness acceptability curve for iloprost versus supportive care, functional class III: alternative price for epoprostenol. QALY, quality-adjusted life-year.*

Alternative iloprost price, reference case epoprostenol price

TABLE 102 *Iloprost versus supportive care, functional class III: alternative iloprost price, reference case epoprostenol price*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	434,000		1.958		
Iloprost	521,000	87,000	2.975	1.017	85,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

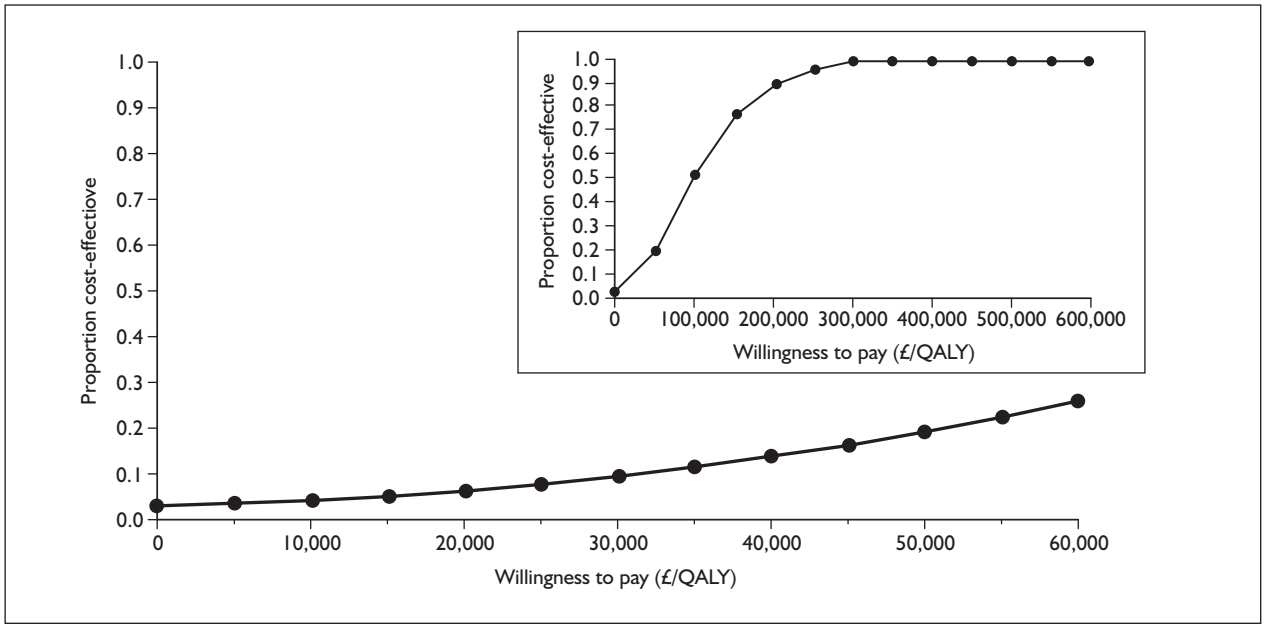

FIGURE 89 *Cost-effectiveness acceptability curve for iloprost versus supportive care, functional class III: alternative iloprost price, reference case epoprostenol price. QALY, quality-adjusted life-year.*

Alternative iloprost and epoprostenol prices

TABLE 103 *Iloprost versus supportive care, functional class III: alternative iloprost and epoprostenol prices*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	197,000		1.958		
Iloprost	283,000	86,000	2.975	1.017	85,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

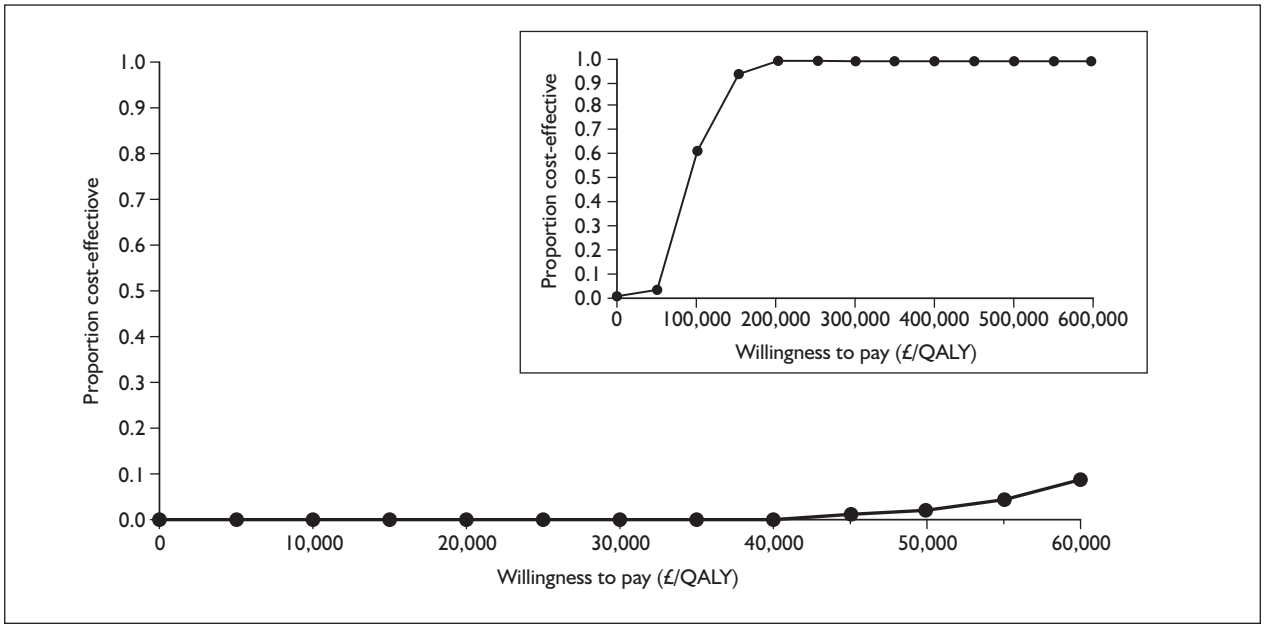

FIGURE 90 *Cost-effectiveness acceptability curve for iloprost versus supportive care, functional class III: alternative iloprost and epoprostenol prices. QALY, quality-adjusted life-year.*

Alternative health state utility values
Utilities from Meads et al.[94]

TABLE 104 *Iloprost versus supportive care, functional class III: alternative health state utility values (Meads* et al.*)*[94]

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	434,000		[Commercial-in-confidence information has been removed]		
Iloprost	537,000	103,000	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

FIGURE 91 *Cost-effectiveness acceptability curve for iloprost versus supportive care, functional class III: alternative health state utility values (Meads* et al.*).*[94] *[Commercial-in-confidence information has been removed].*

Utilities from Kirsch,[76] 2-year time trade-off

TABLE 105 *Iloprost versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 2-year time trade-off)*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	434,000		1.535		
Iloprost	535,000	102,000	2.564	1.030	99,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

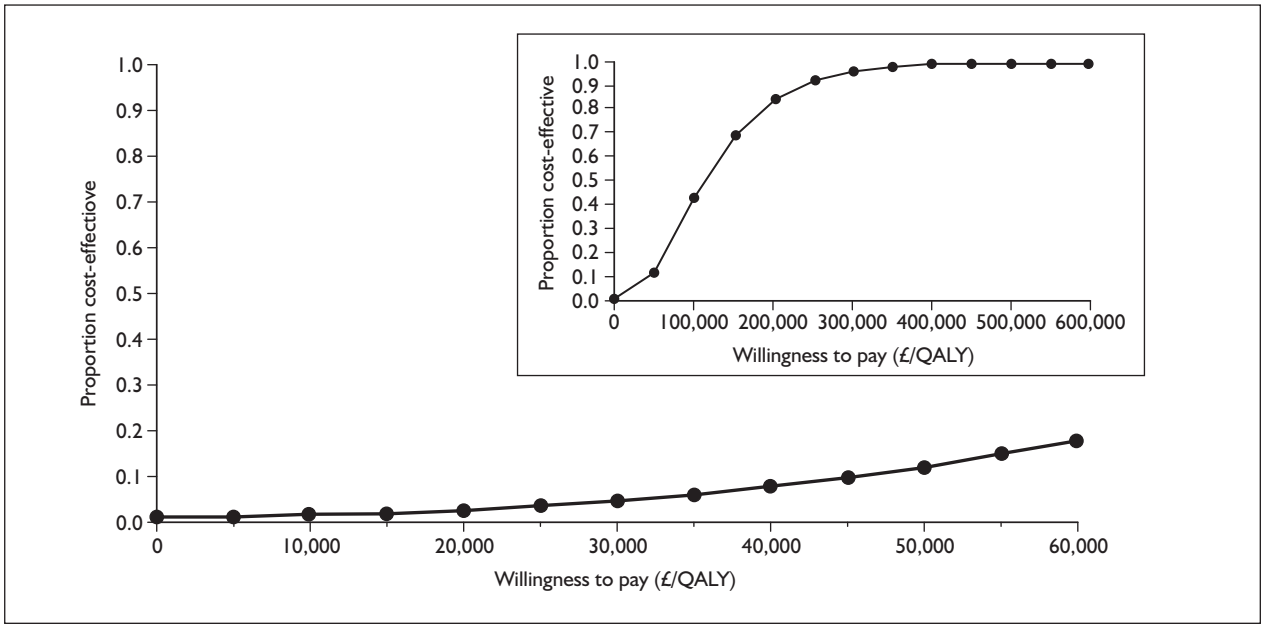

FIGURE 92 *Cost-effectiveness acceptability curve for iloprost versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 2-year time trade-off). QALY, quality-adjusted life-year.*

Utilities from Kirsch,[76] 10-year time trade-off

TABLE 106 *Iloprost versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 10-year time trade-off)*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	434,000		1.269		
Iloprost	535,000	102,000	2.244	0.975	104,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

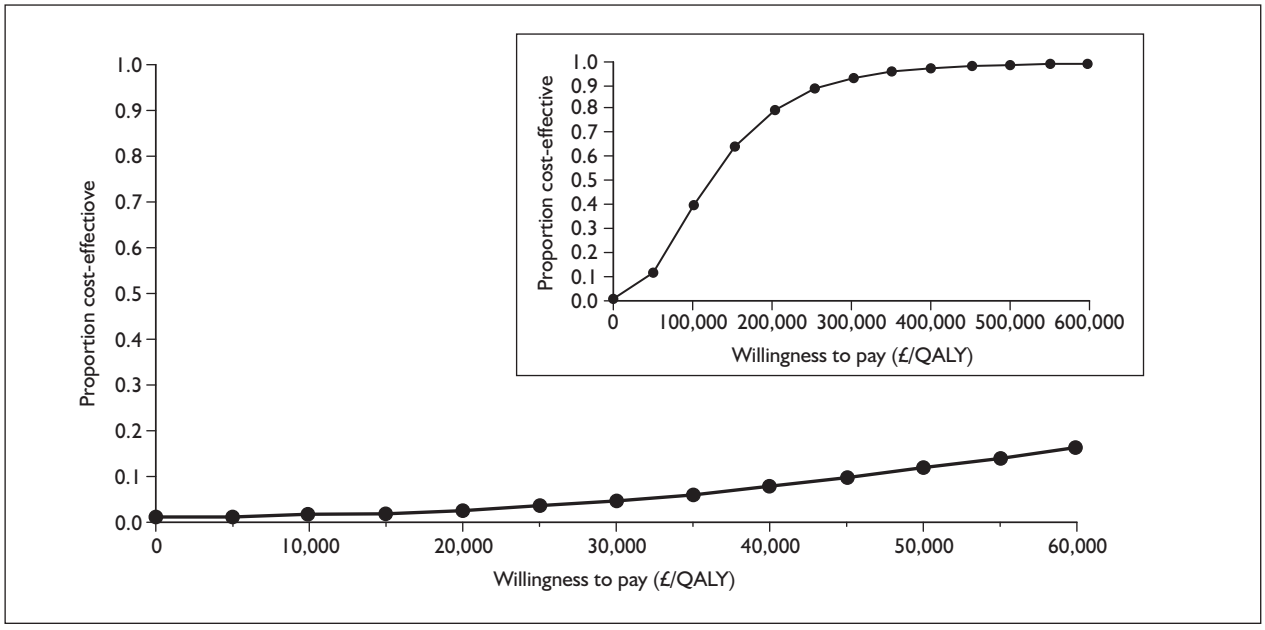

FIGURE 93 *Cost-effectiveness acceptability curve for iloprost versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 10-year time trade-off). QALY, quality-adjusted life-year.*

Utilities from Olschewski et al.[41]

TABLE 107 *Iloprost versus supportive care, functional class III: alternative health state utility values (Olschewski* et al.*)*[41]

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	434,000		1.781		
Iloprost	537,000	103,000	2.854	1.074	96,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

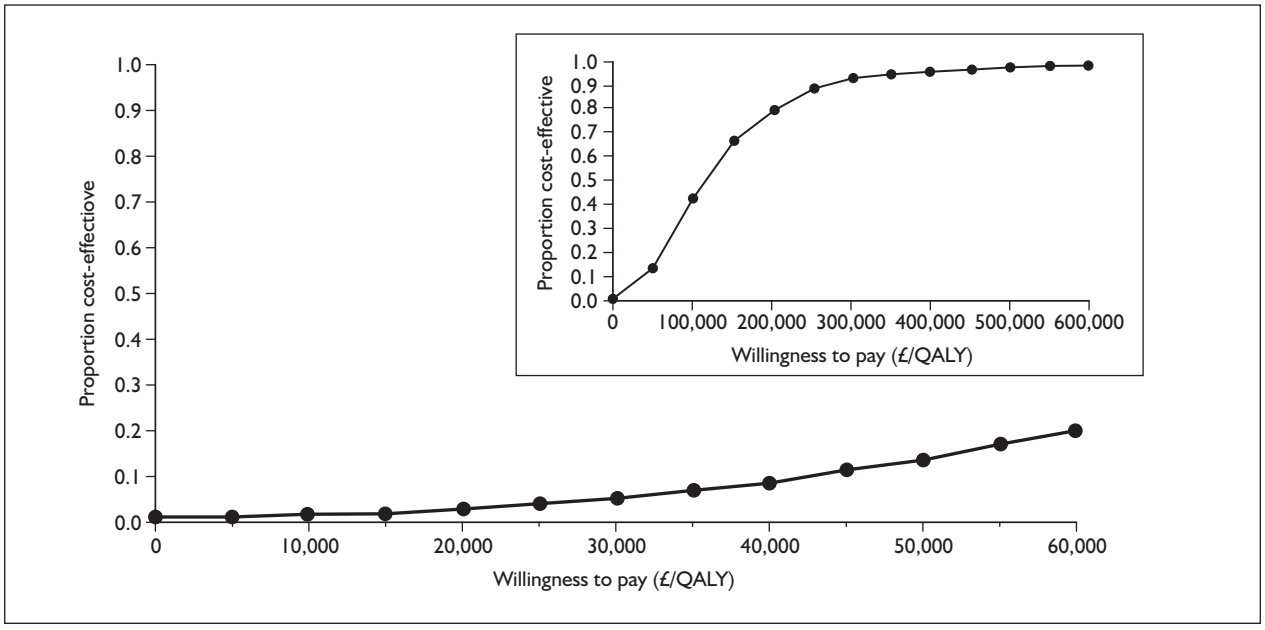

FIGURE 94 *Cost-effectiveness acceptability curve for iloprost versus supportive care, functional class III: alternative health state utility values (Olschewski* et al.*).*[41]

Appendix 12.4 Bosentan with supportive care versus supportive care alone, functional class III

Alternative time horizon

Time horizon of 20 years

TABLE 108 *Bosentan versus supportive care, functional class III: time horizon of 20 years*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	341,000		2.193		
Bosentan	406,000	66,000	5.301	3.108	21,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

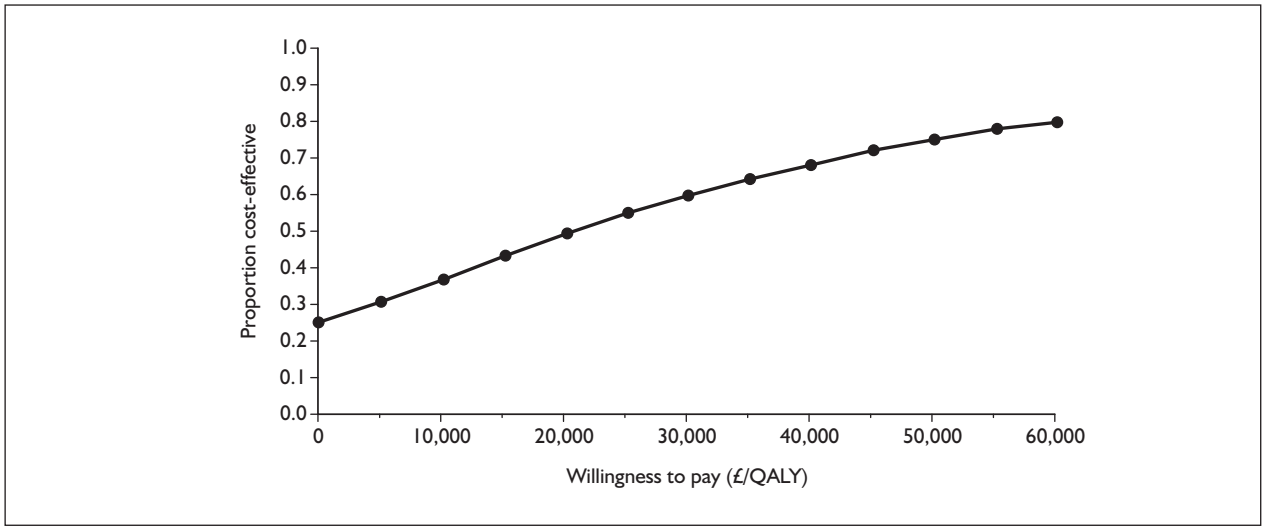

FIGURE 95 *Cost-effectiveness acceptability curve for bosentan versus supportive care, functional class III: time horizon of 20 years. QALY, quality-adjusted life-year.*

