Clinical and cost effectiveness of treatments for pulmonary arterial hypertension (PAH) within their licensed indications

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA Programme. Any errors are the responsibility of the authors.

Contributions of Authors

YFC was lead reviewer for the clinical effectiveness section of this report and also contributed to discussion, conclusions and other sections. SJ reviewed existing economic evaluations, industry submission 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 a methodological advisor and deputised for DM, SG & 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 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 "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 Department of Public Health & Epidemiology, University of Birmingham; however other members are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Facility, University of Birmingham.

WMHTAC produce systematic reviews, health technology assessments and economic evaluations for NHS R&D HTA programme (NCCHTA), the National Institute for Health and Clinical Excellence (NICE), and for 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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1. DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

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

Abbreviations

6MWD	Six minute walking distance
6MWT	Six minute walking test
AE(s)	Adverse event(s)
AIR	Aerosolized Iloprost Randomized study
APAH	Associated pulmonary arterial hypertension
BREATHE	Bosentan Randomized Trial of Endothelin Antagonist Therapy
CEAC	Cost-effectiveness acceptability curve
CHD	congenital heart disease
CI	confidence interval
CTD	connective tissue disease
CTD – APAH	Pulmonary arterial hypertension associated with connective tissue disease
COMBI	COMbination therapy of Bosentan and aerosolised Ilprost 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
ICER	Incremental cost-effectiveness ratio
IPAH	Idiopathic pulmonary arterial hypertension
ITT	Intention to treat
mPAP	mean pulmonary arterial pressure
NCG	National Commissioning Group formerly known as NSCAG (see below).
NICE	National Institute for Health and Clinical Excellence
NSCAG	National Specialist Commissioning Advisory Group
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PCWP	Pulmonary capillary wedge pressure
PH	Pulmonary hypertension
PPH	Primary pulmonary hypertension
PSA	Probability sensitivity analysis
PSS	Personal social service
PVR	Pulmonary vascular resistance
QALY	Quality-adjusted life year
RAP	Right atrial pressure
RCT	Randomised controlled trial
SAE(s)	Serious adverse event(s)
SD	Standard deviation
STEP	Safety and pilot efficacy Trial in combination with bosentan for Evaluation in PAH

STRIDE	Sitaxsentan To Relieve ImpaireD Exercise study
SUPER	Sildenafil Use in Pulmonary Arterial Hypertension Study
WHO	World Health Organisation

Glossary

6MWT - 6 Minute Walk Test	The 6MWT measures the distance that a patient can walk unencouraged on a flat, hard surface in the time of 6 minutes.
Borg dyspnoea index	A measure of perceived breathlessness on a scale of 0 to 10, where 0 = no breathlessness. Initially designed to measure exertion.
Cardiac index	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 section 3.1.1.1). Briefly, patients are classified in to one of the following four categories: FCI (asymptomatic), FCII (mild), FCIII (moderate), FCIV (severe).
Pulmonary arterial hypertension (PAH)	PAH refers to category 1 (excluding subcategory 1.5) of the Venice 2003 classification for pulmonary hypertension (see section 3.1.1.1) throughout this report. 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. Where the term PPH was retained, it was regard as interchangeable with IPAH.
Pulmonary artery pressure (PAP)	Measured directly during right heart catheterisation. Mean pulmonary artery pressure (mPAP) > 25 mm Hg at rest or > 30 mm Hg with exercise is one of the criteria of PAH diagnosis.
Pulmonary capillary wedge pressure (PCWP)	Pulmonary capillary wedge provides an indirect estimate of left atrial pressure. The measurement is made with a balloon-tipped, multi-lumen catheter (Swan-Granz catheter) inserted into a peripheral vein and than advancing it into the right atrium, right ventricle, pulmonary artery and into a branch of the pulmonary artery. The normal value of PCWP is 8-10 mm Hg. A PCWP $\leq$ 15 mm Hg is one of PAH diagnostic criteria. PCWP is used to calculate PVR
Pulmonary hypertension (PH)	Where 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 section 3.1.1.1). This is therefore a broader term that encompasses PAH and other forms of pulmonary hypertension.
Pulmonary vascular resistance (PVR)	(mean pulmonary artery pressure [mm Hg] – pulmonary capillary wedge pressure [mm Hg])/cardiac output (L/min) x 80. Units are dyne s/cm^5. A PVR > 240 dyne s/cm^5 is one of diagnostic criteria of PAH.
Right atrial pressure (RAP)	Right atrial pressure (RAP) is measured at right heart catheterisation. It 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. Normal value is up to 5 mm Hg.
Supportive treatment(s)	Supportive treatment(s) or supportive care refers to anticoagulation therapy, diuretics, oxygen, digoxin and calcium channel blockers

	(see section 3.2.1). They were commonly referred to as conventional therapy or background therapy in the literature.

2. EXECUTIVE SUMMARY

2.1 Background

Pulmonary arterial hypertension (PAH) is a diverse group of diseases of similar pathophysiology and clinical presentation that is characterised by a progressive increase of pulmonary vascular resistance, which leads 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. 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 is therefore a serious condition that has 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 last decade, PAH was managed by supportive treatments, which include anticoagulation therapy, diuretics, oxygen and digoxin that mainly aim at controlling of symptoms. In addition, calcium channel blockers (a specific type of vasodilators) were found to be effective for treating a small proportion of patients with PAH. Since then, 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 associated with PAH but also could 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).

2.2 Objectives

The objectives of the assessment report are:

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 calcium channel blockers 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 the treatment of adults with PAH for whom calcium channel blockers are inappropriate or no longer effective compared to supportive treatment.

2.3 Methods

Clinical effectiveness

A systematic review of RCTs was undertaken of any of the technologies (alone or in combination) compared to placebo, supportive care, any other technologies (alone or in combination) and/or non-licensed drugs in adult PAH patients. 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 National Institute for Health and Clinical Excellence (NICE) by the manufacturers of the technologies. 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.

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 also 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.

2.4 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 (intravenous epoprostenol, inhaled iloprost, bosentan, sitaxentan and sildenafil) 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 they are likely to be under-powered 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 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, however, 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 by the assessment group.

The effectiveness of intravenous epoprostenol has been shown in open-label RCTs that included patients of mixed FC (mainly III and IV) in both patients with PPH and patients with scleroderma. 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 [redacted]/QALY and [redacted]/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. However, the ICERs were sensitive to the price of epoprostenol.

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. 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 PAH populations of IPAH and CTD – APAH and in patients with PAH associated with Eisenmenger syndrome (a specific type of congenital heart disease). 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 populations including IPAH, PAH/CTD and PAH/CHD. 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 populations including IPAH, CTD – APAH and PAH associated with congenital heart disease. 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 (including adding one to another) 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 further 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.

As the model considers progression to FCIV with the initiation of epoprostenol treatment, 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 industry submissions economic evaluations

There was no consensus in the industry 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.

2.5 Discussion

Strengths, limitations of the analyses and uncertainties

The strengths of this assessment report include a systematic review of clinical effectiveness focusing on the most robust evidence from RCTs, comprehensive literature search, inclusion of unpublished data, comprehensive analyses that highlighted the mismatch between the licensed indication and the available evidence, independent assessment of published economic evaluations and industry 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 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 currently 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 cost of epoprostenol.

2.6 Conclusions

All the five technologies (intravenous epoprostenol, inhaled iloprost, bosentan, sitaxentan and sildenafil), 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 direct comparison between 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.

More RCTs of sufficient sample size and duration that evaluate the effectiveness and safety of combinations of the technologies versus monotherapy are required. Some trials are already being carried out.

It is acknowledged that 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. 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 included in this assessment.

Planned analyses of data from previous and future RCTs to investigate possible differences in treatment effects between subcategories of PAH and between patients of different FC at baseline are needed.

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 also needed.

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 group in RCTs also needs to be established.

3. BACKGROUND

3.1 Description of 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, 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 greater than 25 mmHg at rest or greater than 30 mmHg with exercise, a mean pulmonary capillary wedge pressure of <15mmHg and a raised pulmonary vascular resistance of ≥ 240 dynes*sec*cm^{-5}.[1] 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.

3.1.1 Classifications

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

3.1.1.1 Clinical classification

PAH is one of five differing sub-types of Pulmonary Hypertension.

Pulmonary hypertension was traditionally classified into two categories: primary pulmonary hypertension or secondary pulmonary hypertension, depending on the absence or presence of identifiable causes or risk factors. In 1998, the World Health Organisation (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 WHO 1998 classification) includes five major categories, with pulmonary arterial hypertension being one of the categories. The

term 'primary pulmonary hypertension' (PPH) was retained within this category and included subcategories of 'sporadic PAH' and 'familial PAH'. 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 Venice 2003 clinical classification are listed in Table 1.[1]

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)

After Galiè et al[1]

As primary pulmonary hypertension (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 the term PPH is retained it is regarded as interchangeable with IPAH.

3.1.1.2 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 NYHA classification are nearly identical and are sometimes referred to as NYHA/WHO classification, which is listed in Table 2.[1]

Table 2. NYHA/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 pre-syncope.
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 pre-syncope.
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 pre-syncope.
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.