Time horizon of 10 years

TABLE 109 *Bosentan versus supportive care, functional class III: time horizon of 10 years*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	304,000		2.063		
Bosentan	296,000	–8,000	4.027	1.964	Dominates

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

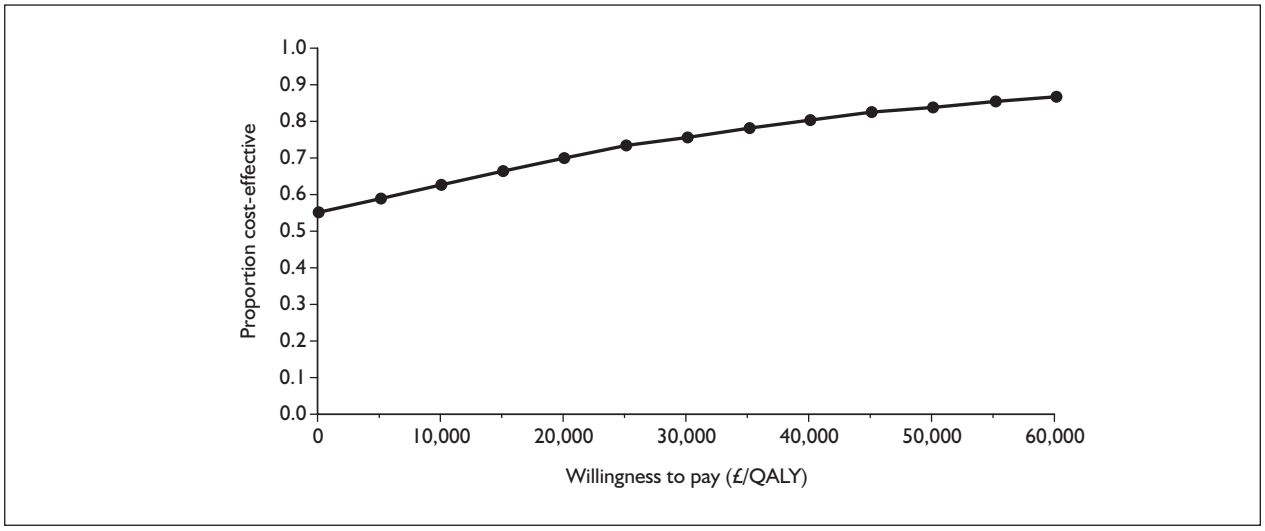

FIGURE 96 *Cost-effectiveness acceptability curve for bosentan versus supportive care, functional class III: time horizon of 10 years. QALY, quality-adjusted life-year.*

Alternative prices

Alternative price for epoprostenol

TABLE 110 *Bosentan versus supportive care, functional class III: alternative price for epoprostenol*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	156,000		2.201		
Bosentan	294,000	137,000	5.696	3.494	39,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

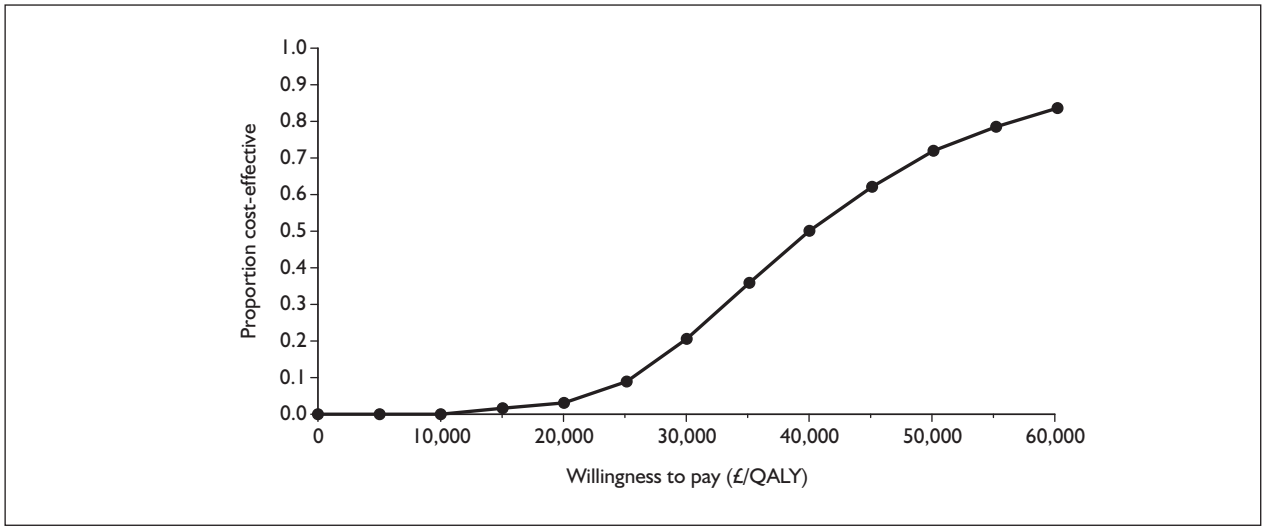

FIGURE 97 *Cost-effectiveness acceptability curve for bosentan versus supportive care, functional class III: alternative price for epoprostenol. QALY, quality-adjusted life-year.*

Alternative health state utility values
Utilities from Meads et al.[94]

TABLE 111 *Bosentan versus supportive care, functional class III: alternative health state utility values (Meads* et al.*)*[94]

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		[Commercial-in-confidence information has been removed]		
Bosentan	436,000	93,000	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

FIGURE 98 *Cost-effectiveness acceptability curve for bosentan versus supportive care, functional class III: alternative health state utility values (Meads* et al.*)*[94]*. [Commercial-in-confidence information has been removed].*

Utilities from Kirsch,[76] 2-year time trade-off

TABLE 112 *Bosentan versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 2-year time trade-off)*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		1.852		
Bosentan	435,000	92,000	5.552	3.700	25,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

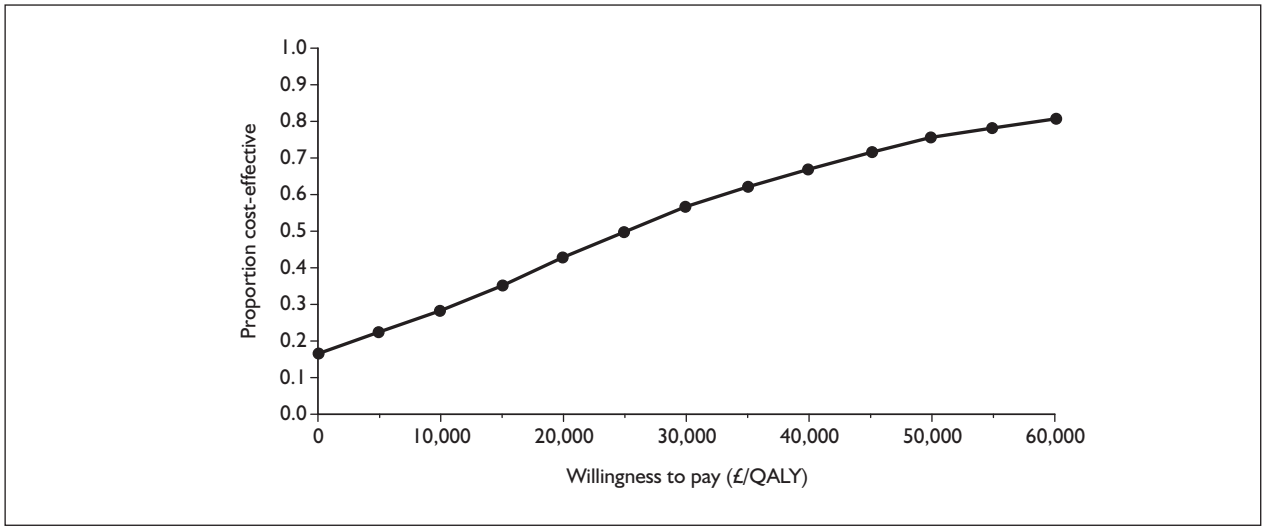

FIGURE 99 *Cost-effectiveness acceptability curve for bosentan versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 2-year time trade-off). QALY, quality-adjusted life-year.*

Utilities from Kirsch,[76] 10 year time trade-off

TABLE 113 *Bosentan versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 10-year time trade-off)*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		1.602		
Bosentan	435,000	92,000	5.151	3.549	26,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

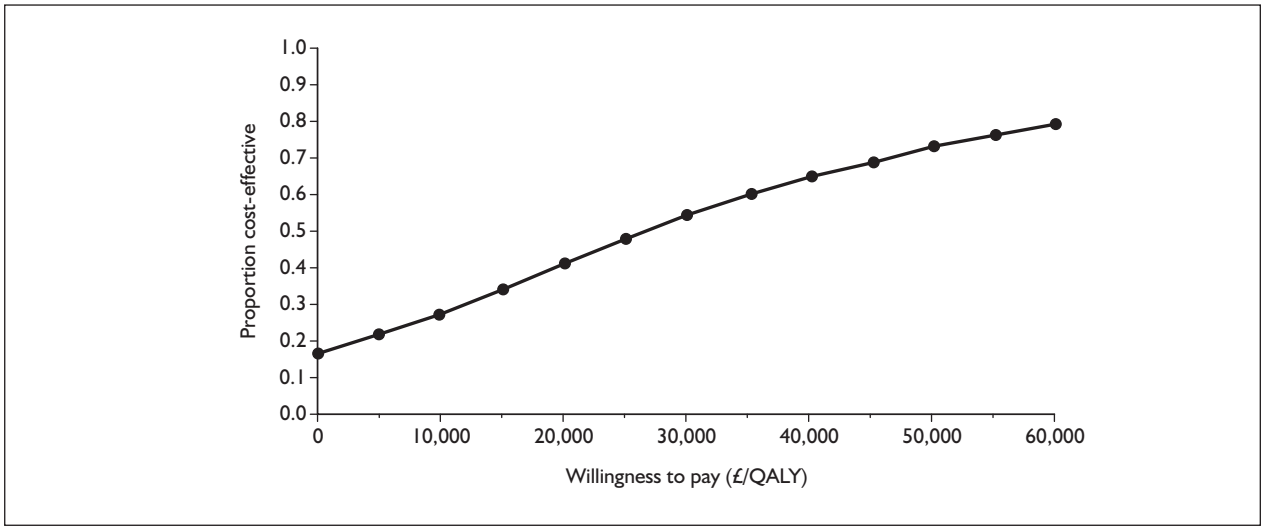

FIGURE 100 *Cost-effectiveness acceptability curve for bosentan versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 10-year time trade-off). QALY, quality-adjusted life-year.*

Utilities from Olschewski et al.[41]

TABLE 114 *Bosentan versus supportive care, functional class III: alternative health state utility values (Olschewski* et al.*)*[41]

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		2.092		
Bosentan	436,000	93,000	5.866	3.774	25,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

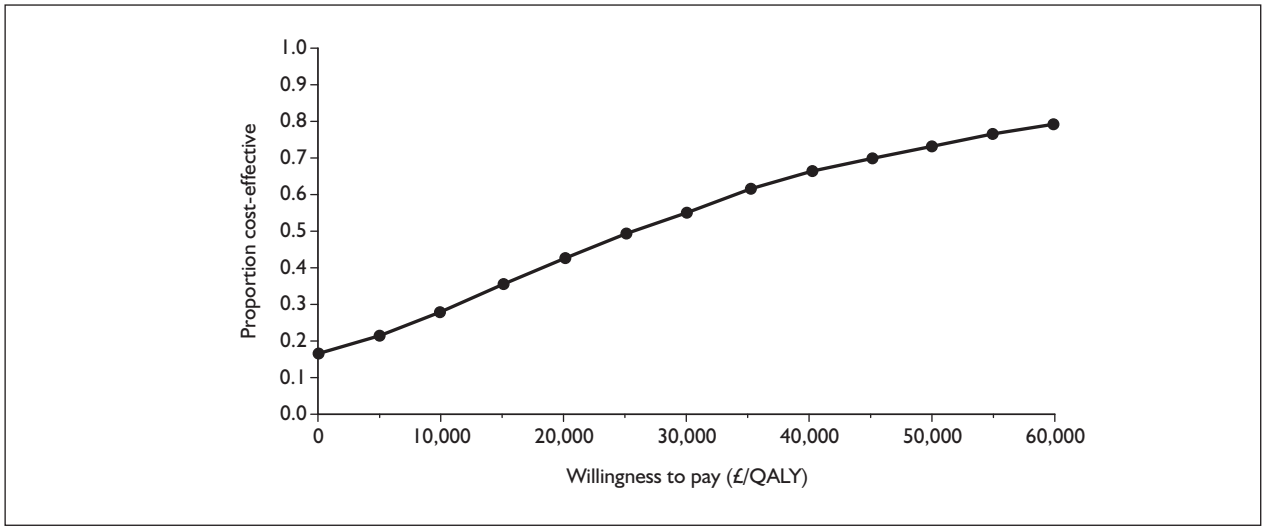

FIGURE 101 *Cost-effectiveness acceptability curve for bosentan versus supportive care, functional class III: alternative health state utility values (Olschewski* et al.*).*[41] *QALY, quality-adjusted life-year.*

Appendix 12.5 Sitaxentan with supportive care versus supportive care alone, functional class III

Alternative time horizon

Time horizon of 20 years

TABLE 115 *Sitaxentan versus supportive care, functional class III: time horizon of 20 years*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	341,000		2.193		
Sitaxentan	393,000	52,000	4.949	2.755	19,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

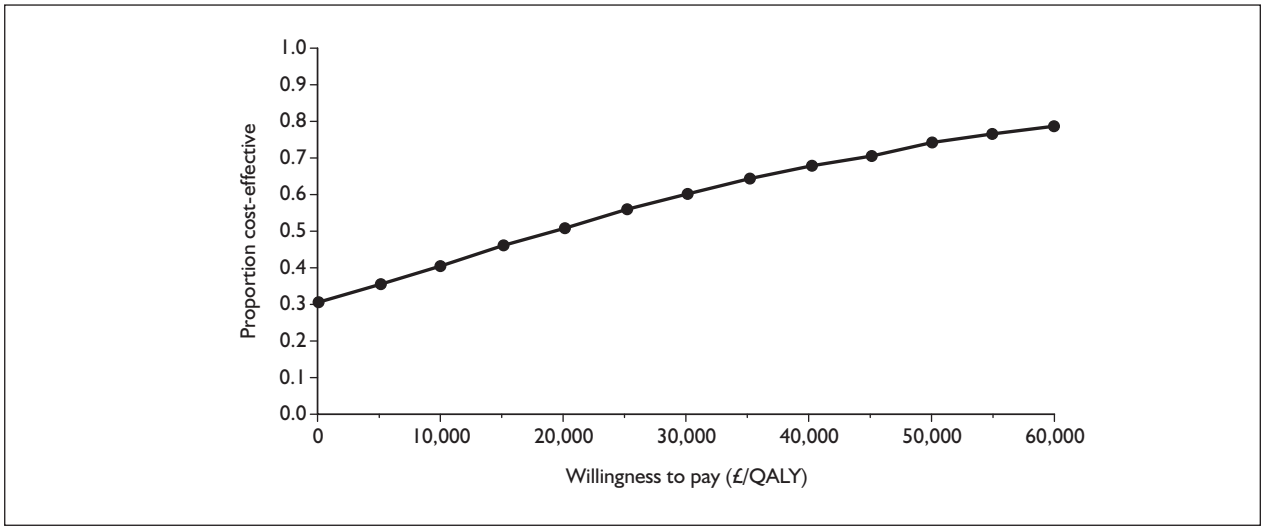

FIGURE 102 *Cost-effectiveness acceptability curve for sitaxentan versus supportive care, functional class III: time horizon of 20 years. QALY, quality-adjusted life-year. QALY, quality-adjusted life-year.*

Time horizon of 10 years

TABLE 116 *Sitaxentan versus supportive care, functional class III: time horizon of 10 years*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	304,000		2.063		
Sitaxentan	293,000	–11,000	3.817	1.754	Dominates

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

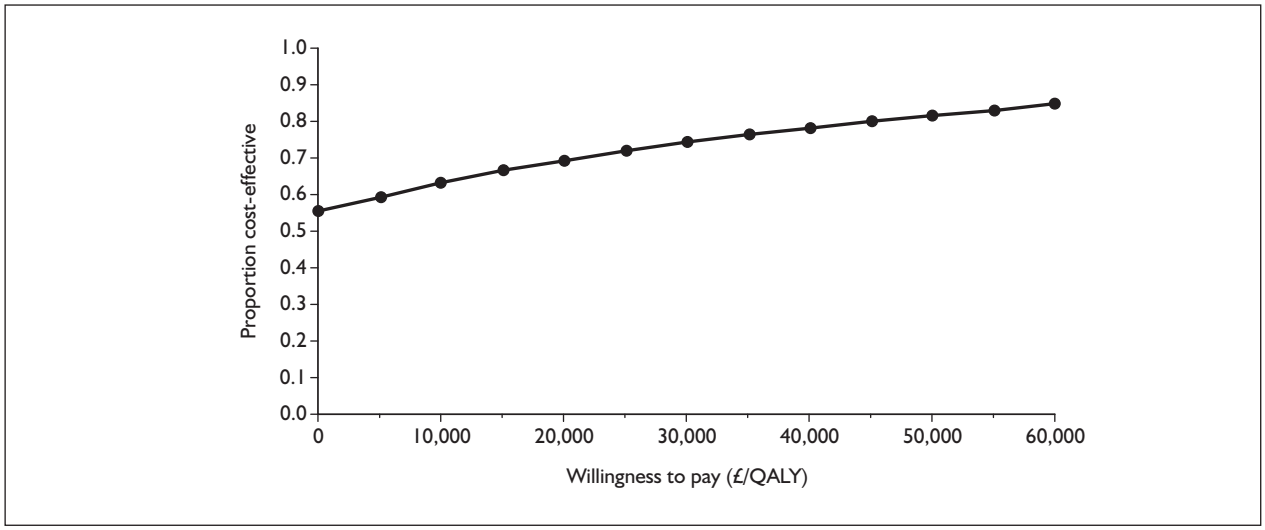

FIGURE 103 *Cost-effectiveness acceptability curve for sitaxentan versus supportive care, functional class III: time horizon of 10 years. QALY, quality-adjusted life-year.*