After Galiè et al[1]

3.1.2 Aetiology

The pulmonary vasculature is normally a low pressure system with little resistance to flow.[2] Pulmonary Hypertension is when pulmonary arterial pressure is elevated. As indicated in the classification system above PAH frequently originates as the result of either 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 which lead to constriction, cellular proliferation and potentially elevated blood clotting in the

pulmonary microcirculation This results in progressively increased pulmonary vascular resistance, elevated pulmonary arterial pressure, the clinical sequalae of PAH and 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 where necessary in this report.

3.1.3 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 long delay from the onset of symptoms until 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 appropriate treatment is commenced. Loss of exercise capacity and latterly capacity for daily living can be devastating to patients' quality of life and also lead to depression and further deterioration in 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).

3.1.4 Significance to the NHS

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

According to UK Hospital Episode Statistics in 2005-6 IPAH accounted for nearly 4000 hospital admissions, nearly 4500 consultant episodes and over 17000 bed days.[3]

Due to the severity of the disease, including the risk of early death, close monitoring and expert care are required and this is recommended to be undertaken at specialist centres (see section 3.3.4).

3.1.5 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 Table 1. Some of the main issues around risk factors are discussed below.

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, CTD, 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 disease, Gaucher's disease, heredity haemorrhagic telangiectasia/ Osler-Weber-Rendu disease);

After Galiè et al[1]

3.1.5.1 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 6 fold increase in risk of developing of PAH. Due to 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]

3.1.5.2 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 females to males varies from study to study it is of the order of 1.3 to 2.2:1[4-6]. In most trials women constitute the majority of patients.

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

3.1.5.3 Diseases

PAH is frequently associated with a number of other diseases. These associations are reflected in the sub-classifications 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 pulmonary arterial hypertension occurs in connective tissue diseases and most commonly in scleroderma where around 12% of patients in a hospital population of scleroderma suffer from PAH.[7]. Survival in scleroderma APAH is worse than IPAH with a median of 1.2 years despite similar haemodynamics.[8]

Congenital heart disease 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's syndrome develops when such patients develop severe PAH with reversal of flow across the shunt and cyanosis. Survival in Eisenmenger's syndrome untreated is much longer than IPAH although it is still markedly reduced compared to 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]

3.1.5.4 Hereditary

PAH in 6-10% of patients is suspected or proven to be of hereditary origin. 50-90% of patients diagnosed with familial PAH have mutations of BMPR2 gene. Patients with familial PAH 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 familial PAH.[10]

3.1.5.5 Prognosis and prognostic factors

The prognosis for patients with PAH on supportive care (see Section 3.2) is considered to be poor. Median survival at time of diagnosis for patients with IPAH (PPH) receiving support care in the 1980's was 2.8 years.[5] Percentages of patients surviving a specified period were

estimated as: 68% (95% CI: 61% to 75%) at 1 year, 48% (95% CI: 41% to 55%) at 3 years and 24% (95% CI: 24% to 44%) at 5 years.[5] One of the key factors influencing prognosis is FC. Patients with FCI or FCII in the 1980's cohort had a median survival of 58.6 months, those with FCIII 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 indicates that median survival times from diagnosis may be longer today.

Haemodynamic variables related to decreased survival have been identified: increased mean pulmonary arterial pressure, increased mean right arterial pressure and decreased cardiac index. These variables also appeared in an equation predicting patient survival based on results of a multivariate analysis of data from a registry established in the 1980s by the National Institute 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 other social-economic factors over the past few decades.

Exercise endurance, usually measured in 6MWT, is also considered to be an important prognostic factor. One of the earliest drug trials in PAH demonstrated that 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.

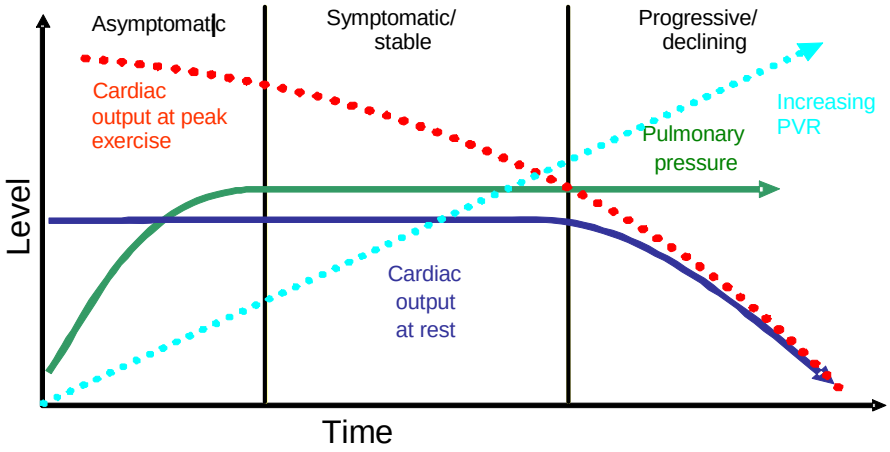


Figure 1 Progression of PAH and Change in Clinical Parameters

After – from Actelion submission; Rich et al. In: Harrison's Principles of Internal Medicine. 15th ed. 2001: 1506-1507. **COPYRIGHT PROTECTED**

3.1.6 Incidence and Prevalence

PAH is a rare condition and as with such conditions the incidence and prevalence has been fairly difficult to assess. Often quoted figures for the incidence are 1-2 case per million general population per year for IPAH and a further 1-2 cases per million 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 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 severer 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.

3.1.6.1 Measurement of disease

A number of measures are used clinically to monitor the severity, progression and response to treatment in 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 below.

Six 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 six minute walk distance (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 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 related to 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

Pulmonary Artery Pressure (PAP) is measured directly during right heart catheterisation. Mean pulmonary artery pressure (mPAP) > 25 mm Hg at rest or > 30 mm Hg with exercise is one of the criteria of PAH diagnosis. Elevated mean PAP, together with other haemodynamic variables, indicate patients with a poor prognosis.[1]

Right Atrial Pressure

Right atrial pressure (RAP) 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. Normal value is up to 5 mm Hg.

Pulmonary capillary wedge pressure

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

Pulmonary Vascular Resistance

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 [mm Hg] – pulmonary capillary wedge pressure [mm Hg])/cardiac output (L/min) x 80.
A PVR > 240 dyne s/cm^5 is one of the diagnostic criteria of 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. Cardiac index is calculated by dividing cardiac output by body surface area, thus relating it to the individual patient. and is usually expressed in l/min/m^2.

3.2 Current service provision

Until ten years ago, PAH was managed mainly by supportive care alone. Since this time many patients have been enrolled in trials of new technologies which aim to be disease modifying

rather than tackling just 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.

3.2.1 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 were 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.

3.2.1.1 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 normalized 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 iv medication (e.g. epoprostenol; see section 3.3.1.1) 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 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 disease patients require frequent monitoring in order to reduce serious adverse effects, such as haemorrhage.

3.2.1.2 Diuretics

Diuretics are used to prevent or reduce fluid retention. The aim 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% patients were treated with diuretics. Due to 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 treatment of PAH include furosemide, amiloride, and spironolactone.

3.2.1.3 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 experienced 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 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 (QOL) or survival.[1]

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

3.2.1.4 Digoxin

The progression of right heart failure often results in depression of myocardial contractility. This condition can be treated with inotropic agents e.g. agents which affect the force of muscle contraction.

Digoxin is used in patients with refractory right heart failure in sinus rhythm.[1]

Digoxin is available as tablets or injection. An increase in cardiac output, as well as a reduction in circulating norepinephrine levels can be obtained by a short-term iv use of digoxin. No evidence indicates 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 ventricular rate.[16] It was used in 18-53% of patients taking part in recent PAH RCTs.[1]

3.2.1.5 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 to 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 iv prostacyclin (see section 3.3.1), adenosine, or inhaled nitric oxide during right heart catheterisation.[18] As a result of a retrospective analysis of 557 patients tested with iv epoprostenol and inhaled nitric oxide, response criteria have been accepted of a fall in mPAP ≥ 10 mm Hg to an absolute mPAP ≤ 40 mm Hg with an unchanged or increased cardiac output.[19]

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

The choice of a calcium-channel blocker can be based on 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 be at times decreased by use of digoxin and/or diuretics (see sections 3.2.1.2 and 3.2.1.4).[1] This therapy requires close monitoring, as the positive effect is not always maintained over time.[20]

3.3 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

- 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), 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. These being: prostanoids, endothelin receptor antagonists and phosphodiesterase inhibitors. Further detail on each technology is given below under the relevant category, and a summary of the technologies, including licensed indication, pharmacological action and mode of delivery is given in Table 4.