Alternative prices

Alternative price for epoprostenol

TABLE 117 *Sitaxentan versus supportive care, functional class III: alternative price for epoprostenol*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	156,000		2.201		
Sitaxentan	279,000	122,000	5.289	3.087	40,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

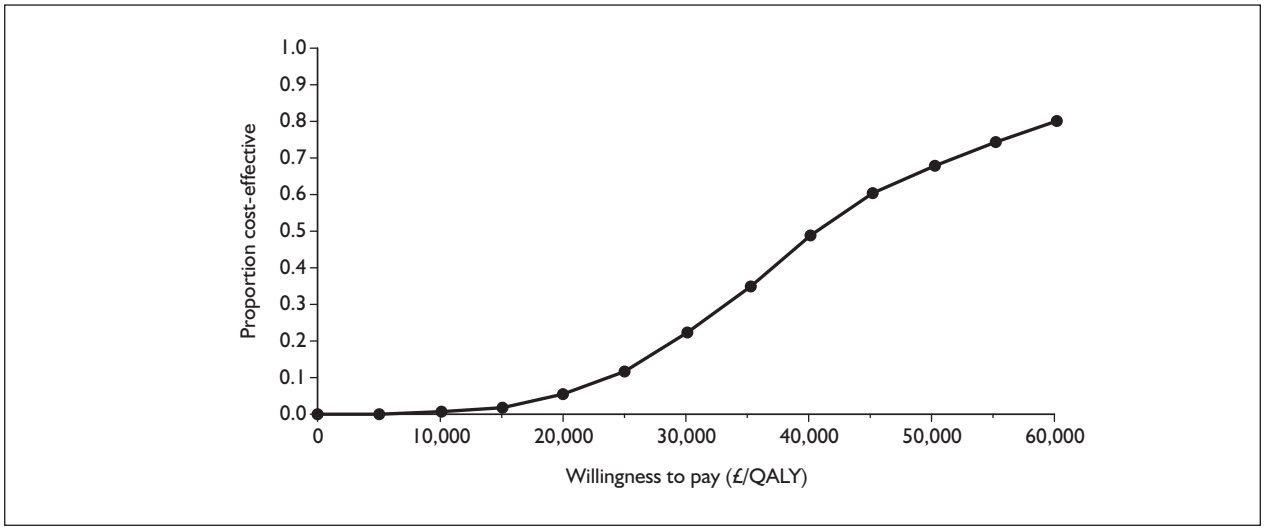

FIGURE 104 *Cost-effectiveness acceptability curve for sitaxentan versus supportive care, functional class III: alternative price for epoprostenol. QALY, quality-adjusted life-year.*

Alternative health state utility values
Utilities from Meads et al.[94]

TABLE 118 *Sitaxentan versus supportive care, functional class III: alternative health state utility values (Meads* et al.*)*[94]

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		[Commercial-in-confidence information has been removed]		
Sitaxentan	419,000	76,000	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

FIGURE 105 *Cost-effectiveness acceptability curve for sitaxentan versus supportive care, functional class III: alternative health state utility values (Meads* et al.*).*[94] *[Commercial-in-confidence information has been removed].*

Utilities from Kirsch,[76] 2-year time trade-off

TABLE 119 *Sitaxentan versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 2-year time trade-off)*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		1.852		
Sitaxentan	418,000	75,000	4.998	3.146	24,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

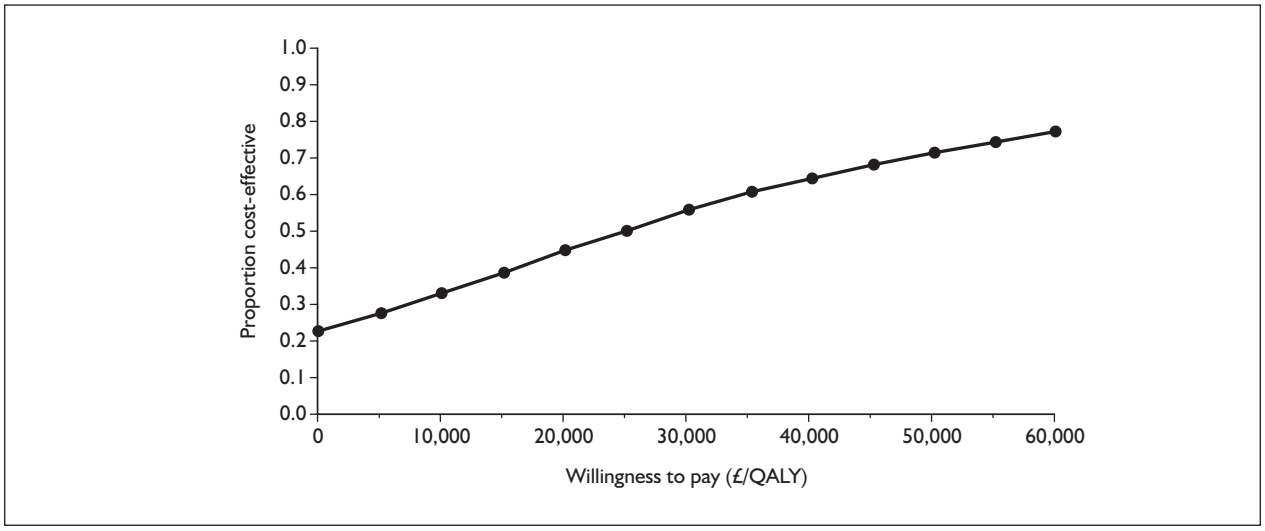

FIGURE 106 *Cost-effectiveness acceptability curve for sitaxentan versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 2-year time trade-off). QALY, quality-adjusted life-year.*

Utilities from Kirsch,[76] 10-year time trade-off

TABLE 120 *Sitaxentan versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 10-year time trade-off)*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		1.602		
Sitaxentan	418,000	75,000	4.600	2.997	25,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

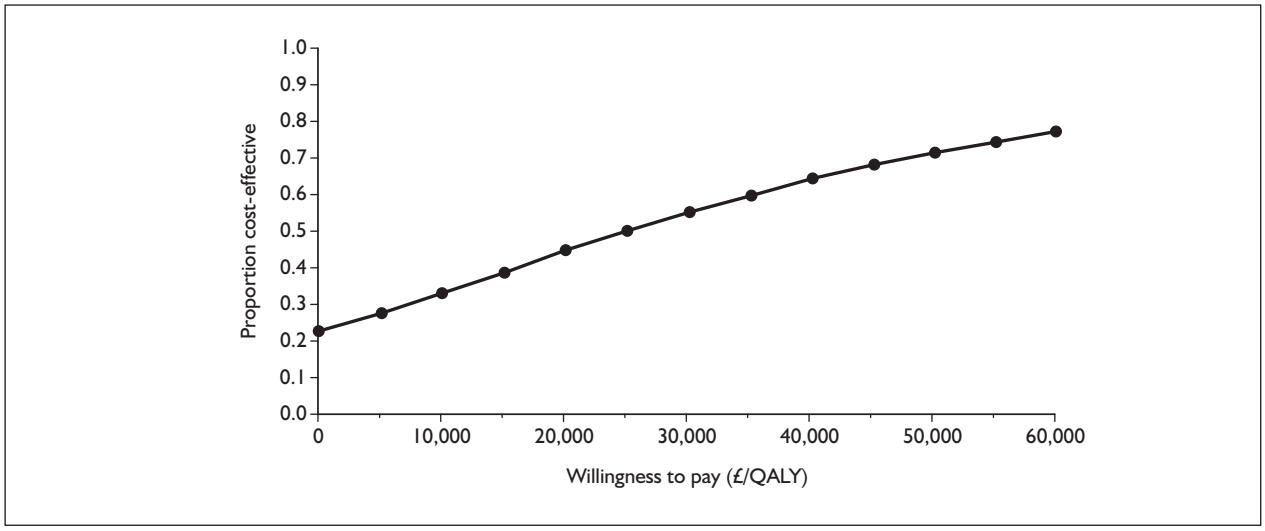

FIGURE 107 *Cost-effectiveness acceptability curve for sitaxentan versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 10-year time trade-off).*

Utilities from Olschewski et al.[41]

TABLE 121 *Sitaxentan versus supportive care, functional class III: alternative health state utility values (Olschewski* et al.*)*[41]

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		2.092		
Sitaxentan	419,000	76,000	5.385	3.294	23,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

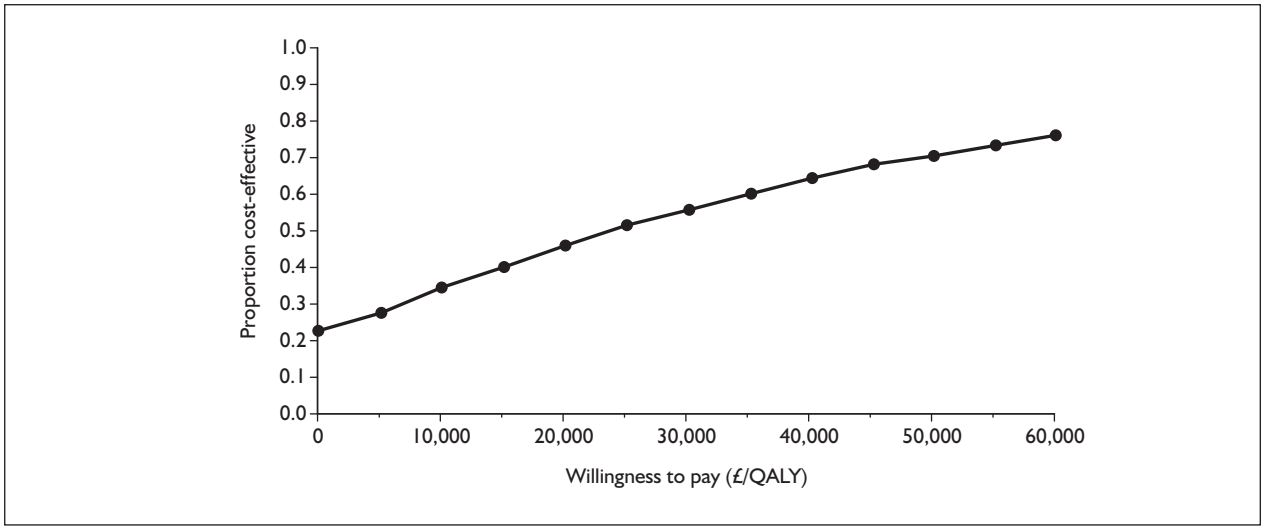

FIGURE 108 *Cost-effectiveness acceptability curve for sitaxentan versus supportive care, functional class III: alternative health state utility values (Olschewski* et al.*).*[41] *QALY, quality-adjusted life-year.*

Appendix 12.6 Sildenafil with supportive care versus supportive care alone, functional class III

Alternative time horizon

Time horizon of 20 years

TABLE 122 *Sildenafil versus supportive care, functional class III: time horizon of 20 years*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	341,000		2.193		
Sildenafil	288,000	–53,000	5.071	2.878	Dominates

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

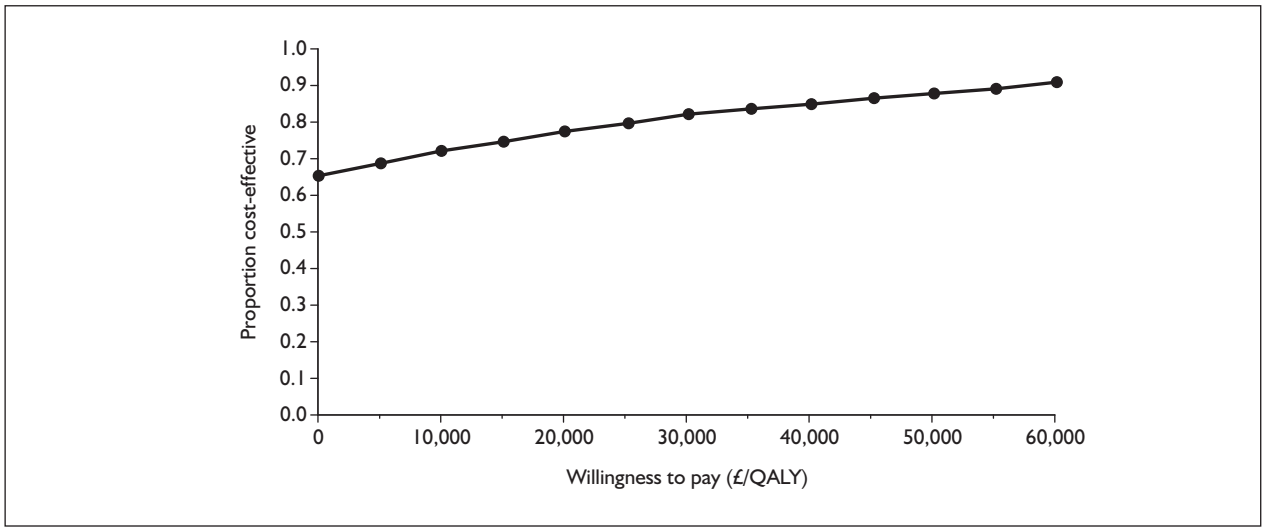

FIGURE 109 *Cost-effectiveness acceptability curve for sildenafil versus supportive care, functional class III: time horizon of 20 years. QALY, quality-adjusted life-year.*

Time horizon of 10 years

TABLE 123 *Sildenafil versus supportive care, functional class III: time horizon of 10 years*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	304,000		2.063		
Sildenafil	209,000	–95,000	3.887	1.823	Dominates

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

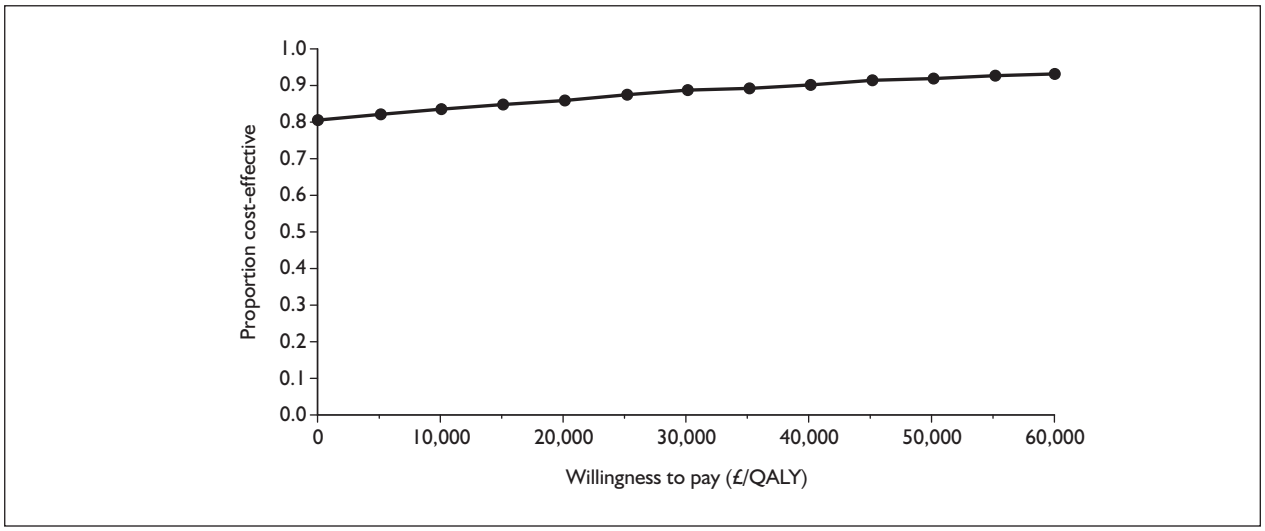

FIGURE 110 *Cost-effectiveness acceptability curve for sildenafil versus supportive care, functional class III: time horizon of 10 years. QALY, quality-adjusted life-year.*

Alternative prices

Alternative price for epoprostenol

TABLE 124 *Sildenafil versus supportive care, functional class III: alternative price for epoprostenol*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	156,000		2.201		
Sildenafil	168,000	12,000	5.436	3.235	3700

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

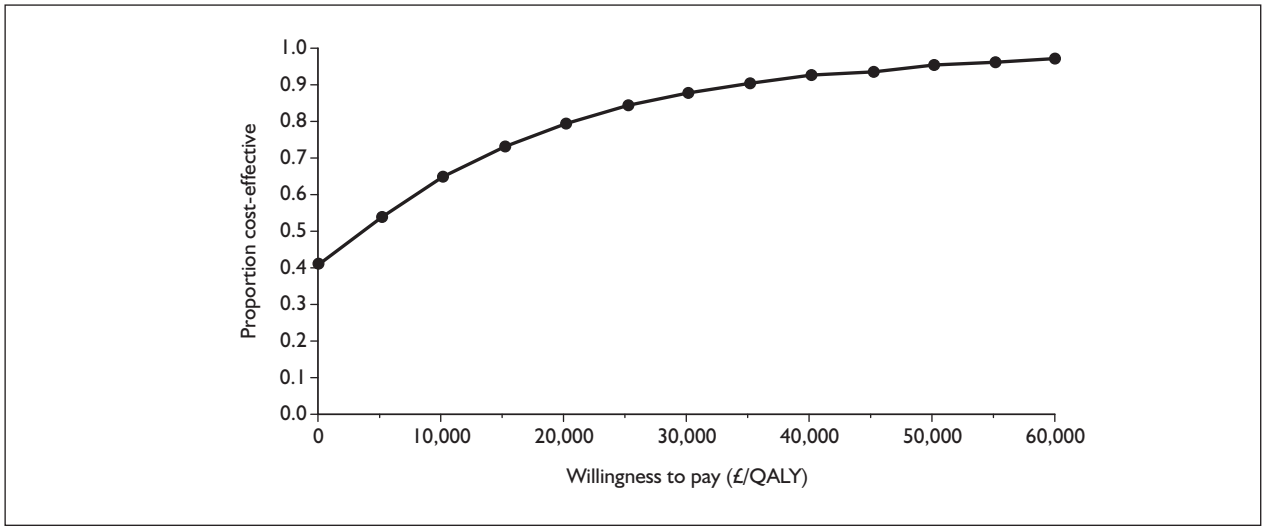

FIGURE 111 *Cost-effectiveness acceptability curve for sildenafil versus supportive care, functional class III: alternative price for epoprostenol. QALY, quality-adjusted life-year.*

Alternative health state utility values
Utilities from Meads et al.[94]

TABLE 125 *Sildenafil versus supportive care, functional class III: alternative health state utility values (Meads* et al.*)*[94]

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		[Commercial-in-confidence information has been removed]		
Sildenafil	307,000	–36,000	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]	[Commercial-in-confidence information has been removed]

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

FIGURE 112 *Cost-effectiveness acceptability curve for sildenafil versus supportive care, functional class III: alternative health state utility values (Meads* et al.*).*[94] *[Commercial-in-confidence information has been removed].*

Utilities from Kirsch,[76] 2-year time trade-off

TABLE 126 *Sildenafil versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 2-year time trade-off)*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		1.852		
Sildenafil	309,000	–34,000	5.228	3.376	Dominates

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

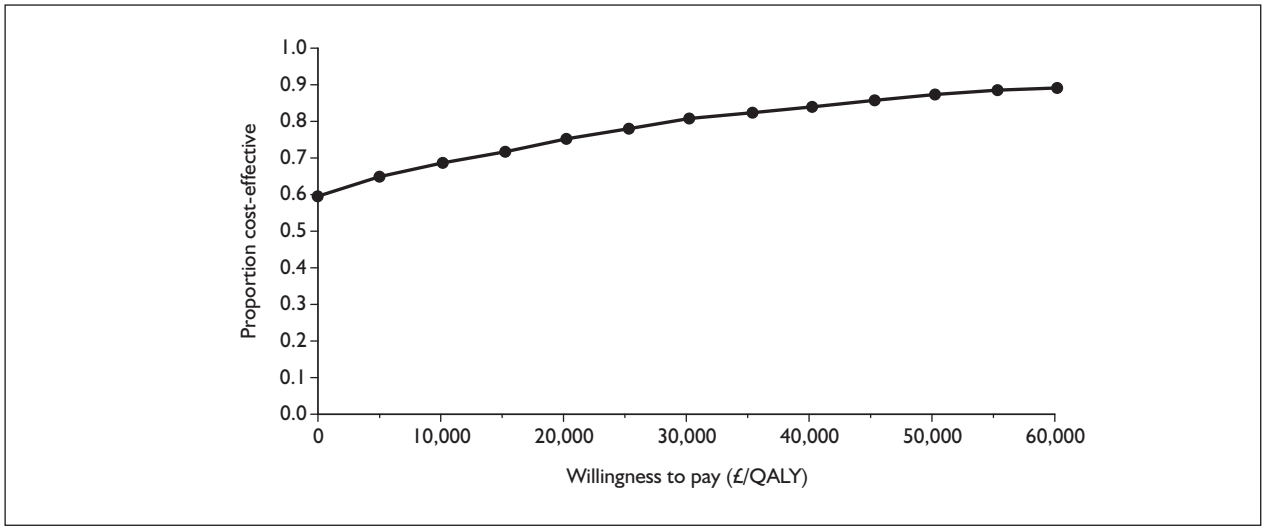

FIGURE 113 *Cost-effectiveness acceptability curve for sildenafil versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 2-year time trade-off). QALY, quality-adjusted life-year.*

Utilities from Kirsch,[76] 2-year time trade-off

TABLE 127 *Sildenafil versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 10-year time trade-off)*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		4.830		
Sildenafil	309,000	–34,000	1.602	3.227	Dominates

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

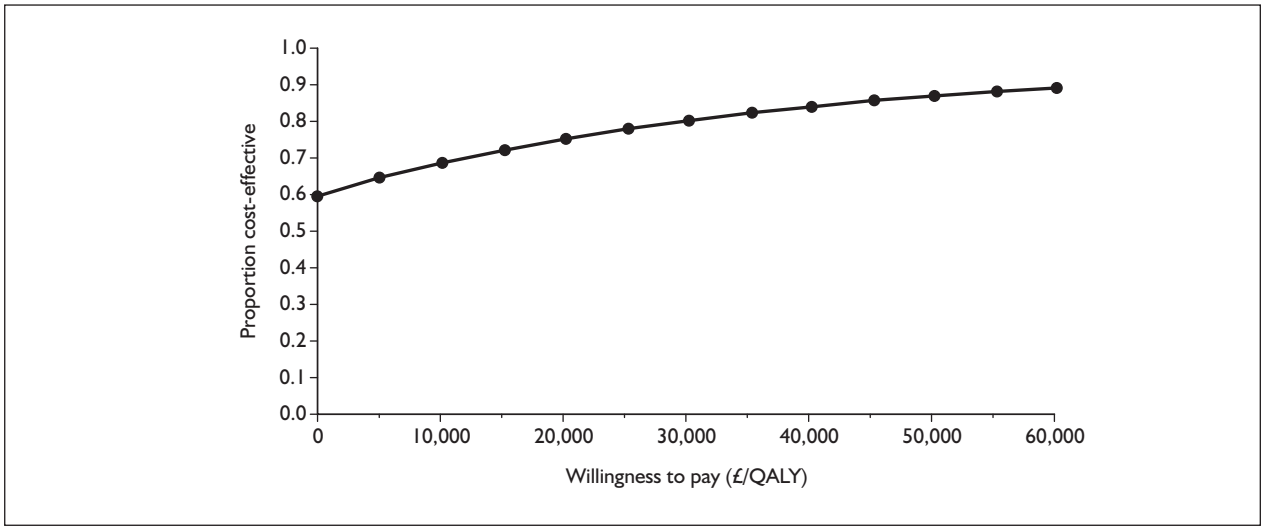

FIGURE 114 *Cost-effectiveness acceptability curve for sildenafil versus supportive care, functional class III: alternative health state utility values (Kirsch,[76] 10-year time trade-off).*

Utilities from Olschewski et al.[41]

TABLE 128 *Sildenafil versus supportive care, functional class III: alternative health state utility values (Olschewski* et al.*)*[41]

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		5.572		
Sildenafil	307,000	–36,000	2.092	3.480	Dominates

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

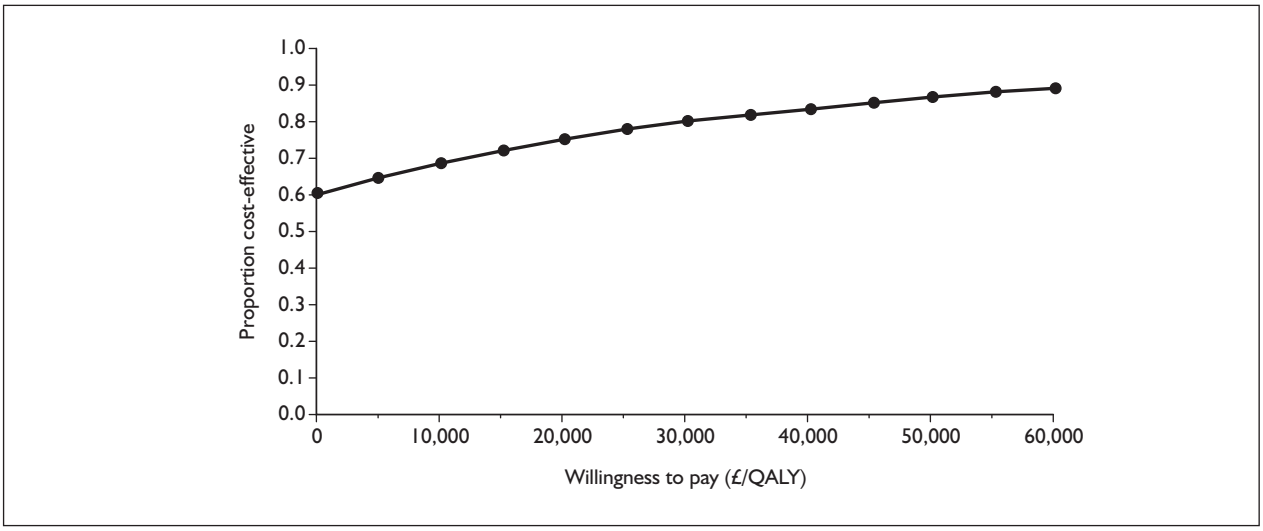

FIGURE 115 *Cost-effectiveness acceptability curve for sildenafil versus supportive care, functional class III: alternative health state utility values (Olschewski* et al.*). QALY, quality-adjusted life-year.*

Appendix 13

Additional analyses requested by the NICE Appraisal Committee

Appendix 13.1 Assuming that patients in functional class IV (for both active treatment and supportive care arms) receive supportive care only (without epoprostenol)

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 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 to the reference case in which 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.

Epoprostenol in addition to supportive care versus supportive care alone, functional class III

Table 129 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 116* 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.

Iloprost with supportive care versus supportive care alone, functional class III

Table 130 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 117* 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.

Bosentan in addition to supportive care versus supportive care alone, functional class III

Table 131 shows the results for bosentan, with the intervention more expensive than supportive

TABLE 129 *Epoprostenol with supportive care versus supportive care alone, functional class III*

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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

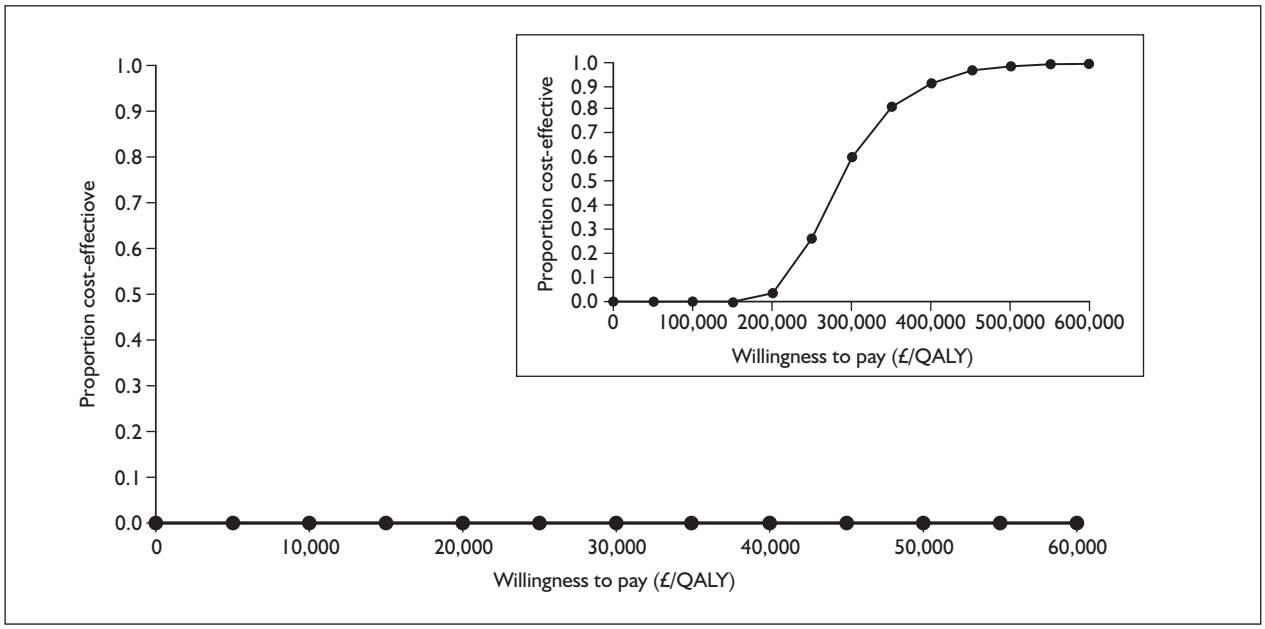

FIGURE 116 *Cost-effectiveness acceptability curve for epoprostenol with supportive care versus supportive care alone, functional class III. Inset graph shows larger x-axis scale. QALY, quality-adjusted life-year.*

TABLE 130 *Iloprost with supportive care versus supportive care alone, functional class III*

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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

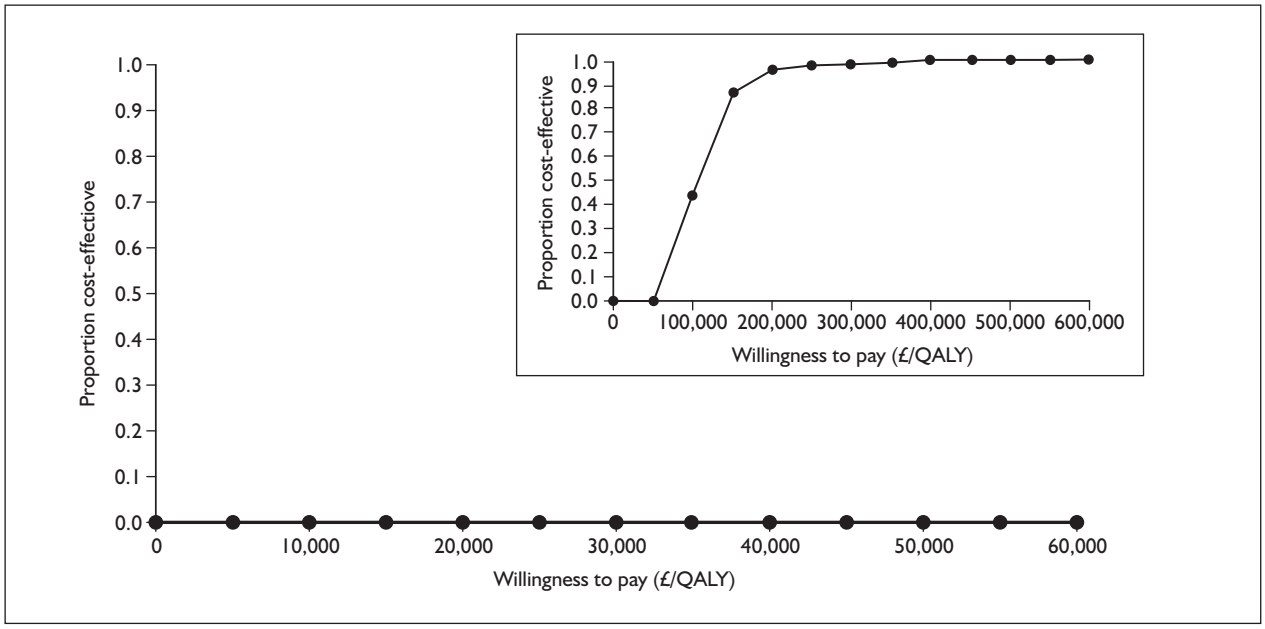

FIGURE 117 *Cost-effectiveness acceptability curve for iloprost with supportive care versus supportive care alone, functional class III. Inset graph shows larger x-axis scale.* QALY, quality-adjusted life-year.