Table 4 Technologies: Licensed indications, pharmacology and route of administration

Technology	Pharmacology	Licensed Indication			Route of Administration
		Population	Functional Class	Other	
Epoprostenol (Flolan®, GlaxoSmithKline)[21]	Prostacyclin (synthetic)	Primary pulmonary hypertension	III & IV[a]		Continuous intravenous infusion
Iloprost (Ventavis®, Schering Health Care)[22]	Prostacyclin (analogue)	Primary pulmonary hypertension	III[a]	To improve exercise capacity and symptoms	Inhaled via nebuliser
Bosentan (Tracleer®, Actelion Pharmaceuticals)[23]	Endothelin receptor antagonist (non-selective)	PAH	III[b]	To improve exercise capacity and symptoms	Oral
Sitaxentan (Thelin®, Encysive)[24]	Endothelin receptor antagonist (selective)	PAH	III[c]	To improve exercise capacity	Oral
Sildenafil (Revatio®, Pfizer)[25]	Phosphodiesterase-5 inhibitor	PAH	III[c]	To improve exercise capacity	Oral

FC system: [a]NYHA, [b]Not Stated, [c]WHO

3.3.1 Prostanoids

Prostacyclin is mainly produced in the vascular endothelium. It is a powerful vasodilator of both the pulmonary and 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.[1,18,20] 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 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.

3.3.1.1 Epoprostenol

Epoprostenol is a synthetic sodium salt of prostacyclin. It is indicated for the intravenous treatment of primary pulmonary hypertension in NYHA functional Class III and Class IV patients who do not respond adequately to conventional/background therapy.[21] For this indication epoprostenol is licensed in vial sizes of 1.5mg.[i] Conventional/background therapy whilst not explicitly defined can be considered to be those treatments not classed as interventions in this assessment and as specified in the current service provision above (section 3.2).

Epoprostenol is contraindicated in patients with known hypersensitivity to the drug, congestive heart failure from severe left ventricular dysfunction and/or who develop pulmonary oedema during dose-ranging.[21]

Epoprostenol has a short half life in the circulation (3-5minutes) 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 prior to infusion with ice-packs. Given the route of delivery, continuous administration

[i] 1.5 mg vials along with 0.5mg vials are also licensed for renal dialysis when use of heparin is otherwise contraindicated or heparin use carries a high risk of causing or exacerbating bleeding.[21,26]

and limited stability the treatment is not without complication. 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 in-patient under specialist care due to the intensive training of patients and/or their carers, and close monitoring and emergency back up required. Initiation of treatment is by a short term dosing to determine the patient specific infusion rate (this process can also be undertaken using a peripheral rather than 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 to 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 in patient care and district nursing services.

Over time the infusion rate is gradually increase by 1-2ng/kg/min steps to assess clinical response and overall gradually dose increases are to be expected in most patients to arrest deterioration in symptoms.[21] Typical doses might be in the range of 15 to 50ng/kg/min (higher upper doses have been used in USA) depending on length of time on treatment, resistance of the disease to adequate control and severity of any adverse effects.

Patients who deteriorate appreciably whilst 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 due to rebound pulmonary hypertension and rapid clinical deterioration which may result in death. For this reason once initiated epoprostenol treatment is considered to be life-long by many.

Due to 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 below 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 Sections 3.3.2, 3.3.3 and 3.3.6). Patients presenting with aggressive disease and/or in FCIV will receive epoprostenol.

The price of epoprostenol is approximately £130- 390 per day (15ng/kg/min – 45ng/kg/min per 70kg patient; 1 – 3 vials per day; net price).[27] This price only includes epoprostenol powder and diluent and not pumps, consumables, delivery or any other costs associated with administration (insertion of Hickman line), monitoring, in-patient time and training. The price for some of these items is difficult to ascertain and/or contained in confidential service agreements.

3.3.1.2 Iloprost (inhaled)

Iloprost is a stable prostacyclin analogue which has been developed for iv, oral and inhaled administration. Only the latter is part of this assessment.

Inhaled iloprost has EU marketing authorisation for the treatment of primary pulmonary hypertension patients in NYHA FCIII to improve exercise capacity and symptoms.[22] Two vial sizes are licensed; 1 and 2 ml.

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 aerosol particles small enough. Three types of deliver systems (nebulisers) are available: compressed air, ultrasonic and vibrating mesh nebulisers. The recommended dose is 2.5 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 patient breathing pattern.[22] The serum half life of iloprost is about 20-25 minutes and this short duration requires 6-9 inhalation session 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 two 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 (section 3.3.1.1) is accepted by the patient and initiated.

Inhaled iloprost is often seen as an additional treatment to the oral drugs 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 epoprostenol is not suitable treatment for them.

Iloprost is contraindicated in patients with known hypersensitivity to the drug, conditions where 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 MI), 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, lactation. Furthermore, iloprost is not recommended in patients with unstable pulmonary hypertension, with advanced right heart failure.[22]

The cost of iloprost nebuliser solution is approximately £85 – 127 per day (1 vial 6 -9 times per day; net price same for each vial size).[27] This price is only for the solution, not nebulisers, consumables, service, delivery, in-patient time and training. The price for some of these items is difficult to ascertain and/or contained in confidential service agreements.

3.3.2 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.[1,20] It is unclear whether increases in ET-1 are a consequence or a cause of PAH. Irrespective the ET-1system 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 cell 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.[1,20] 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 which bind to the receptors without eliciting a biological response and 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. Ambrisentan (Volibris/Letairis) is not as it is not licensed in the UK. It has only recently (June 2007) been approved for sale in the USA for PAH and marketing authorisation is being sought in the EU.[28,29]

3.3.2.1 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.[23] Two tablet sizes are available 62.5mg and 125mg.

Treatment should be initiated and monitored under specialist care. Initially dosing is 62.5mg twice daily (morning and evening with or without food) for four weeks, and then increased thereafter to a maintenance dose of 125mg twice daily. Some patient's dose may be increased to 250mg 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 deterioration of condition at anytime requires re-evaluation of treatment. This usually entails either the addition of, or replacement with, other treatments. Withdrawal of bosentan requires careful management.

Bosentan is metabolised by the liver and has been associated with dose-dependant increase in the liver enzymes aspartate and alanine aminotransferases (more than 8 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 125mg rather than 250mg twice daily. This is not a unique feature of bosentan as it occurs with sitaxentan. Regular monitoring of hepatic enzymes (usually monthly) is required as long as the drug is taken.

Bosentan is not indicated in patients with a known hypersensitivity to the drug, hepatic impairment (including aminotransferases more than three times the upper limit of normal) and those taking cyclosporin A (amplifies the plasma concentration of bosentan by an unknown

mechanism). Bosentan is contra-indicated in pregnancy as it is assumed to be teratogenic and therefore women with child bearing 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 (2x62.5 or 2x125mg as the net price is the same for each tablet size).[27] This price is only for the drug, not delivery , monitoring of liver function or in-patient time etc.

3.3.2.2 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.[24] One tablet size is available: 100mg.

Treatment should be initiated and monitored under specialist care. Dosing is 100mg 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 of deterioration of condition at any time requires re-evaluation of treatment.[24] This usually entails either addition of, or 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.[24]

Contra-indications are similar to that of bosentan (see section 3.3.2.1). There is significant drug interaction between sitaxentan and warfarin. Reducing the dose of warfarin upon starting sitaxentan and regular monitoring of INR is required to reduce the risk of bleeding.

The cost of sitaxentan tablets is approximately £55 per day (1x100mg; net price).[27] This price is only for the drug, not delivery, monitoring of liver function or in-patient time etc.

3.3.3 Phosphodiesterase-5 inhibitors

PAH is associated with a defect in the production of nitric oxide.[1,18,20] Nitric oxide is an endogenous pulmonary arterial vasodilator which 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 due its rapid degradation by phosphodiesterases. Phosphodiesterase-5 is strongly expressed in the lung and its expression and activity are elevated in chronic PH.[20] Thus inhibitors of phospodiesterase-5, will decrease cGMP degradation, enhancing nitric oxide dependant cGMP mediated pulmonary vasodilation.[1,18,20]

3.3.3.1 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.[25] It is available as 20mg tablets.

Treatment should be initiated and monitored under specialist care. Dosing is 20mg three times per day (6-8 hours apart) with or without food.[25]

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 re-evaluation of treatment.[25] This usually entails either addition of, or 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 MI, and severe hypotension at initiation. Furthermore it is contraindicated in some specific eye conditions.[25]

The cost of sildenafil tablets is approximately £12.45 per day (20mgx3; net price).[27] This price is only for the drug; not delivery, in-patient time and training etc.

3.3.4 Current guideline for use in the NHS

Since 2001, in the UK patients 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 National Specialist Commissioning Advisory Group or NSCAG).[30] There is one 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.[30]

3.3.5 Treatment guidelines

At the time of writing, there are no current up to date national treatment guidelines for the treatment of PAH.

In 2001 the British Cardiac Society sought for the first time to gain a consensus on the treatment of PH.[10] The resulting recommendations set out criteria for the use of disease targeting therapies, such as the technologies in this assessment, primarily based on the 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. An update to the recommendations, including new treatment algorithms, has been submitted for publication.[31]

Guidelines published by the European Society for Cardiology (ESC) in 2004 are considered the most current with regard to practice in the UK.[1] Guidelines have also been produced by the American College of Chest Physicians. Both organisations are believed to be updating their guidelines for 2008.[31]

The ECS guidelines cover all aspects of the diagnosis, monitoring and treatment of PAH. It contains an evidence based algorithm for the treatment of PAH FCIII&IV. This algorithm is reproduced below in Figure 2. The text below the table clearly describes the algorithm and therefore this will not be repeated in the main body of this report.

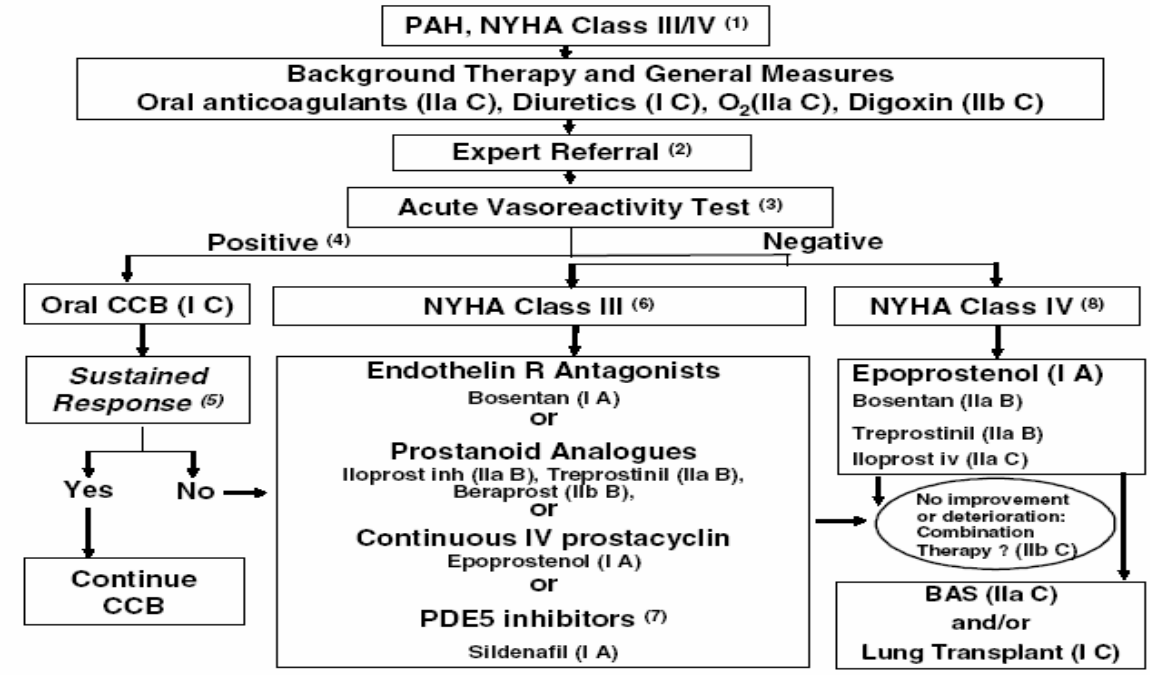


Figure 2 European Cardiac Society Treatment Algorithm

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 scleroderma or to anorexigen use. Extrapolation of these recommendations to other PAH subgroups should be done with caution. (2) Due to 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 positive response is achieved in patients with IPAH and PAH associated to 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 less than or equal to 40 mmHg with an increase or unchanged cardiac output during acute challenge with inhaled NO, iv epoprostenol or iv 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 iv 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 unstable condition should be treated with iv epoprostenol (survival improvement, worldwide experience and rapidity of action). A, B, C grading according to definitions in Table 4 & Table 5 of the ESC guidelines. CCB: calcium channel blockers, inh: inhaled, iv: intravenous, PDE: phosphodiesterase, R: receptors.

ECS guidelines treatment algorithm reproduced here is taken from the GSK submission. We need to use the original. NICE/NCCHTA will need to get copyright approval.

3.3.6 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 Collage of Physicians for this appraisal, which contains year on year utilisation of the technologies from 2004-7 collated by the National Pulmonary Hypertension Service of UK and Ireland.[31] This data has been requested to remain confidential. The data is available for all PH and thus the census is likely cover a wider population than just PAH. A small number of patients may not be seen at the PH service and therefore will be missing from the census.

[redacted] The 2007 census contains data from [redacted] UK designated centres [redacted] This data is reproduced in Appendix 1 (Table 64,**********
Table 65, **********
Table 66 & **********
Table 67) and outlined below and summarised in Table 5._There are currently about [redacted] UK patients attending the PH service. Of these just under [redacted] are children. Of the adult patients nearly [redacted] are in Scotland. The remaining [redacted] patients are seen in England (there are no Welsh or Northern Irish PH service centres).

In England, over [redacted] adult patients are receiving mono-therapy, [redacted] dual therapy and [redacted] triple therapy with disease targeting drugs (the five technologies, treprostinil (iv or sc) and/or iloprost (iv)). A small number of patients are on unspecified trial drugs (see Table 5).
[redacted] for this assessment. Sitaxentan has however only recently been given marketing authorisation. [redacted] is utilised by a [redacted] patients ([redacted] monotherapy[ii]). [redacted] are the [redacted] oral mono-therapies (utilised by [redacted] and

ii [redacted]

[redacted] patients respectively) and together the [redacted] dual therapy ([redacted] patients). In total there are just over [redacted] patients receiving oral therapies. Over [redacted] patients are receiving [redacted] and an [redacted] number ([redacted] to less than [redacted][iii]) [redacted] neither of which are currently licensed in the UK for PAH.

Table 5 Current Service Utilisation: National Pulmonary Hypertension Service Census 31st March 2007

Name of Therapy		English Patients[a]
Epoprostenol (iv)		[redacted]
Treprostinil (sc)		[redacted]
Treprostinil (iv)		[redacted]
Iloprost (iv)		[redacted]
Iloprost (nebulised)		[redacted]
Bosentan		[redacted]
Sitaxentan		[redacted]
Sildenafil		[redacted]
Trial Drug[b]		[redacted]
	Mono Therapy Total	[redacted]
Bosentan & Sildenafil		[redacted]
Sitaxentan and Sildenafil		[redacted]
Bosentan + Epoprostenol (iv)		[redacted]
Bosentan + Iloprost (iv or neb)		[redacted]
Bosentan + Treprostinil (sc or iv)		[redacted]
Sildenafil + Iloprost (iv or neb)		[redacted]
Sildenafil + Treprostinil (sc or iv)		[redacted]
Sildenafil + Epoprostenol (iv)		[redacted]
Trial Drug[b]		[redacted]
	Dual Therapy Total	[redacted]
Bosentan + Sildenafil + Epoprostenol (iv)		[redacted]
Bosentan + Sildenafil + Iloprost (iv or neb)		[redacted]
Bosentan + Sildenafil + Treprostinil (sc or iv)		[redacted]
Treprostinil (sc) + bosentan + sildenafil + iloprost (neb)		[redacted]
	Triple Therapy Total	[redacted]

[redacted]

[b]not specified

4. DEFINITION OF THE DECISION PROBLEM

4.1 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 are:

- Whether epoprostenol, iloprost, bosentan, sitaxentan and sildenafil, when used within their licensed indications, are clinically effective and cost-effective compared to supportive treatments (see Section 3.2.1) 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 pulmonary arterial hypertension according to Venice 2003 clinical classification (see section 3.1.1).
- Whether significant differences in clinical and cost-effectiveness exist between the interventions being considered (either used alone or in combination) when compared to 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) While 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 connective tissue diseases (see section 3.1.1.1).
(2) The five interventions being considered in this technology appraisal have different routes of administration, demand on patients' self-management, speed of action, adverse effect profile and contraindications. The selection of treatments is to some extent dependent on the nature of the underlying condition, clinical circumstances and patient ability and acceptance. As such the choice of treatment and appropriate comparators is therefore dependent on all 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 resource available to undertake this assessment report was comparable to that of other assessment reports and therefore not limitless.

Bearing these in mind, the assessment group planned to undertake a systematic review of randomised controlled trials (RCTs) and a review of industry 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 due to 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 done only for a specific population according to the evidence), disease severity (e.g. it may be necessary to model patients in functional class III and IV 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 functional class IV).

4.1.1 Population and relevant subgroups

The population considered is adults with pulmonary arterial hypertension (Category 1 of the Venice 2003 clinical classification) in NYHA/WHO functional classes III (and also functional class IV for epoprostenol) for whom calcium channel blockers are inappropriate or no longer effective.

Potentially relevant subgroups include:

- Subcategories of PAH (e.g. idiopathic PAH) 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 than 'subgroups' of a well characterised disease. Given the likely volume of available evidence and the resources available for this technology assessment, the key specific subgroups to be examined was patients with idiopathic PAH in functional class III.

4.1.2 Definition of the interventions

For patients in functional class III, 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 micrograms to 5.0 micrograms as delivered at the mouthpiece per inhalation session)
- Bosentan (Tracleer®, Actelion Pharmaceuticals), administered orally, 62.5 mg to 250 mg twice daily
- Sitaxentan (Thelin®, Encysive), administered orally, 100 mg once daily
- Sildenafil (Revatio®, Pfizer), administered orally, 20 mg three times daily

For patients in functional class IV:

- Epoprostenol administered by continuous intravenous infusion was the only intervention considered

4.1.3 Relevant comparators

- *Supportive treatments*: these include digoxin, diuretics, anticoagulants and oxygen (see section 3.2.1).
- *Placebo or no treatment*: whilst 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 to 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 randomised controlled trials (RCTs).
- Intravenous iloprost was considered as a comparator if evidence was available from RCTs.