TABLE 131 *Bosentan with supportive care versus supportive care alone, functional class III*

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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

TABLE 132 *Sitaxentan with supportive care versus supportive care alone, functional class III*

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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

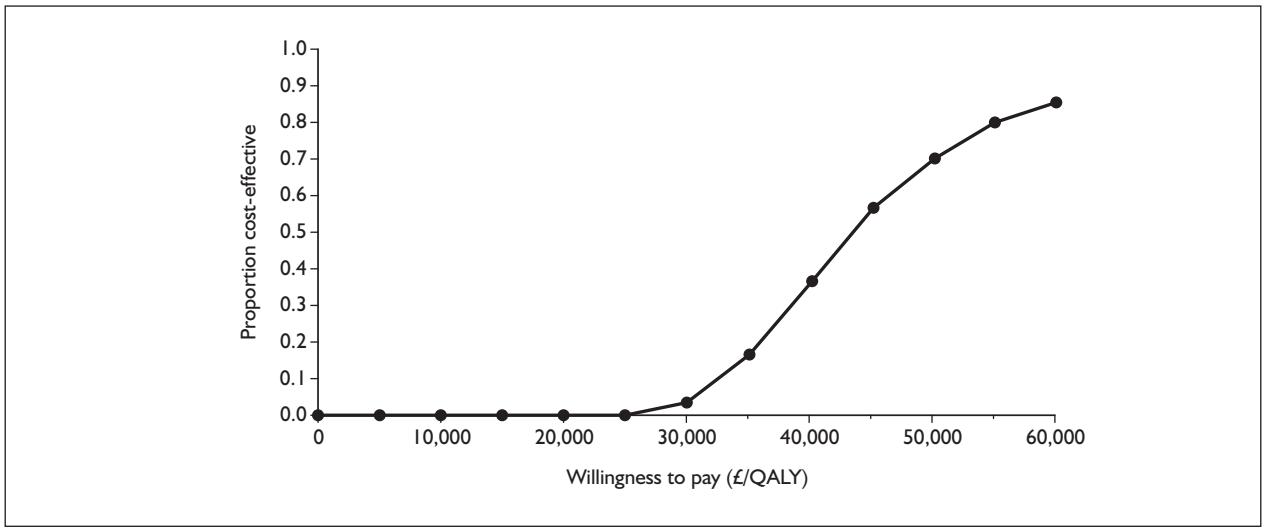

FIGURE 118 *Cost-effectiveness acceptability curve for bosentan with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

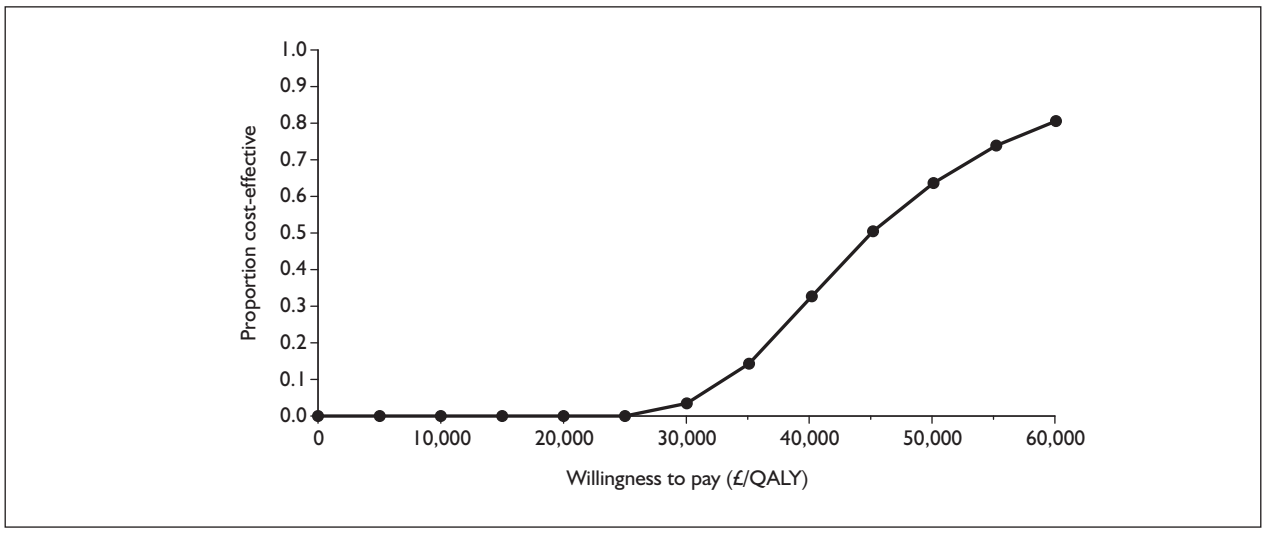

FIGURE 119 *Cost-effectiveness acceptability curve for sitaxentan with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

care alone and producing a greater amount of QALYs, resulting in an ICER of £42,000 per QALY gained. The CEAC in *Figure 118* 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.

Sitaxentan in addition to supportive care versus supportive care alone, functional class III

Table 132 shows the results for sitaxentan, with the intervention more expensive than supportive care alone and producing a greater amount of QALYs, resulting in an ICER of £44,000 per QALY gained. The CEAC presented in *Figure 119* demonstrates that at thresholds of £20,000 and £30,000 per QALY gained, the probability of sitaxentan being cost-effective is 0% and 3% respectively.

Sildenafil in addition to supportive care versus supportive care alone, functional class III

Table 133 shows the results for sildenafil, with the intervention more expensive than supportive care alone and producing a greater amount of QALYs, resulting in an ICER of £9000 per QALY gained. The CEAC presented in *Figure 120* shows that sildenafil has a probability of being cost-effective of 83% at £20,000 per QALY and 92% at £30,000 per QALY.

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 £9000 per QALY gained compared with being dominant in the reference case. The difference in QALYs

TABLE 133 *Sildenafil with supportive care versus supportive care alone, functional class III*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	84,000		1.532		
Sildenafil	115,000	31,000	4.950	3.418	9000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

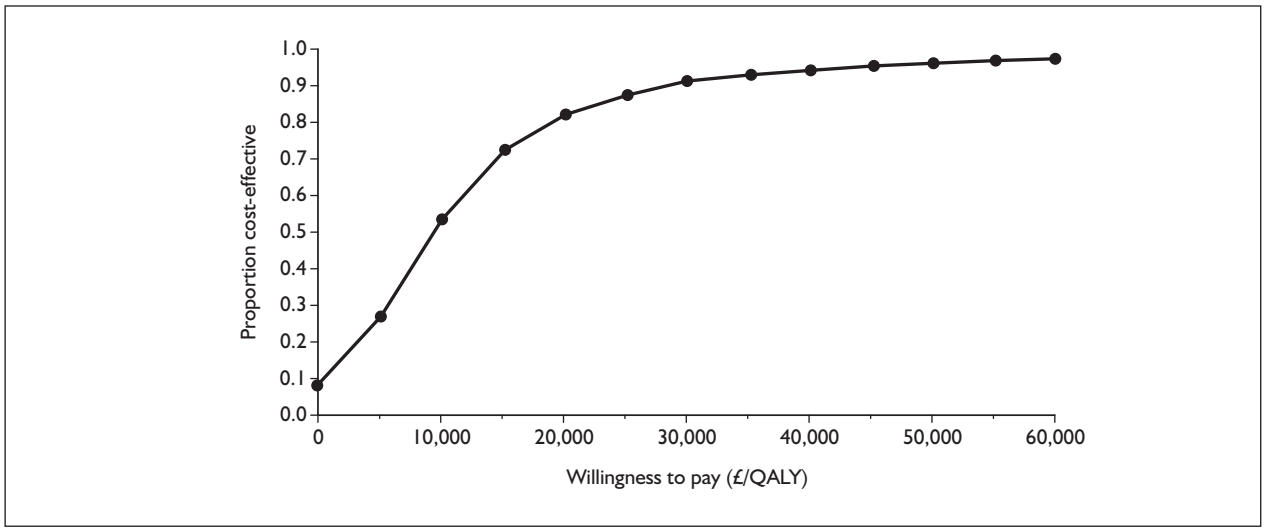

FIGURE 120 *Cost-effectiveness acceptability curve for sildenafil with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

increases; however, the direction on the difference in costs changes and so costs are now greater in the sildenafil arm.

Explanation of results

When comparing treatments that start in FCIII patients, in the reference case the main driver 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 in this arm more patients reach FCIV and they do so quicker compared with the treatment arm (i.e. treatment of FCIII patients reduces progression to FCIV). The supportive care option therefore became relatively cheap. The removal of epoprostenol also meant that there was a greater loss of QALYs (which would be saved by using epoprostenol) in the supportive care arm, but this had less impact on the ICERs than 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.

Appendix 13.2 Assuming that the three oral treatments result in the same mortality rates on treatment and on supportive care as those used for epoprostenol in functional class III

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 are used for epoprostenol in FCIII?

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 rates on treatment and on supportive care as are used for epoprostenol in FCIII.

The data on mortality for epoprostenol (0.021 per cycle, 95% CI 0.017–0.025) and the corresponding data on mortality for supportive care (0.051 per cycle, 95% CI 0.041–0.069) were used in the model, replacing those mortalities used in the reference

TABLE 134 *Bosentan with supportive care versus supportive care alone, functional class III*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	349,000		2.236		
Bosentan	364,000	14,000	4.857	2.620	6000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

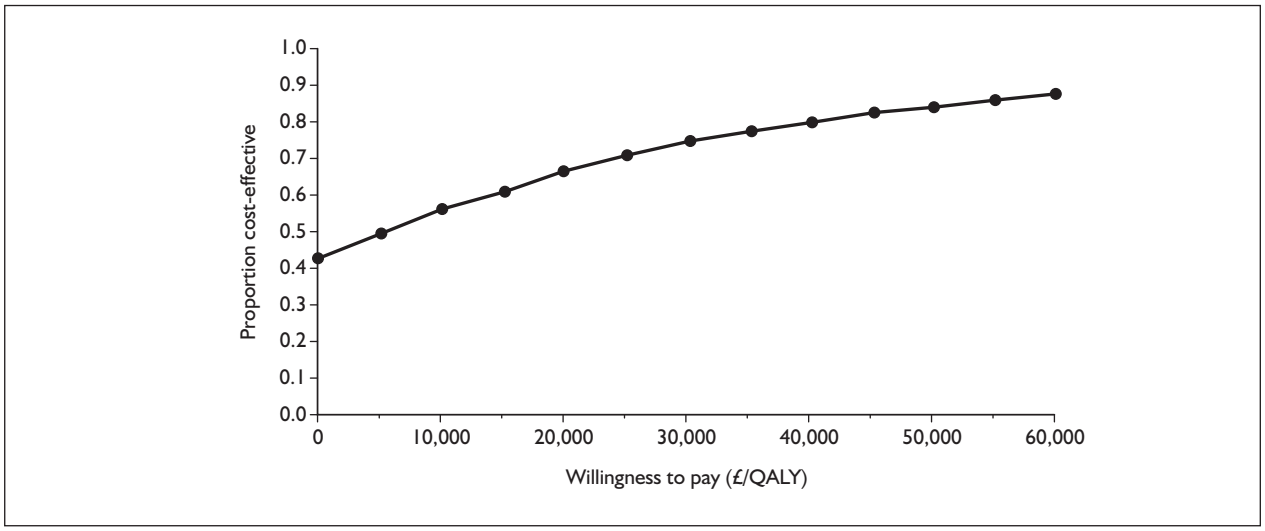

FIGURE 121 *Cost-effectiveness acceptability curve for bosentan with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

case analysis for each intervention (see Appendix 9).

Bosentan in addition to supportive care versus supportive care alone, functional class III

Table 134 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 £6000 per QALY gained. The CEAC presented in *Figure 121* shows that at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, bosentan has a 67% and 75% probability, respectively, of being cost-effective.

Sitaxentan in addition to supportive care versus supportive care alone, functional class III

Table 135 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 £1400 per QALY gained. The CEAC presented in *Figure 122* shows that at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, bosentan has a 67% and 73% probability, respectively, of being cost-effective.

Sildenafil in addition to supportive care versus supportive care alone, functional class III

Compared with supportive care alone, sildenafil is less costly and more effective resulting in dominance for the intervention (*Table 136*). The CEAC presented in *Figure 123* shows that sildenafil has a probability of being cost-effective of 86% at £20,000 per QALY and 89% at £30,000 per QALY.

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 £6000. 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 £1400. Although the difference in QALYs decreases, the difference in costs is now very small.

TABLE 135 *Sitaxentan with supportive care versus supportive care alone, functional class III*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	349,000		2.236		
Sitaxentan	352,000	3000	4.409	2.173	1400

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

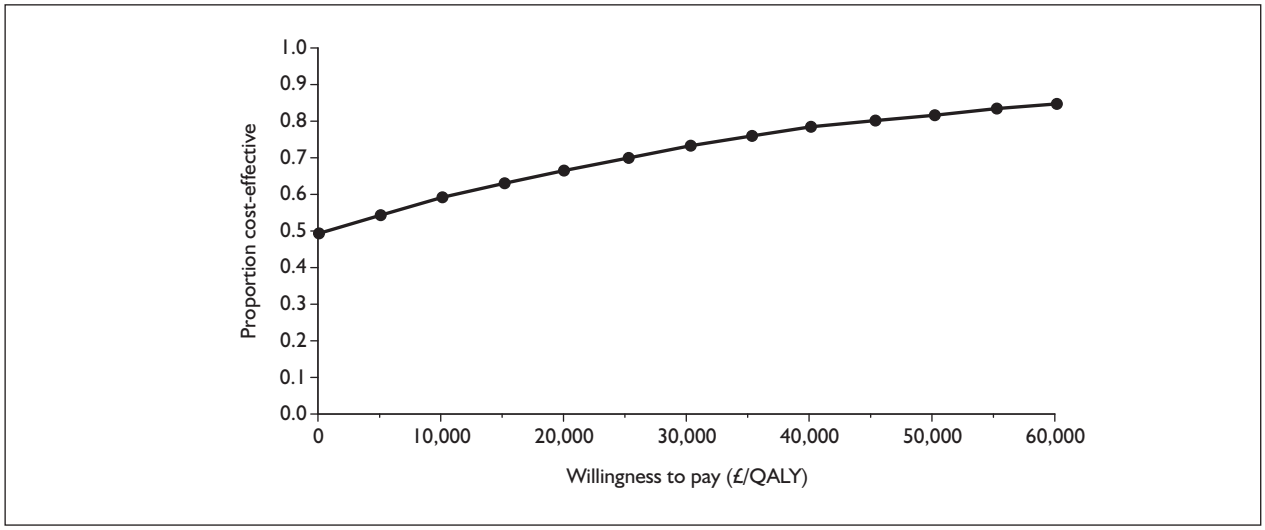

FIGURE 122 *Cost-effectiveness acceptability curve for sitaxentan with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

TABLE 136 *Sildenafil with supportive care versus supportive care alone, functional class III*

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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

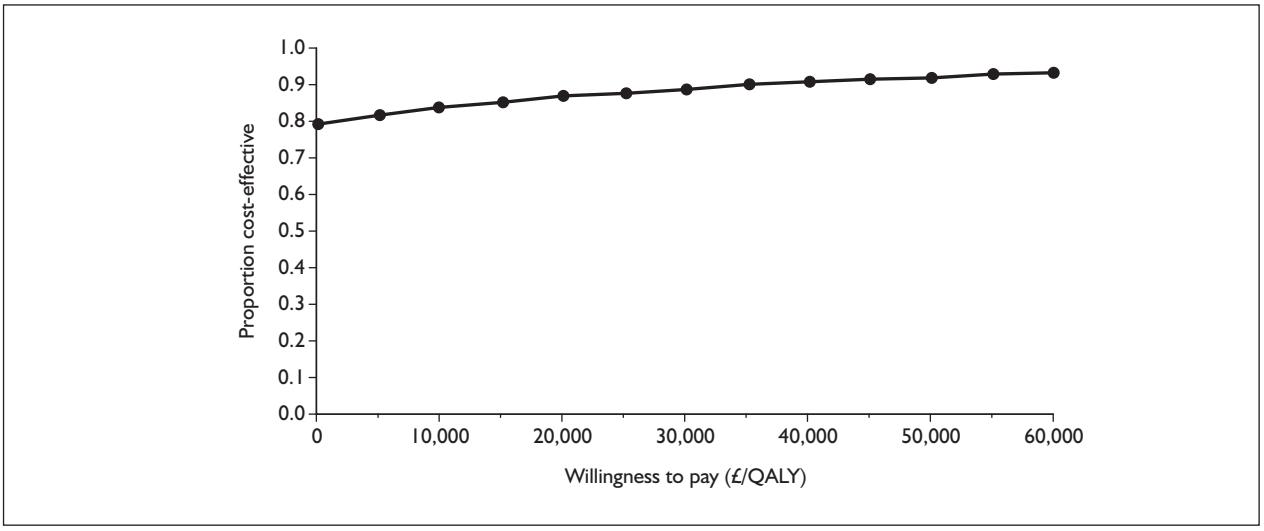

FIGURE 123 *Cost-effectiveness acceptability curve for sildenafil with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

- In both the reference case and this additional analysis, sildenafil is dominant when compared with 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 than in the reference case.

Explanation of results

This sensitivity analysis explored a scenario in which the mortality rate on treatment and the mortality rate on supportive care in FCIII for the three oral treatments are the same as those for epoprostenol, i.e. these treatments offer the same survival benefit and there is no difference in 'baseline mortality' between patients treated with different drugs. Compared with the reference case the mortality rate 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), whereas the mortality rate 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 with the reference case. Although the QALY gain in the oral treatment groups was reduced and the QALY gain in the supportive care arms was slightly increased compared with the reference case the changes in cost appear to have a greater impact than the changes in QALYs.

Appendix 13.3 Exploring the minimal survival benefit required to meet incremental cost-effectiveness thresholds of £20,000, £30,000 and £40,000 per QALY

Question: What would be the minimum survival benefit required for the oral drugs to meet cost-effectiveness thresholds of £20,000, £30,000 and £40,000 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 £20,000, £30,000 and £40,000 per QALY.

Data for mortality on treatment were 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 to determine at what level of survival benefit the oral drugs reached 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 with 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 ratios giving ICERs in the region of £20,000, £30,000 and £40,000 per QALY gained. As can been seen in *Tables 137–139* the ICERs increase (the treatments become less cost-effective) as the survival benefits increase (the odds ratios become smaller).

Explanation of results

The results are consistent with those from the sensitivity analysis described in Appendix 13.2.

TABLE 137 *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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).
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 138 *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	9000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).
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 139 *Results for sildenafil*

Odds ratio	12-week cycle mortality on supportive care[a]	Strategy	Cost (£)[c]	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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).
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.

Both analyses show that by reducing the survival benefit of the active treatment, either by increasing the mortality on treatment (as in Appendix 13.2) or by increasing the odds ratio towards 1 (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 with the reference case, either a smaller proportion of patients in the oral treatment arm survive to reach FCIV (which would incur expensive epoprostenol treatment) or a larger proportion of patients in the supportive care arm survive 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 group was increased compared with the reference case, the changes in costs appear to have a greater impact on the ICERs than the changes in QALYs.

Appendix 13.4 Assuming that no death occurs while patients stay in functional class III

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 five technologies) which assumes that no deaths occur while patients stay in FCIII.