4.1.4 Outcomes

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

4.1.5 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 are either 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 (where evidence was available from RCTs). One exception to this was epoprostenol as second line treatment for patients progressing to FCIV as many such patients would have received other listed interventions first.

4.2 Key Issues

4.2.1 Potentially problematic factors

- **Trials including patients with mixed functional classes:** given that none of the interventions are licensed for functional class II and only one of them (epoprostenol) is licensed for functional class IV, the main focus of the technology assessment was on patients in functional class III. Nevertheless, existing trials have included patients of various functional classes (e.g. functional classes II-IV)(see section 3.1.1.2). Data for the specific subgroup of patients in functional class III was believed in many cases to be unlikely to be readily available and therefore was to be requested from the sponsors/investigators of the trials.

- **Trials including patients of mixed clinical classification of PAH:** existing trials may include PAH of very different nature. Separate data for specific patient clinical classifications (see section 3.1.1.1) may not be available and therefore was to be requested from the sponsors/investigators of the trials.

- **Insufficiency of data for subgroup analysis:** as described above, 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 controls 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 algorithm and patient pathway:** different treatment guidelines have been drawn by various organisations, and are being updated rapidly. For example, we are aware that the guidelines issued by the European Society of Cardiology are being updated and new guidelines will be issued in 2008. It was unlikely that there would be sufficient evidence to deal with the issues around the

sequencing of the technologies and as stated above only first use of the technologies was considered; except for epoprostenol where second line use for patients in FCIV was considered (see section 4.1.5).

- **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 was to be requested from individual trial sponsors and therefore the assessment report was somewhat reliant on the availability of such data.

4.2.2 Areas that are considered outside the scope of the appraisal

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

Drugs and preparations that are not currently licensed for treating PAH in the UK, such as treprostinil (Remodulin®, United Therapeutics), Beraprost® (United Therapeutics), ambrisentan (Volibris/Letaris, GlaxoSmithKline) and iloprost iv 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 where evidence permitted according to the final scope of the appraisal.

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

4.3 Overall aims and objectives of assessment

The aim of this technology assessment was:

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 to supportive treatment (and/or iv iloprost).

To assess, as far as available 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 to supportive treatment (and/or iv 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 randomised controlled trials (RCTs) that investigated the effectiveness of the technologies in PAH. Variations in the effectiveness between the drugs and/or between different PAH populations was 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 the National Institute for Health and Clinical Excellence (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 National Health Service.

5. ASSESSMENT OF CLINICAL EFFECTIVENESS

5.1 Methods for reviewing effectiveness

5.1.1 Search strategy

The following resources were searched for relevant primary studies:

- Bibliographic databases: Cochrane Library (CENTRAL) 2007 Issue 1, MEDLINE (Ovid) 1950 – Feb 2007, MEDLINE in Process & Other Non-Indexed Citations (Ovid) and EMBASE (Ovid) 1980 – Feb 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. Where 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
- Industry submissions.

Searches were not limited by date 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 duplicates entries were removed.

5.1.2 Study Selection

One reviewer screened titles and abstracts for relevance and this was checked by a second reviewer; any disagreements were resolved by consensus. 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)), where the duration of the RCT(s) was greater than one week.

Intervention(s)

Any of: Epoprostenol (i.v.), 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 section 4.2.2), or any combination of these.

Population

Adult patients diagnosed with PAH (even if not all 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.

5.1.3 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 industry submissions, unpublished manuscripts and clinical study reports were extracted by only one reviewer due to time constraints.

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

5.1.4 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 table 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; pre-numbered or coded identical containers which 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 QOL 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.

5.1.5 Methods of data synthesis

5.1.5.1 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 QOL
- Exercise capacity (6MWT)
- Symptomatic improvement
- Frequency and duration of hospitalisation and outpatient/GP visits
- Serious adverse events
- Adverse events that are considered as clinically relevant or having potential impact on tolerability
- Withdrawal for any reasons
- Withdrawal due to lack of efficacy
- Withdrawal due to adverse events
- Haemodynamic assessment, e.g. cardiac index, right atrial pressure, pulmonary arterial oxygen saturation, pulmonary arterial pressure and pulmonary vascular resistance.

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), serious adverse events and withdrawal for any reasons.

- Continuous outcomes: exercise capacity (6MWT), haemodynamic assessment including mPAP, RAP, PVR and cardiac index.

Where 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 due to lack of efficacy and withdrawal due to 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 reasons 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.

5.1.5.2 Handling of data and presentation of results

For dichotomous outcomes, results are presented as relative risks (RR). 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 relative risks for this outcome were also calculated and presented. In addition, where 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 section 6.3).

For outcomes with continuous data, the values of mean change from baseline (i.e. mean value measured at the end of trial minus the mean value measured at baseline) were used in meta-analysis. Where possible, the standard deviation (SD) was taken directly from the reported results, or derived from the standard error of the mean (SEM) or confidence intervals (CIs). SDs for mean change from baseline, if not available, were imputed using the SDs of baseline values and SDs of post-treatment values assuming an intercorrelation coefficient of 0.5.[32] This was used only for the 6MWD data for Barst 1996.[11] When only the SD for the post-treatment value was available, it was used as the SD for the mean change from baseline. This was used only for the 6MWD data for Badesch 2000.[33]

5.1.5.3 Approaches for meta-analysis

Meta-analyses were carried out using Review Manager 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 FC III (and FC IV 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 comparison or mixed treatment comparison 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 that was 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/CTD 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 these were stated in an analyses checklist under each section of specific comparisons. The aims for 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 other potentially relevant evidence could also be considered.

Table 6 Planned analyses

Planned analysis		Population/doses/data to be included
A	Primary analysis	All PAH, FC III[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, FC III (or all FC), licensed dose(s)
H	Subgroup analysis – PAH/CTD	PAH/CTD, FC III (or all FC), licensed dose(s)

[a] plus FCIV for epoprostenol

5.1.5.4 Assessment of heterogeneity

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

5.1.5.5 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 the companies and the number of trials for each of the technology was small, publication bias was not formally assessed.

5.1.6 Ongoing studies

Ongoing studies (RCTs/open label studies) were identified by the above search strategy (section 5.1.1). These were not included in the systematic review but were tabulated separately for information.

5.1.7 Long term Follow up Studies

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

5.2 Results

5.2.1 Overall quantity of research available

The searches resulted in the identification 1354 articles after duplicates had been removed. Screening of the title and abstract of these articles indicated that 1309 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 8 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. Further 3 unpublished RCTs[36-38] were identified through screening of the five industry submissions for this assessment. All of these met the inclusion criteria. This resulted in 20 RCTs being included in the review. Figure 3 below 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 (iv), Beraprost®, ambrisentan).

The assessment of effectiveness of the technologies is reported below in six sections one for each of the technologies and one on head to head comparisons (sections 5.2.2 to 5.2.7). Where RCTs assessed combination of the technologies this is addressed as a subsection of the main technology under assessment (sections 5.2.3.3, 5.2.4.3).