The assessment model was run including the assumption that no PAH-related mortality was

TABLE 140 *Epoprostenol with supportive care versus supportive care alone, functional class III*

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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

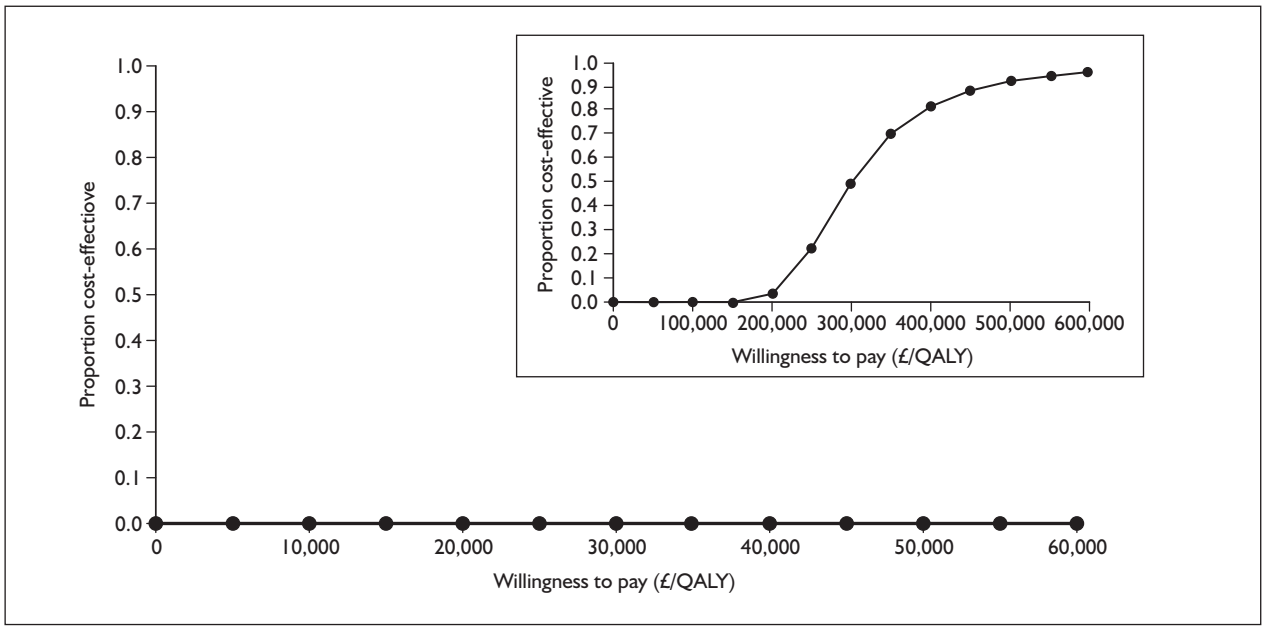

FIGURE 124 *Cost-effectiveness acceptability curve for epoprostenol with supportive care versus supportive care alone, functional class III. Inset graph shows larger x-axis scale. QALY, quality-adjusted life-year.*

possible in FCIII; patients had to be in FCIV before this type of mortality was possible.

Epoprostenol in addition to supportive care versus supportive care alone, functional class III

Table 140 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 124* 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.

Epoprostenol in addition to supportive care versus supportive care alone, functional class IV

Table 141 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 125* 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.

Iloprost with supportive care versus supportive care alone, functional class III

Table 142 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 126* 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.

Bosentan in addition to supportive care versus supportive care alone, functional class III

Table 143 shows the results for bosentan, with the intervention less expensive than supportive

TABLE 141 *Epoprostenol with supportive care versus supportive care alone, functional class IV*

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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

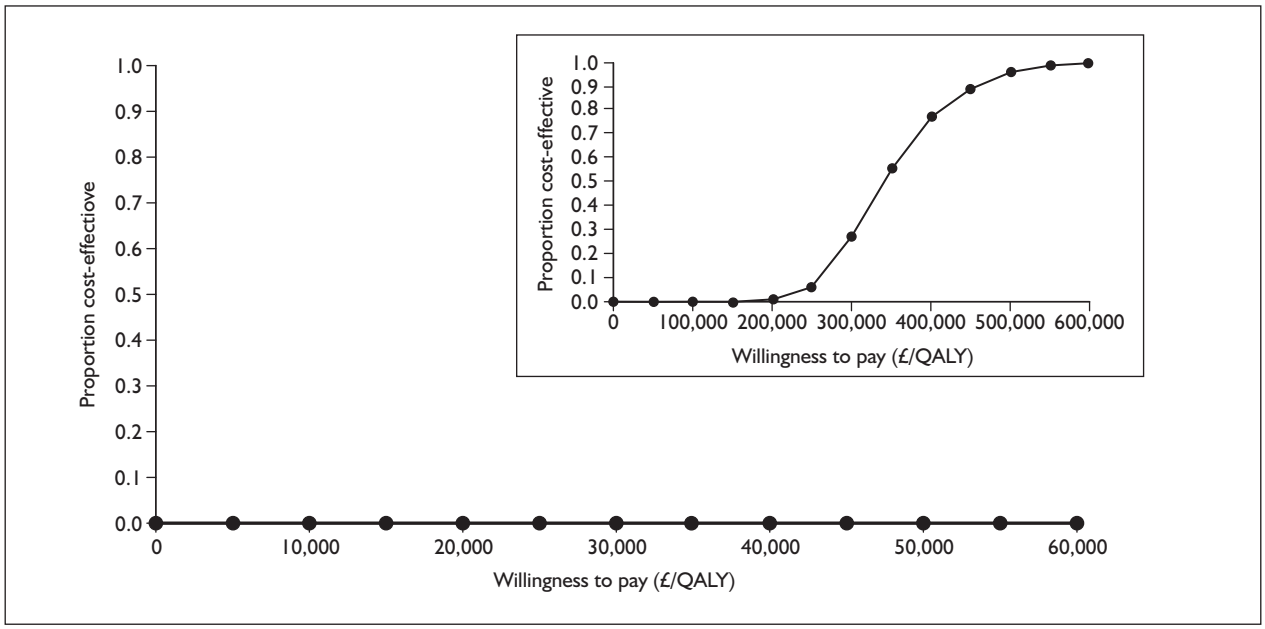

FIGURE 125 *Cost-effectiveness acceptability curve for epoprostenol with supportive care versus supportive care alone, functional class IV. Inset graph shows larger x-axis scale. QALY, quality-adjusted life-year.*

TABLE 142 *Iloprost with supportive care versus supportive care alone, functional class III*

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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

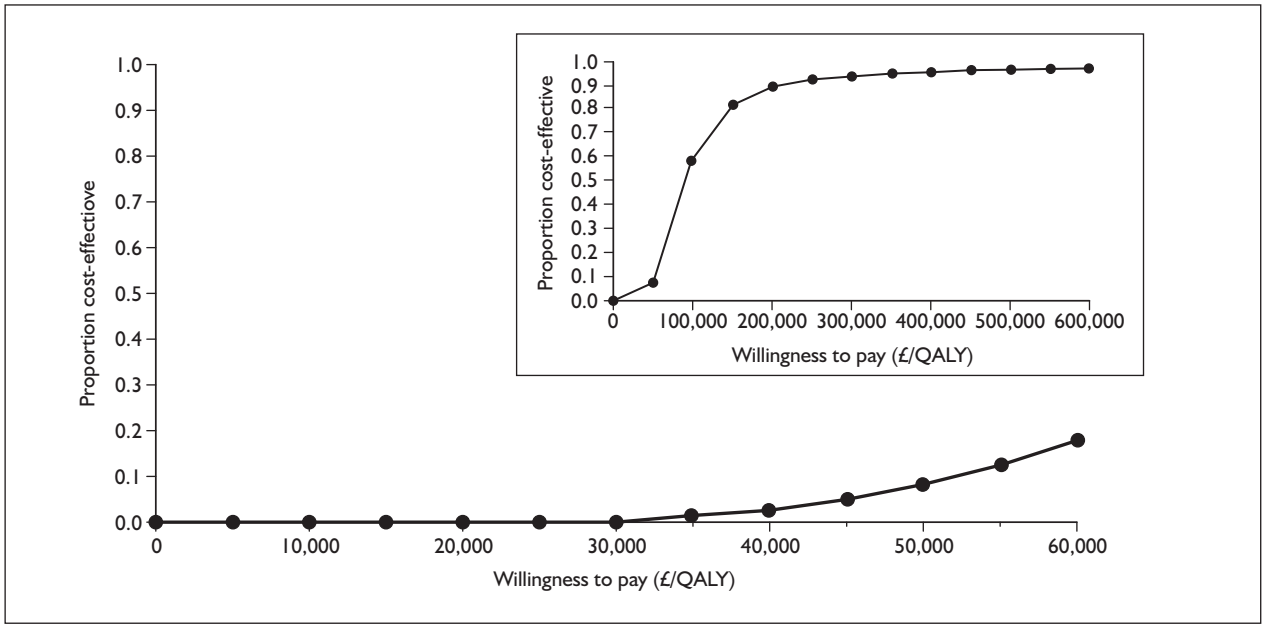

FIGURE 126 *Cost-effectiveness acceptability curve for iloprost with supportive care versus supportive care alone, functional class III. Inset graph shows larger x-axis scale. QALY, quality-adjusted life-year.*

care alone and producing a greater amount of QALYs, resulting in bosentan being dominant over supportive care. The CEAC in *Figure 127* 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.

Sitaxentan in addition to supportive care versus supportive care alone, functional class III

Table 144 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 128* demonstrates that at thresholds of £20,000 and £30,000 per QALY gained, the probability of sitaxentan being cost-effective is 79% and 85% respectively.

Sildenafil in addition to supportive care versus supportive care alone, functional class III

Table 145 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 129* shows that sildenafil has a probability of being cost-effective of 98% at both £20,000 and £30,000 per QALY.

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.

TABLE 143 *Bosentan with supportive care versus supportive care alone, functional class III*

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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

TABLE 144 *Sitaxentan with supportive care versus supportive care alone, functional class III*

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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

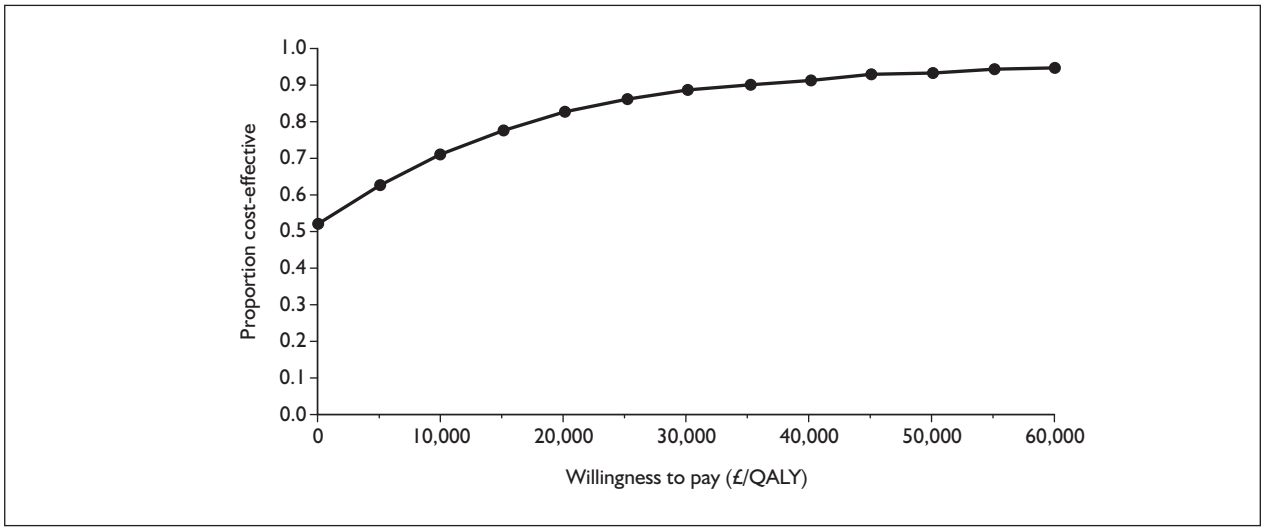

FIGURE 127 *Cost-effectiveness acceptability curve for bosentan with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

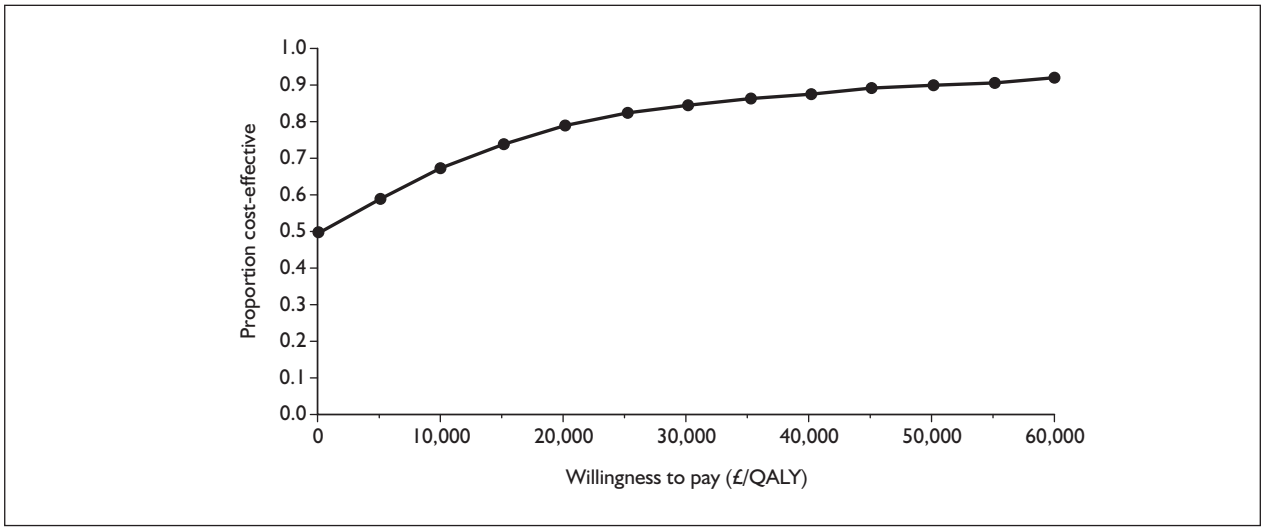

FIGURE 128 *Cost-effectiveness acceptability curve for sitaxentan with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

TABLE 145 *Sildenafil with supportive care versus supportive care alone, functional class III*

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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

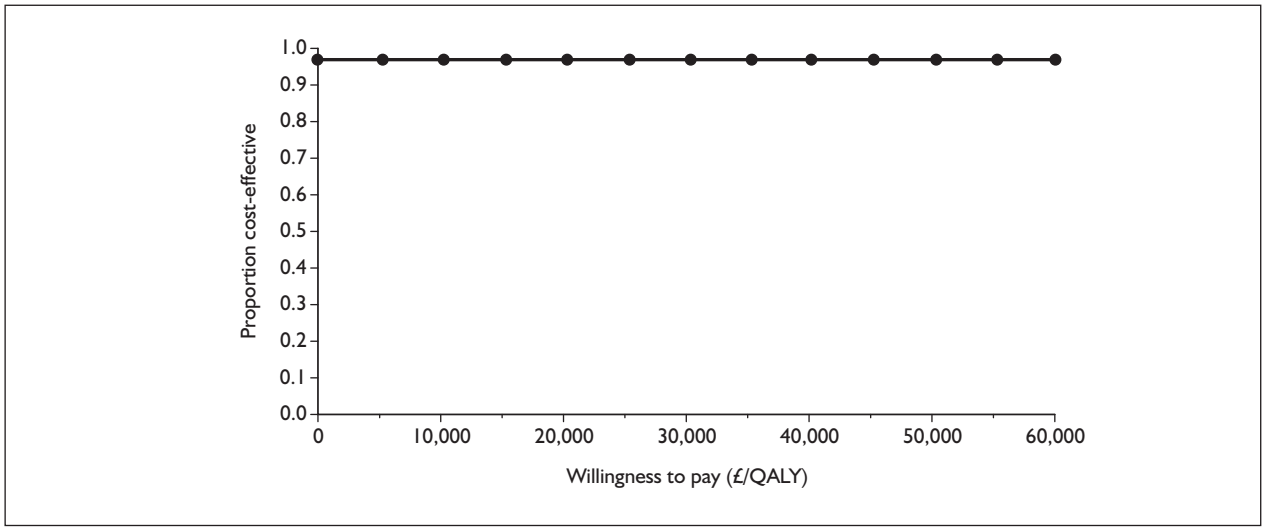

FIGURE 129 *Cost-effectiveness acceptability curve for sildenafil with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

- 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 differences in costs and 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 compared with supportive care; however, the probability of sildenafil being cost-effective at thresholds of £20,000 and £30,000 per QALY gained is greater in this additional analysis.

Explanation of results

In this extreme analysis in which patients cannot die from PAH-related causes in FCIII the oral therapies become much more cost-effective.

In the reference case the mortality rates on individual treatments for patients in FCIII were obtained from observational studies. In these studies patients started treatment in FCIII and were followed up for a certain period of time (e.g. 1 year or 3 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). The estimated PAH-specific mortality assumed that all of 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 the associated cost of epoprostenol treatment) before death. The mortality on treatment for FCIII patients in the model might therefore have been overestimated as some of the deaths would have been accounted for through deterioration to FCIV and subsequent death in this FC.

Because of the lack of data it is not clear what proportion of patients would die 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 a greater QALY gain for the supportive care arm because of a proportionately greater reduction in mortality for this arm than for the active treatment arm under this assumption, but the impact due to changes in costs outweighs the impact due to changes in QALYs.