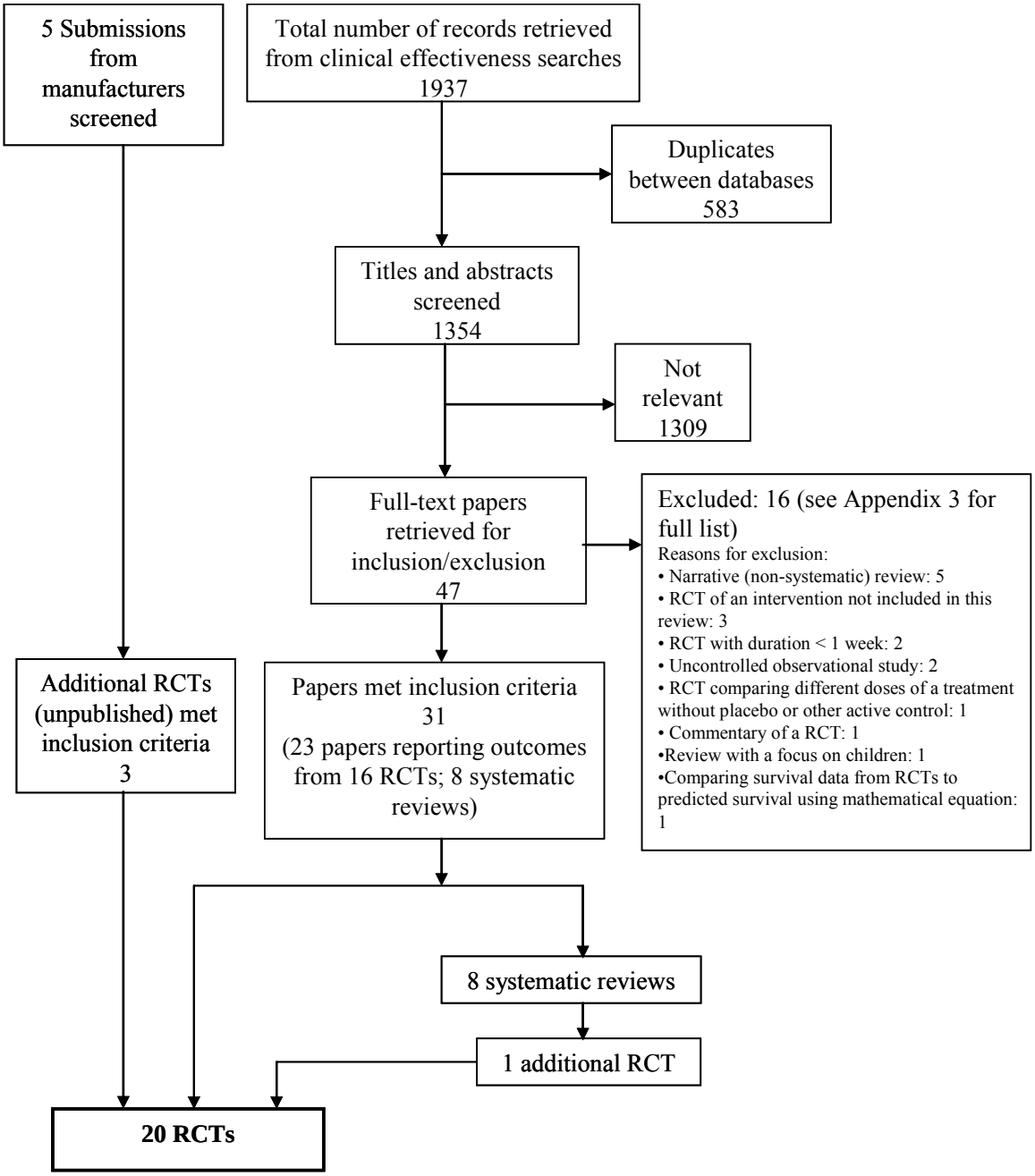


Figure 3 Flow Chart of Clinical Effectiveness Study Selection

Table 7 Distribution of comparisons undertaken in RCTs

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

*Newly initiated for BREATHE-2, ongoing for PACES-1 **Newly initiated for STRIDE-2 and SERAPH, ongoing for COMBI and STEP

5.2.2 Epoprostenol

5.2.2.1 Quantity and quality of included studies

Three RCTs (Rubin 1990,[39] Barst 1996,[11,40] Badesch 2000,[33]) compared epoprostenol (added to supportive treatment) to supportive treatment.[iii] 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, Barst 1996,[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 USA. The number of patients randomised ranged from 23[39] to 111[33] and study duration was between 8[39] and 12 weeks.[11,33] Rubin 1990[39] and Barst 1996[11] recruited exclusively patients with PPH, while Badesch 2000[33] recruited exclusively PAH patients with 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 FC IV at baseline. The mean/median 6MWD at baseline was less than 300 metres in all three trials. The primary endpoint was change in 6MWD for Barst 1996[11] and Badesch 2000[33] and was not stated for Rubin 1990.[39]

Quality assessment of these trials is summarised in Table 9. All the trials were open-label studies as double-blind, placebo-controlled design was not considered possible due to the known incidence of sepsis caused by central venous catheters and unique or highly predictable symptoms during long-term epoprostenol treatment.[11] However assessors for 6MWT were blinded in Barst 1996[11] and Badesch 2000[33]. With the exception of survival and 6MWD in Barst 1996[11] and 6MWD in Badesch 2000,[33] intention-to-treat analysis was not

[iii] An additional study (BREATHE-2)[56] which compared the initiation of bosentan-epoprostenol combination to epoprostenol alone will be described in the bosentan section (section 5.2.4.3). A further study (PACES-1[36]) which compared sildenafil to placebo in patients who were stable on epoprostenol treatment will be described in the sildenafil section (section 5.2.6).

used. Treatment withdrawal/loss to follow up was not clearly reported in Rubin 1990[39] and Badesch 2000.[33]

Table 8 Characteristics of included epoprostenol trials

Trial name/key paper (protocol number); location/centres	Duration; design; number of patients randomised	Intervention[a] (od: once daily; bd: twice daily; tid: three times daily)	Comparator[a]	Type of PAH[b]	Functional class	Age (years), mean (SD) % female	Baseline exercise capacity and haemodynamic measures,[c,d] mean (SD)			
Rubin 1990[39]; USA, 4 centres	8 weeks; open-label, parallel; n=23	Epoprostenol (iv infusion) individualised dose (n=11)	None (n=12)	PPH (100%)	II (9%) III (65%) IV (26%)	36 (14) 70%	6MWD Cardiac index mPAP	227 (NR)[n=19] NR 61.3 (NR)	PVR RAP SvO_2	NR NR NR
Barst 1996[11]; USA, multicentre	12 weeks; open-label, parallel; n=81	Epoprostenol (iv infusion) individualised dose (n=41)	None (n=40)	PPH (100%)	III (74%) IV (26%)	40 (15) 73%	6MWD Cardiac index mPAP	294 (126) 2.1 (0.8) 60 (13)	PVR RAP SvO_2	1280 (560)[e] 12 (7) 61 (13)
Badesch 2000[33]; USA, 17 centres	12 weeks, open-label, parallel; n=111	Epoprostenol (iv infusion) individualised dose (n=56)	None (n=55)	Scleroderma spectrum of disease (100%)	II (5%) III (78%) IV (17%)	55 (12) 86%	6MWD Cardiac index mPAP	272/240[f] 2.0 (0.7) 50 (10)	PVR RAP SvO_2	1016 (504)[e] 12 (5) 58.1 (10.4)

[a] With ongoing conventional therapy unless otherwise specified. [b] PPH: primary pulmonary hypertension. [c] NR: not reported. [d] 6-MWD: 6-minute walk distance (metres); Cardiac index (liter/min/m^2); mPAP: mean pulmonary arterial pressure (mm Hg); PVR: pulmonary vascular resistance (dyn*sec*cm^{-5}); RAP: right atrial pressure; SvO_2: mixed venous oxygen saturation (%). [e] Converted from mm Hg/litre/min (Wood units). [f] Median value for intervention/comparator arms; mean values were not reported.

Table 9 Quality assessment of included epoprostenol trials

Study	Truly random allocation (strata for randomisation)	Adequate allocation concealment	Blinding	Use of ITT analysis* (n included in analysis/N randomised)		% patient completed the trial	Comments
Rubin 1990[39] 8 wks	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 1996[11] 12 wks	Yes (FC, study centre, baseline vasodilator use)	Unclear	Open-label (assessor for 6MWT and QoL 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 2000[33] 12 wks	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	

*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). Where analysis for the outcome was performed but the number of patients

included was not reported, this was noted as ‘unclear’. Where ITT analysis was not used, the number of patients included in the analysis (or a range of numbers where more than one outcomes were analysed/more than one analysis were preformed with various numbers of patients used) over the number that should have been used in an ITT analysis is shown.

5.3.2 Epoprostenol (added to supportive treatment) versus supportive treatment

Planned meta-analyses for this comparison and those actually carried out were 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 IV), 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 the findings presented in this section are on analyses that could be performed and these are associated with patient populations of mixed FC (III & IV). The results of meta-analyses (or of individual trials where only one trial provided the data) are listed in Table 11. Results for individual outcomes are summarised in the following sub-sections.

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, FC III, licensed doses	No	All trials included patients with mixed FC but data stratified by FC were not available.
A2. Primary analysis	All PAH, FC IV, 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 (Rubin 1990[39], Barst 1996[11], Badesch 2000[33]) 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 dose and above licensed dose	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 was unlikely to have significant impact on the results.
F. Sensitivity analysis – excluding open-label trial	All PAH, all FC, licensed doses, excluding open-label trials	No	Not applicable – all the epoprostenol trials were open-label.
G. Subgroup analysis – IPAH	IPAH (PPH), mixed FC, licensed doses	Yes	Data from Rubin 1990[39] and Barst 1996[11] were included. This analysis matches most closely with epoprostenol's licensed indication (FC III and IV, PPH), although two patients from Rubin 1990[39] were in FC II at baseline.
H. Subgroup analysis – PAH/CTD	PAH/CTD, mixed FC, licensed doses	Yes	Data from Badesch 2000[33] were included.

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

Analysis (see analysis checklist Table 10**)**		**A1 & A2. Primary analyses**			**B. Sensitivity analysis – mixed FC**		**G. Subgroup analysis – IPAH**		**H. Subgroup analysis – PAH/CTD**	
PAH population		**All PAH subcategories**			**All PAH subcategories**		**IPAH only**		**PAH/CTD only**	
Functional class (FC)		**A1: III; A2: IV**			**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 1990**[39] **and Barst 1996**[11] **were included)**		**≤111 (data from Badesch 2000 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 to 1.57)	104[11,39]	0.18 (0.03 to 1.18)	111[33]	0.79 (0.22 to 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 to 36.50)**	104[11,39]	**7.45 (2.55 to 21.77)**	111[33]	**42.25 (2.62 to 680.61)**
FC maintained or improved	**RR**	0	Data not available		81[11]	1.22 (0.96 to 1.55)[c]	81[11]	1.22 (0.96 to 1.55)[c]	0	Data not available
Withdrawal for any reason	**RR**	0	Data not available		81[11]	**0.29 (0.09 to 0.99)**	81[11]	**0.29 (0.09 to 0.99)**	0	Data not available
6-minute walk distance[a] **(meters)**	**WMD**	0	Data not available		213[11,33,39]	**81 (45 to 117)**	102[11,39]	**58 (6 to 110)**	111[33]	**100 (55 to 144)**
Haemodynamics										
Mean pulmonary arterial pressure (mPAP)[b] **(mm Hg)**	**WMD**	0	Data not available		200[11,33,39]	**-6.3 (-8.7 to -3.9)**	89[11,39]	**-6.8 (-10.6 to -3.0)**	111[d33]	**-6.0 (-9.0 to -2.9)**
Right atrial pressure (RAP)[b] **(mm Hg)**	**WMD**	0	Data not available		176[11,33]	**-2.4 (-4.1 to -0.7)**	65[11]	[redacted]	111[d33]	**-2.5 (-4.6 to -0.4)**

Analysis (see analysis checklist Table 10**)**		**A1 & A2. Primary analyses**			**B. Sensitivity analysis – mixed FC**		**G. Subgroup analysis – IPAH**		**H. Subgroup analysis – PAH/CTD**	
Pulmonary vascular resistance (PVR)[b] (dynes*sec*cm^{-5})	**WMD**	0	Data not available		176[11,33,39]	**-427 (-548 to -306)**	65[11,39]	**-401 (-613 to -189)**	111[d33]	**-440 (-588 to -292)**
Cardiac index[a]	**WMD**	0	Data not available		179[11,33]	**0.6 (0.4 to 0.8)**	68[11]	[redacted]	111[d33]	**0.6 (0.4 to 0.8)**
Safety										
Serious adverse events	**RR**	0	Data not available		0	Data not available	0	Data not available	0	Data not available

[a] Mean change from baseline; positive value favours epoprostenol.
[b] Mean change from baseline; negative value favours epoprostenol
[c] Intention-to-treat analysis in which patients who died or had lung transplantation in Barst 1996 (n=1 for epoprostenol group and n=10 for control group) were assumed to have their functional class worsened. Original data reported in Barst 1996 excluded these patients.
[d] The number of patients contributed to the data was not stated in Badesch 2000. The number of patients randomised was used in the analysis.

Survival

A total of 21 deaths (5 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 1996,[11] in which eight deaths occurred in the control group versus none in the epoprostenol group (RR = 0.06, 95% CI 0.00 to 0.96). The pooled relative risk also shows a trend in favour of epoprostenol although it does not reach statistical significance (RR = 0.37, 0.09 to 1.57, I^2 = 39%).

Time to clinical worsening

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

Functional class

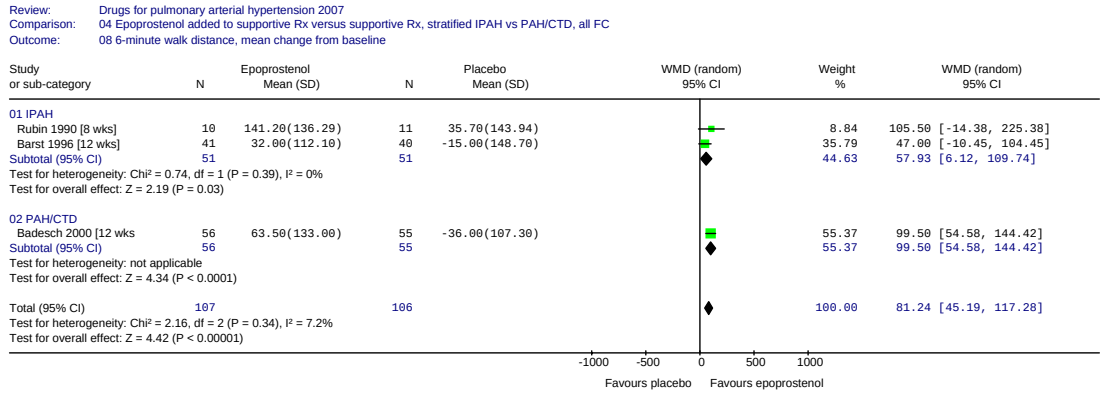
The proportion of patients that had their FC unchanged/worsened was not reported in Rubin 1990[39] or Badesch 2000.[33]

Results from Barst 1996[11] showed a non-significant relative risk of 1.22 (0.96 to 1.55) for having FC improved or maintained (the planned dichotomous outcome for FC) for epoprostenol group compared to control group.

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

Exercise capacity

The mean changes from baseline in 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 weighted mean difference was an increase of 81 metres (95% CI 45 to 117, I^2 = 25%) for epoprostenol groups compared to control groups.



Note: the standard deviations for Barst 1996 and Badesch 2000 were not reported and were imputed using the methods described in the method section.

Figure 4 Forest Plot: Epoprostenol added to supportive treatment versus supportive treatment alone – change in 6MWD

Quality of life

This outcome was reported only in Barst 1996.[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 epoprostenol group compared to control group was observed for all four parts of the Chronic Heart Failure Questionnaire (dyspnoea, fatigue, emotional function, and mastery) and two (emotional reaction and sleep) of the six parts of the Nottingham Health Profile, but not for four (energy, pain, physical mobility and social isolation).

Haemodynamic measures

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

Other effectiveness measures

Both Barst 1996[11] and Badesch 2000[33] reported a significant improvement in Dyspnoea-Fatigue rating for epoprostenol group compared with control group. A significant improvement in the Borg dyspnoea index in favour of epoprostenol was also observed in Badesch 2000.[33]

Serious adverse events and other adverse events

Serious adverse events (SAEs) were not described separately from other adverse events in all 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 comparison 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 ranged from 8 to 12 weeks.

- Except Barst 1996[11] for which allocation concealment was not clear, methods of randomisation and allocation concealment were adequate in the trials. The reporting of treatment withdrawal and serious adverse events was poor. Intention-to-treat 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 due to deterioration, and these occurred more frequently in the control groups.

- The trials included predominantly FCIII and IV patients who were likely to be the sickest of any trials in PAH, 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 to 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 symptom (dyspnoea), certain domains of quality of life measures were also observed in individual trials.

- No significant difference was 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]

5.2.3 Iloprost

5.2.3.1 Quantity and quality of included studies

Two RCTs (AIR/Olschewski 2002,[41] AIR-2[36]) compared iloprost (added to supportive treatment) to supportive treatment. The AIR-2 study 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/Hoeper 2006,[58] STEP/McLaughlin 2006[59]) compared iloprost (added to ongoing bosentan therapy and supportive treatment) to ongoing bosentan therapy and supportive treatment.

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

Both the AIR and the AIR-2 studies were carried out in mixed populations including IPAH, other PAH within Category 1 of the Venice classification, as well as other pulmonary 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 IV patients, while the AIR-2 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 [redacted].

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

Table 12 Characteristics of included iloprost trials

Trial name/key paper (protocol number); location/centres	Duration; design; number of patients randomised	Intervention[a] (od: once daily; bd: twice daily; tid: three times daily)	Comparator[a]	Type of PAH[b]	Functional class	Age (years), mean (SD, range)[c] % female	Baseline exercise capacity and haemodynamic measures,[c,d] mean (SD)			
AIR / Olschewski 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[e] (n=101)	Placebo (inhalation) (n=102)	PPH (50%)[f], collagen vascular disease (17%), appetite suppressant (4%), non-PAH[g] (28%)	III (59%) IV (41%)	52 (13, 20-70) 68%	6MWD Cardiac index mPAP	323 (95) NR 53 (13)	PVR RAP SvO_2	1035 (446) [n=187] NR 60.5 (7.9) [n=169]
AIR-2[36] (A02237); [redacted], multicentre	12 weeks, open-label, parallel; n=63	Iloprost (inhalation) 24 µg daily divided into 6 or 9 doses[h] (n=30)	None (n=33)	PPH (63%), [redacted]	II (33%) III (48%) IV (19%)	46 (12, 24-78) 70%	6MWD Cardiac index mPAP	[redacted] NR [redacted]	PVR RAP SvO_2	[redacted] NR [redacted]
COMBI / Hoeper 2006[58]; Germany, multicentre	12 weeks, open-label, parallel; n=40	Iloprost (inhalation) 5 µg six times daily + ongoing bosentan (oral) 125 mg bd (n=19)	Ongoing bosentan (oral) 125 mg bd (n=21)	IPAH (100%)	III (100%)	52 (NR) 78%	6MWD Cardiac index mPAP	306 (77) 2.1 (0.6) 57 (16)	PVR RAP SvO_2	1056 (536)[j] 9 (5) 62 (9)

Trial name/key paper (protocol number); location/centres	Duration; design; number of patients randomised	Intervention[a] (od: once daily; bd: twice daily; tid: three times daily)	Comparator[a]	Type of PAH[b]	Functional class	Age (years), mean (SD, range)[c] % female	Baseline exercise capacity and haemodynamic measures,[c,d] mean (SD)			
STEP / McLaughlin 2006[59]; USA, multcentre	12 weeks, double-blind, parallel; n=67	Iloprost (inhalation) 5 µg six to nine times daily + ongoing bosentan (oral) 125 mg bd (n=34)	Placebo + ongoing bosentan (oral) 125 mg bd (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, range 10-77) 79%	6-MWD Cardiac index mPAP	335 (67) NR 52 (12)[n=57]	PVR RAP SvO_2	799 (381) NR 63.8 (7.7)

[a] With ongoing supportive treatment unless otherwise specified. [b] CTD: PAH associated with connective tissue disease; IPAH: idiopathic PAH; :PPH: primary pulmonary hypertension. [c] NR: not reported. [d] 6-MWD: 6-minute walk distance (metres); Cardiac index (litre/min/m^2); mPAP: mean pulmonary arterial pressure (mm Hg); PVR: pulmonary vascular resistance (dyn*sec*cm^{-5}); RAP: right atrial pressure; SvO_2: mixed venous oxygen saturation (%). [e] Individualised total daily dose of 15 to 45 µg depending on how well the patient tolerated the treatment. [f] 53% according to industry submission and Ghofrani 2002[42]. [g] Chronic thromboembolic pulmonary hypertension.