Appendix 13.5 Assuming that patients on supportive care alone in functional class IV receive only intermittent care rather than hospitalisation until death

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 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, whereas 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 that for all of the other analyses 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 that altering the assumption regarding continuous hospitalisation would impact on analysis is in the additional analysis presented in Appendix 13.1 in which 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.

Alternative supportive care costs in FCIV: epoprostenol available in functional class IV

Epoprostenol in addition to supportive care versus supportive care alone, functional class IV

Table 146 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 130* 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.

Alternative supportive care costs in FCIV: supportive care only in functional class IV

Epoprostenol in addition to supportive care versus supportive care alone, functional class III

Table 147 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 131* 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.

Iloprost in addition to supportive care versus supportive care alone, functional class III

Table 148 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*

TABLE 146 *Epoprostenol with supportive care versus supportive care alone, functional class IV*

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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

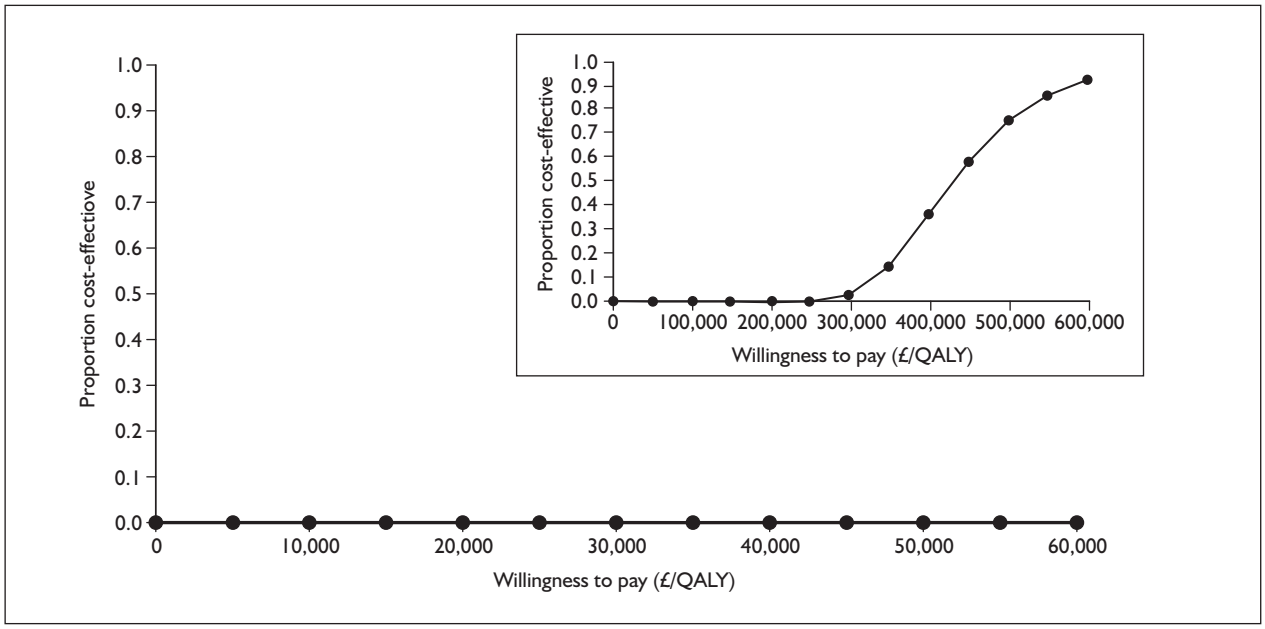

FIGURE 130 *Cost-effectiveness acceptability curve for epoprostenol with supportive care versus supportive care alone, functional class IV. Inset graph shows larger x-axis scale. QALY, quality-adjusted life-year.*

132 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.

Bosentan in addition to supportive care versus supportive care alone, functional class III

Table 149 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 133* demonstrates that bosentan has a zero probability of being cost-effective at both £20,000 and £30,000 per QALY gained.

Sitaxentan in addition to supportive care versus supportive care alone, functional class III

Table 150 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 134* 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.

Sildenafil in addition to supportive care versus supportive care alone, functional class III

Table 151 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 135* 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.

Summary of results

Comparison with the reference case

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

TABLE 147 *Epoprostenol with supportive care versus supportive care alone, functional class III*

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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

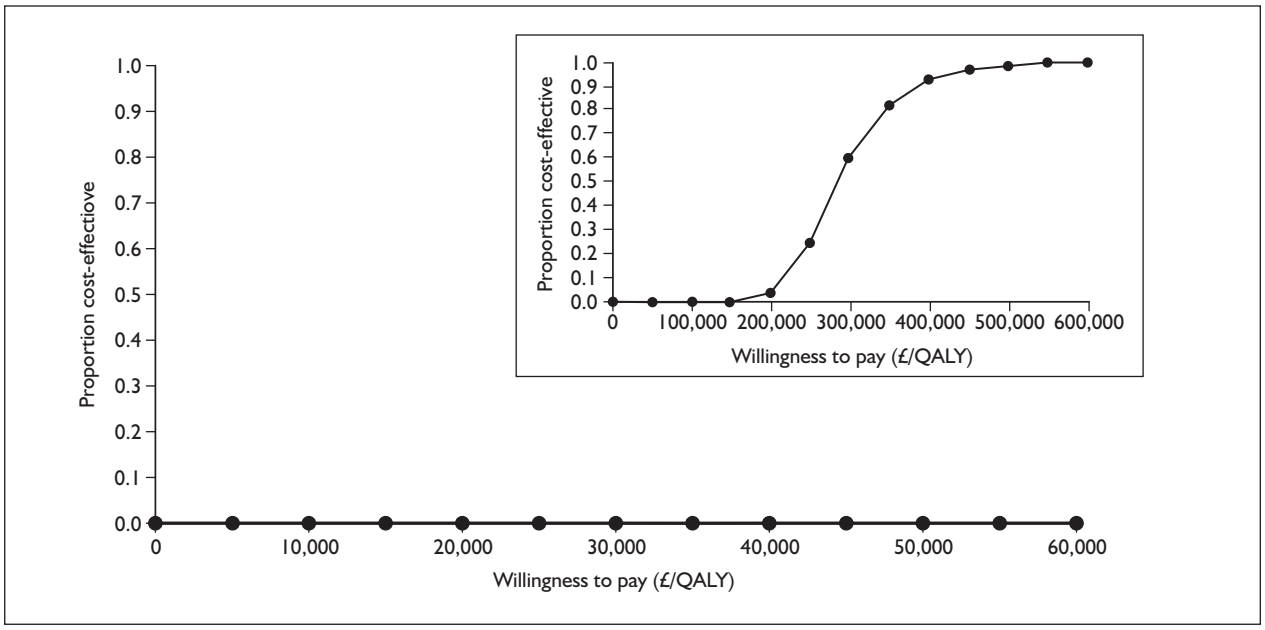

FIGURE 131 *Cost-effectiveness acceptability curve for epoprostenol with supportive care versus supportive care alone, functional class III. Inset graph shows larger x-axis scale. QALY, quality-adjusted life-year.*

Comparison of results with analysis in which epoprostenol is not available in functional class IV (Appendix 13.1)

- The ICER for epoprostenol in FCIII increases from £273,000 per QALY gained to £278,000 per QALY gained as the difference in costs increases very slightly.
- The ICER for iloprost increases marginally from £98,000 per QALY gained to £99,000 per QALY gained as the difference in costs increases very slightly.
- The result for bosentan increases from an ICER of £42,000 per QALY gained to £46,000 per QALY gained as there is a rise in the difference in costs.
- The result for bosentan increases from an ICER of £44,000 per QALY gained to £48,000 per QALY gained as there is a rise in the difference in costs.
- The ICER for sildenafil increases from £9000 per QALY gained to £13,000 per QALY gained, again because the difference in costs increases.

Explanation of results

As explained at the beginning of this section this sensitivity analysis is applicable only 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 with the results of the additional analysis described in Appendix 13.1. This is because the differential costs between treatment options accrued in FCIV under these scenarios (without epoprostenol) were small compared with the differential costs accrued in FCIII (costs of active treatment versus costs of supportive care), which drive the ICERs.

TABLE 148 *Iloprost with supportive care versus supportive care alone, functional class III*

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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

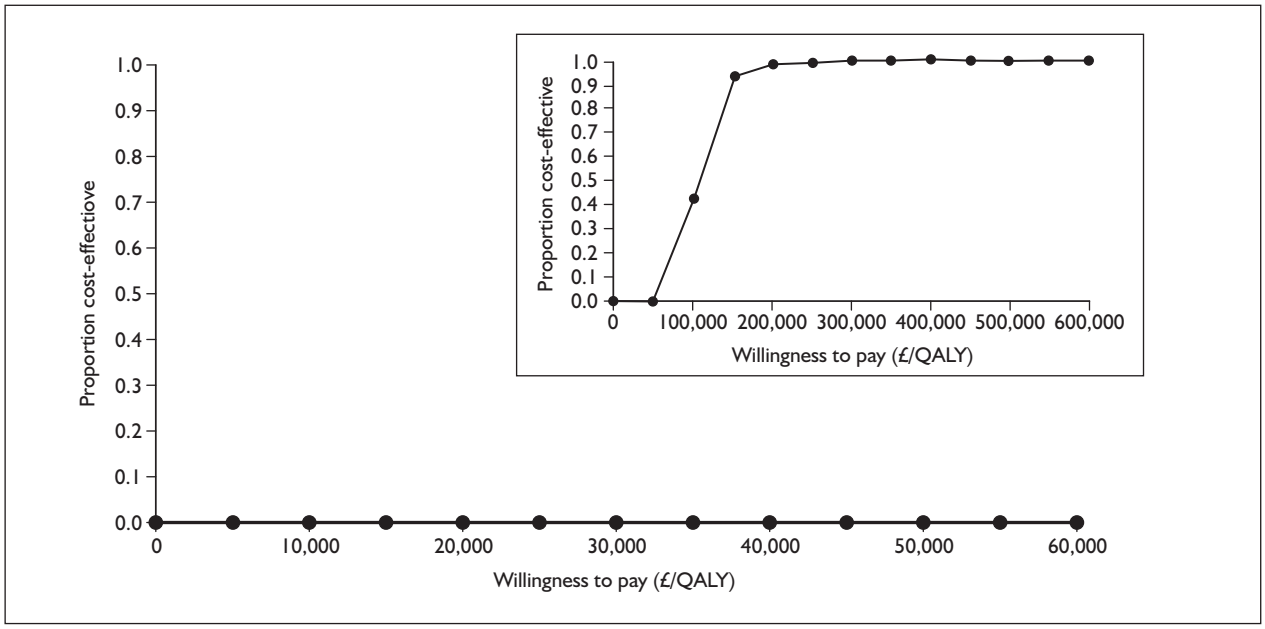

FIGURE 132 *Cost-effectiveness acceptability curve for iloprost with supportive care versus supportive care alone, functional class III. Inset graph shows larger x-axis scale. QALY, quality-adjusted life-year.*

TABLE 149 *Bosentan with supportive care versus supportive care alone, functional class III*

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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

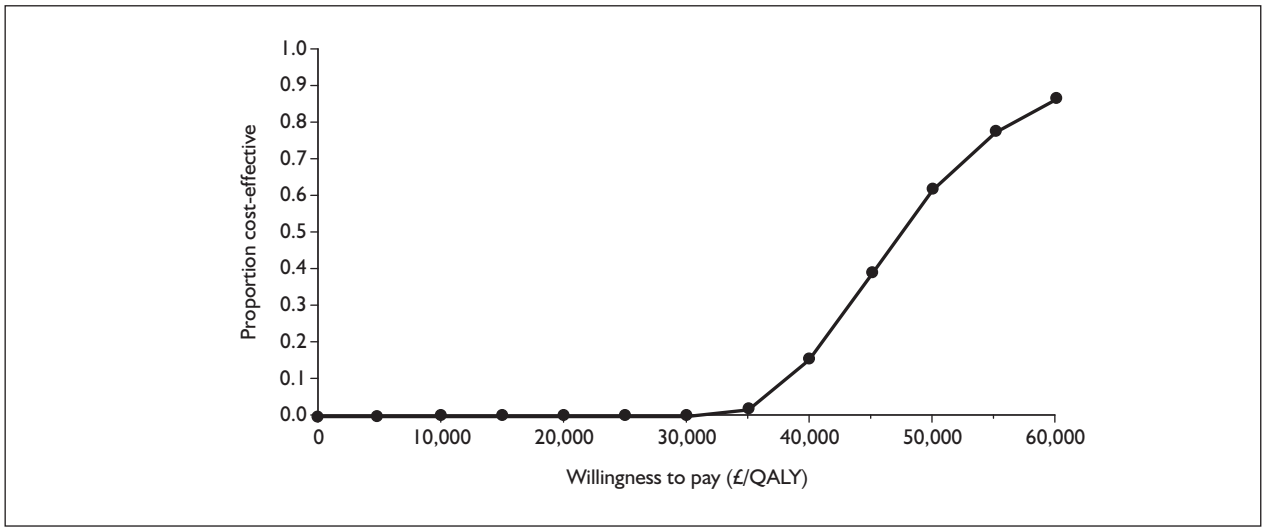

FIGURE 133 *Cost-effectiveness acceptability curve for bosentan with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

TABLE 150 *Sitaxentan with supportive care versus supportive care alone, functional class III*

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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

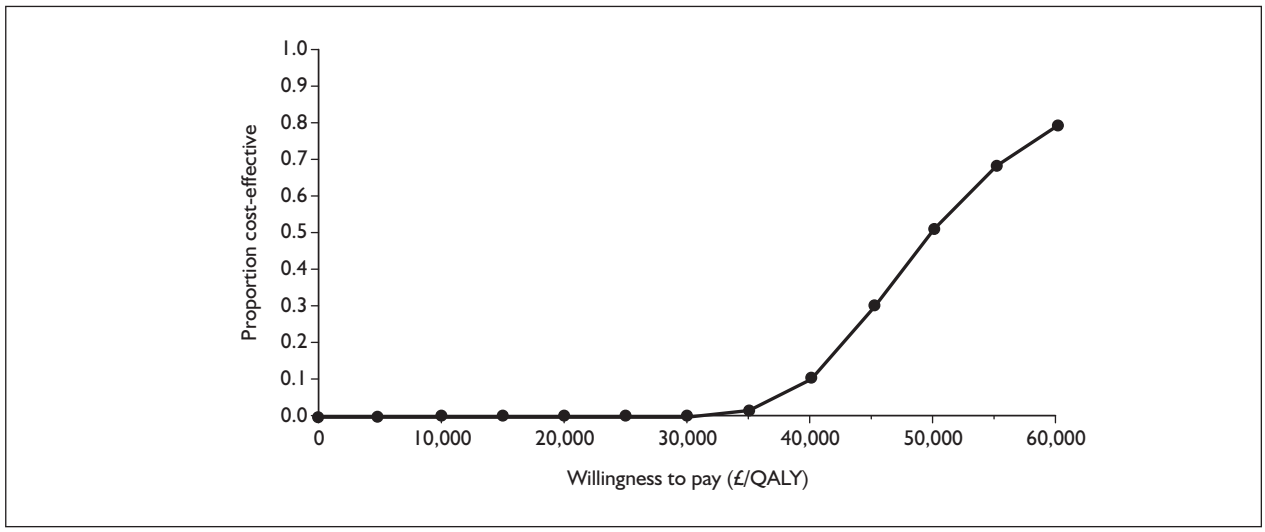

FIGURE 134 *Cost-effectiveness acceptability curve for sitaxentan with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

TABLE 151 *Sildenafil with supportive care versus supportive care alone, functional class III*

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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

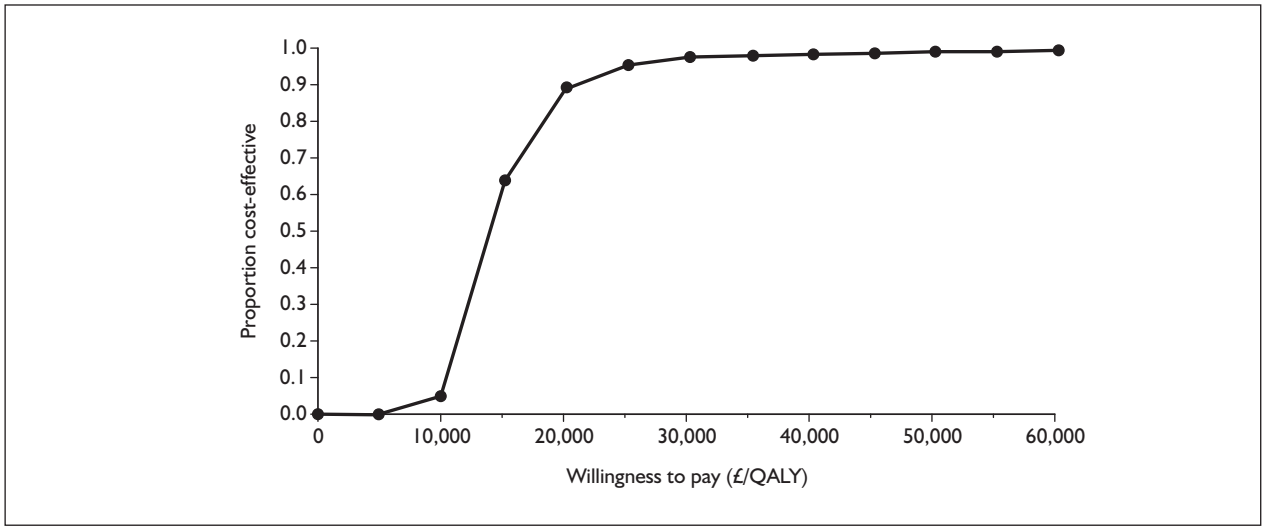

FIGURE 135 *Cost-effectiveness acceptability curve for sildenafil with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

Appendix 13.6 Combining the assumptions of no epoprostenol in functional class IV (Appendix 13.1) and equal mortality between epoprostenol and oral treatments (Appendix 13.2)

TABLE 152 *Bosentan with supportive care versus supportive care alone, functional class III*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	85,000		1.559		
Bosentan	201,000	116,000	4.447	2.888	40,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

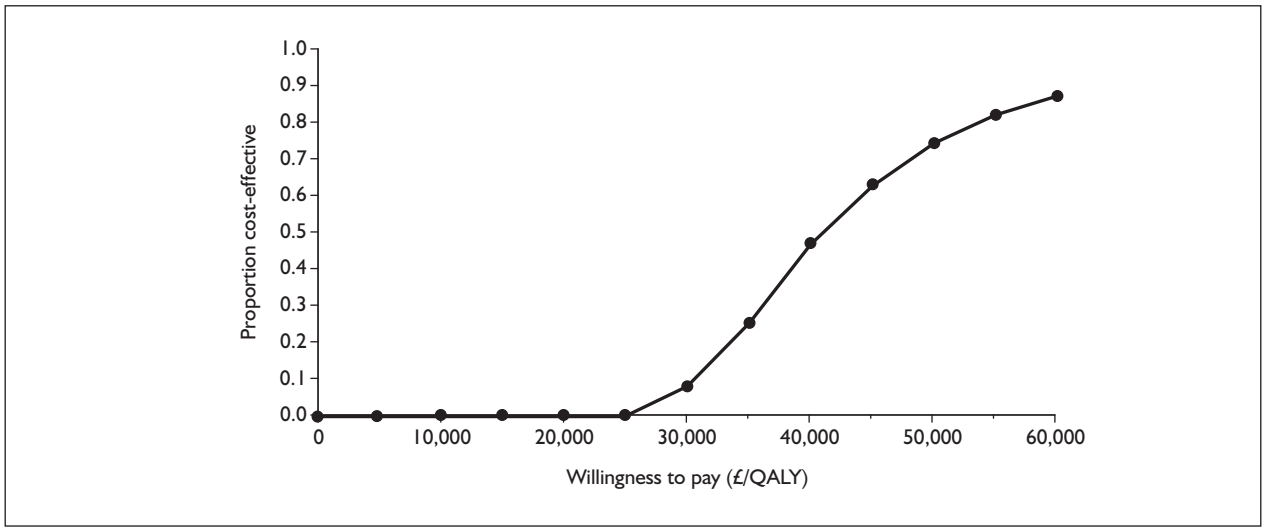

FIGURE 136 *Cost-effectiveness acceptability curve for bosentan with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

TABLE 153 *Sitaxentan with supportive care versus supportive care alone, functional class III*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	85,000		1.559		
Sitaxentan	188,000	103,000	3.995	2.435	42,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

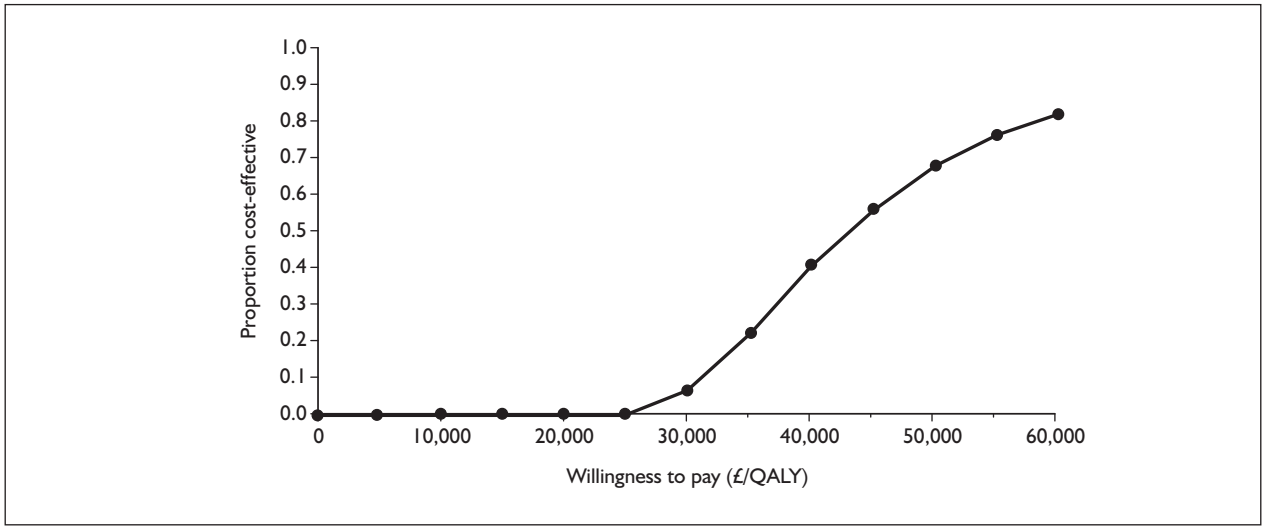

FIGURE 137 *Cost-effectiveness acceptability curve for sitaxentan with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

TABLE 154 *Sildenafil with supportive care versus supportive care alone, functional class III*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	85,000		1.559		
Sildenafil	96,000	11,000	4.206	2.647	4,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

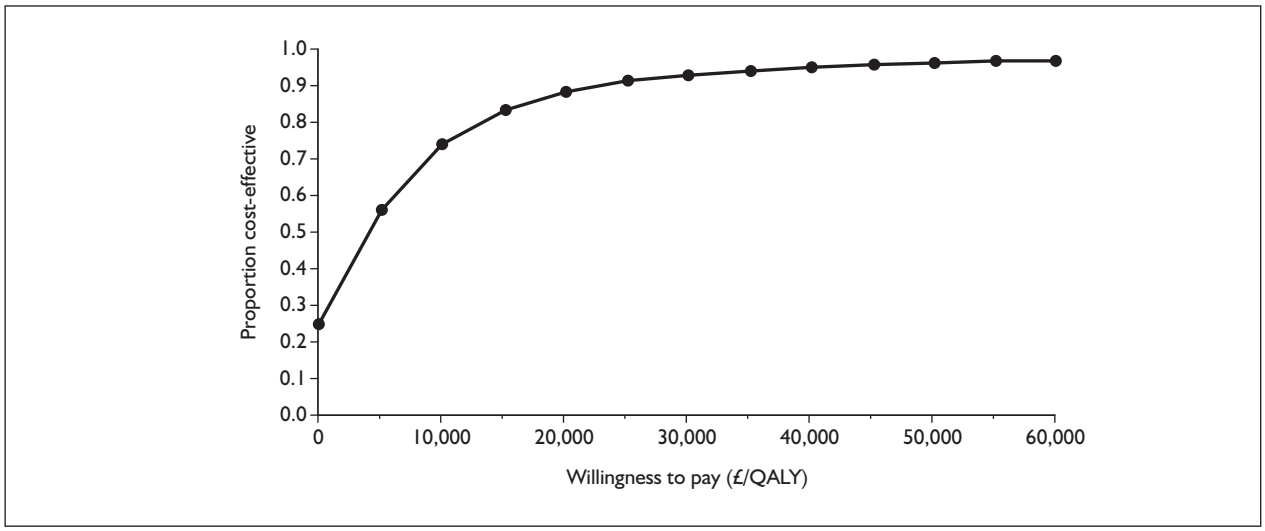

FIGURE 138 *Cost-effectiveness acceptability curve for sildenafil with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

Appendix 13.7 Combining the assumptions of no epoprostenol in functional class IV (Appendix 13.1), equal mortality between epoprostenol and oral treatments (Appendix 13.2) and intermittent care for functional class IV patients on supportive care alone (Appendix 13.5)

TABLE 155 *Bosentan with supportive care versus supportive care alone, functional class III*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	25,000		1.559		
Bosentan	164,000	139,000	4.447	2.888	48,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

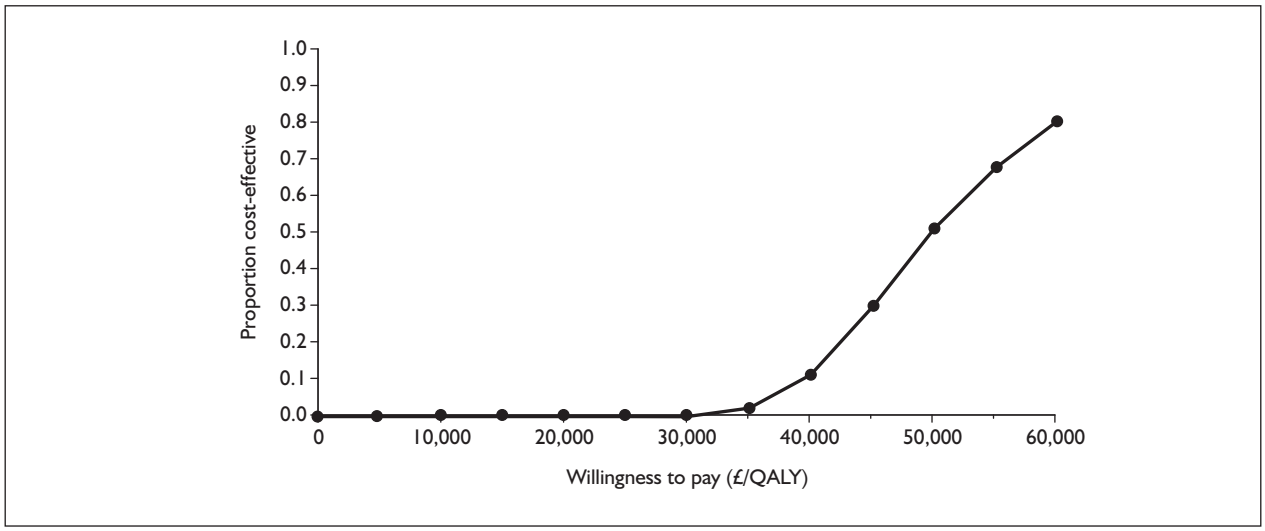

FIGURE 139 *Cost-effectiveness acceptability curve for bosentan with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

TABLE 156 *Sitaxentan with supportive care versus supportive care alone, functional class III*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	25,000		1.559		
Sitaxentan	151,000	13,000	3.995	2.435	52,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

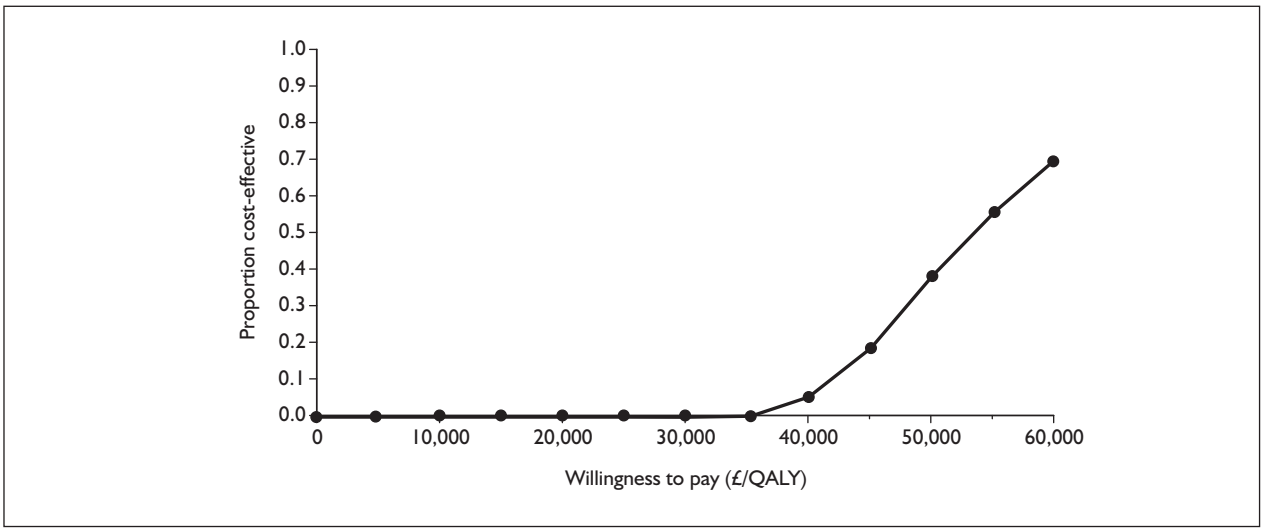

FIGURE 140 *Cost-effectiveness acceptability curve for sitaxentan with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

TABLE 157 *Sildenafil with supportive care versus supportive care alone, functional class III*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	25,000		1.559		
Sildenafil	59,000	34,000	4.206	2.647	13,000

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s).

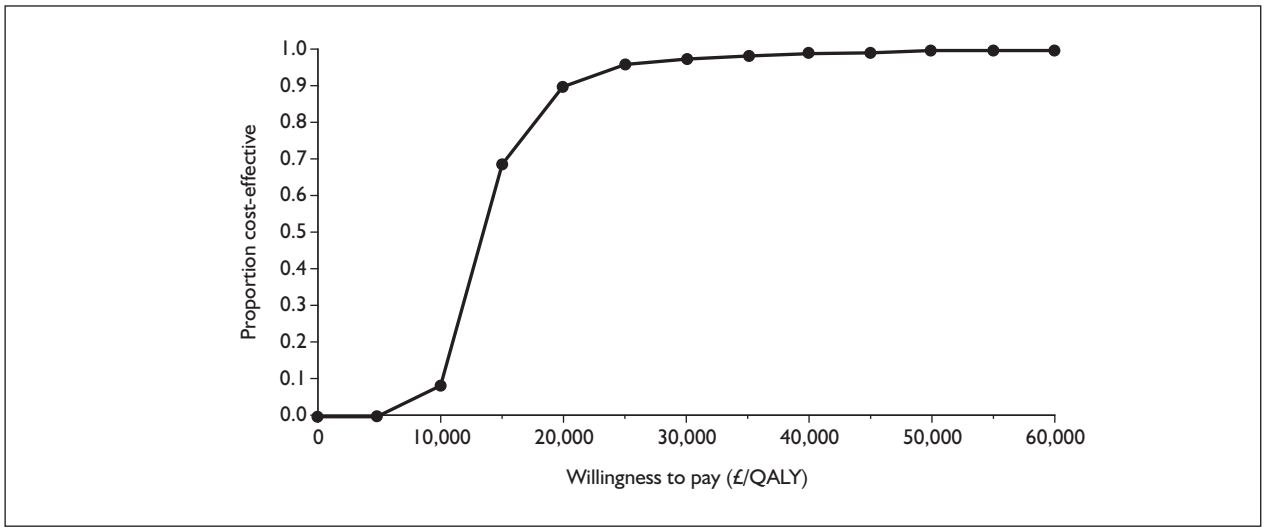

FIGURE 141 *Cost-effectiveness acceptability curve for sildenafil with supportive care versus supportive care alone, functional class III. QALY, quality-adjusted life-year.*

Appendix 13.8 Overall summary of additional analyses

- A summary of the ICERs for the reference case and various sensitivity analyses is shown in *Table 158*.
- By assuming that 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 £10,000 per QALY gained.
- Applying data on mortality for epoprostenol in FCIII to the oral therapies reduces the ICERs for all oral therapies to 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 for iloprost decreases 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 (when 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.

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TABLE 158 *Summary of incremental cost-effectiveness ratios for the 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	96,000	106,000	101,000	39,000	40,000	3700
Additional analyses						
Supportive care without epoprostenol in FCIV	Same as base case	273,000	98,000	42,000	44,000	9000
Assume epoprostenol mortality on supportive care and on treatment	–	–	–	6000	1400	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

FC, functional class; PAH, pulmonary arterial hypertension.

Appendix 14
Budget impact

The annual budgetary impact of uptake of the five technologies was assessed using the drug (licensed dose) and service fee cost for each intervention, as outlined in *Table 159*, multiplied by the number of patients likely to be receiving the intervention. Additional care was presumed to be already funded and therefore was not considered. No consideration was given to any drug-specific monitoring of patients as such costs were presumed to be small in comparison to drug costs. Where different costs for a technology were known these were also used, for example the iloprost VENTafee scheme. Different costs for the first year and subsequent years of use of epoprostenol were also used to reflect the likely dose escalation beyond the first year of treatment. Graphs showing the budgetary impact per annum of each technology for a range of patient uptakes were produced. The budgetary impacts per annum for epoprostenol, for iloprost and for bosentan, sitaxentan and sildenafil are shown in *Figures 142–144* respectively.

FIGURE 142 *Budgetary impact per annum – epoprostenol. [Commercial-in-confidence information has been removed].*

FIGURE 143 *Budgetary impact per annum – iloprost. [Commercial-in-confidence information has been removed].*

FIGURE 144 *Budgetary impact per annum – bosentan, sitaxentan and sildenafil. [Commercial-in-confidence information has been removed].*

TABLE 159 *Budgetary impact – annual cost (£) of each technology*

	Epoprostenol year 1		Epoprostenol year 2+		Iloprost				
	List price	**Reduction**	**List price**	**Reduction**	**List price**	**VENTafee**	**Bosentan**	**Sitaxentan**	**Sildenafil**
Drug	55,869	[Commercial-in-confidence information has been removed]	127,702	[Commercial-in-confidence information has been removed]	36,178	29,600	20,102	20,089	4547
Service fee	9464	9464	9464	9464	5512	5512	542	542	542
Total	65,333	[Commercial-in-confidence information has been removed]	137,166	[Commercial-in-confidence information has been removed]	41,690	35,112	20,644	20,631	5089

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We look forward to hearing from you.

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