[h] [redacted]

[redacted] [I] [redacted] [j] Converted from mm Hg/litre/min (Wood units).

Table 13 Quality assessment of included iloprost trials

Study	Truly random allocation (strata for randomisation)	Adequate allocation concealment	Blinding	Use of ITT analysis* (n included in analysis/N randomised)		% patient completed the trial	Comments
AIR / Olschewski 2002[41] 12 wks	Yes (FC III or IV; PPH or non-PPH)	Yes	Double-blind	Survival analysis – N/A Clinical worsening – yes Functional class – no (184/203)	6-MWD – yes Haemodynamic – unclear Quality of life – no (177/203)	Placebo: 86% (88/102) Iloprost: 96% (97/101)	
AIR-2[36] 12 wks	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)	6-MWD – no (49/63) Haemodynamic – no (43-50/63) Quality of life – no (49/63)	Control: 79% (26/33) Iloprost: 73% (22/30)	
COMBI / Hoeper 2006[58] 12 wks	Unclear	Yes	Open-label	Survival analysis – no death Clinical worsening – yes Functional class – yes	6-MWD – yes Haemodynamic – N/A Quality of life - yes	Control: 100% (21/21) Iloprost: 100% (19/19)	
STEP / McLaughlin 2006[59] 12 wks	Yes	Yes	Double-blind	Survival analysis – no death Clinical worsening – no (65/67) Functional class – no (64/67)	6-MWD – 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.

*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). Where analysis for the outcome was performed but the number of patients included was not reported, this was noted as 'unclear'. Where ITT analysis was not used, the number of patients included in the analysis (or a range of numbers where more than one outcome were analysed/more than one analysis were preformed with various numbers of patients used) over the number that should have been used in an ITT analysis is shown.

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 were open-label studies. Methods of randomisation and allocation concealment were adequate except in the COMBI study in which method of randomisation was unclear. Neither of the open-label studies[36,58] mentioned blinding of outcome assessors. Only the COMBI study used intention-to-treat (ITT) analysis across all the outcomes examined. The AIR study used ITT analysis for its primary composite endpoint, 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 were excluded from analysis than the control arms 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 sections 5.3.2 and 5.3.3 given the different nature of 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 pre-inhalation measures (which represent chronic effects) are also discussed.

5.2.3.2 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 were 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 available evidence that may help inform the technology appraisal. The results of meta-analyses (or of individual trials where only one trial provided the data) are listed in Table 15. Results for individual outcomes are summarised in the following sub-sections. As there is a paucity of results that were directly applicable to iloprost's licensed indication (PPH, FCIII), findings presented here were mainly based on overall results of the AIR and AIR-2 studies that included patients with mixed pulmonary hypertension and FC.

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 AIR[41] and AIR-2[36] studies included non-PAH patients (category 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 AIR[41] and AIR-2[36] studies included non-PAH patients (category 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 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 Analysis F (excluding open-label trial) below.
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 AIR-2 study[36] which was open-label. This analysis also serves as sensitivity analysis of excluding confidential information as most data from AIR-2 study were academic in confidence.
G. Subgroup analysis – IPAH	IPAH (PPH), FC III, licensed doses	Yes	This analysis matches iloprost's licensed indication. Data were available only for the outcome of change in FC from AIR[41] and AIR-2[36] studies.
H. Subgroup analysis – PAH/CTD	PAH/CTD, FC III, licensed dose(s)	No	No data available.

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 Category 1-5)**		**All pulmonary hypertension (Venice Category 1-5)**		**IPAH only**	
Functional class (FC)		**All FC (II-IV)**		**All FC (II-IV)**		**All FC (II-IV)**		**FC III**	
Doses		**Licensed doses**		**Licensed doses**		**Licensed doses**		**Licensed doses**	
Total no. eligible for analysis		[redacted][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)**	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]	[redacted][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)**	0	Data not available
6-minute walk distance[a] (metres)	**WMD**	0	Data not available	203[41]	**36 (12 to 60)**	203[41]	**36 (12 to 60)**	0	Data not available
Haemodynamics									

Mean pulmonary arterial pressure (mPAP)[b] (mm Hg)	**WMD**	0	Data not available	201[c41]	**-4.4 (-6.7 to -2.1)**	201[c41]	**-4.4 (-6.7 to -2.1)**	0	Data not available
Right atrial pressure (RAP)[b] (mm Hg)	**WMD**	0	Data not available	203[c41]	**-2.2 (-3.5 to -0.9)**	203[c41]	**-2.2 (-3.5 to -0.9)**	0	Data not available
Pulmonary vascular resistance (PVR)[b] (dynes*sec*cm^{-5})	**WMD**	0	Data not available	187[c41]	**-335 (-421 to -249)**	187[c41]	**-335 (-421 to -249)**	0	Data not available
Cardiac index[a]	**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[c41]	1.13 (0.71 to 1.80)	0	Data not available

[a] Mean change from baseline; positive value favours iloprost.

[b] Mean change from baseline; negative value favours iloprost

[c] The number of patients contributed 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.

Survival

A total of 9 deaths (3 for iloprost, 6 for supportive treatment) were reported in the AIR[41] and AIR-2[36]. The number is too small to draw any firm conclusion.

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, less than 85 mm Hg); 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 percent in the distance walked in six minutes; 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 to the control arm (12/102), but this did not reach statistical significance (RR = 0.42, 0.15 to 1.15). This outcome was not reported in the AIR-2 study[36].

Functional class (FC)

Both the AIR[41] and AIR-2[36] trials failed to report this outcome according to the intention-to-treat 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]

[redacted] In both studies the proportion of patients (non-ITT population) who maintained or improved FC was not significantly different between iloprost and control arms, although there was a trend approaching statistical significance in favour of iloprost in the AIR study[41] (RR = 1.07, 0.97 to 1.18), which was also observed in the subgroup of patients with PPH, FCIII (RR = 1.22, 0.98 to 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, 1.13 to 3.48, $I^2 = 0$).

Exercise capacity

The mean changes from baseline in 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 AIR-2 study

[redacted]

[redacted] hence the data shown for this study needs to be interpreted with great caution. A significant improvement of 36 metres (95% CI 12 to 60) in 6MWD was seen for iloprost group compared to placebo group in the post-inhalation measurement of the AIR study (mixed pulmonary hypertension and FC).[41] On the contrary, [redacted] No data specifically for PPH, FCIII were available.

ACADEMIC IN CONFIDENCE - FIGURE REMOVED

Figure 5 Forest Plot: Iloprost added to supportive treatment versus supportive treatment – change in 6MWD (academic in confidence)

Note that the data shown were measured post-inhalation for the AIR study (top) and pre-inhalation for the AIR-2 study (bottom).

Quality of life

[redacted] in EuroQol visual analogue scale (0-100) for iloprost group compared to control group (weighted mean difference 7.07, 2.42 to 11.73, I^2 = 0%, non-ITT). An improvement of 0.09 in EuroQol health state score in iloprost group compared to no change in placebo group was also reported in the AIR study[41] but the difference was not statistically significant (P=0.11 by analysis of covari ance). 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 post-inhalation measures from the AIR study[41] shown in Table 15 demonstrated that iloprost significantly reduced mPAP, RAP and PVR compared to supportive treatment although it is unclear if ITT analysis was used. Pre-inhalation 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. The differences in pre-inhalation values between groups were not significantly different for mPAP and RAP but was significantly in favour of iloprost for PVR (-105 dynes*sec*cm^{-5}, -191 to -19).

[redacted]

[redacted]. No data specifically for PPH, FCIII were available.

Other effectiveness measures

The AIR study[41] reported a significant improvement in Mahler Dyspnoea Index transition score for the iloprost group compared to the placebo group.

Serious adverse events and other adverse events

There was no significant difference in the risk of SAEs between iloprost and control groups in the two trials (Pooled RR = 1.16, 0.77 to 1.75, I^2 = 0%). Significantly more syncope classified as a SAE was reported in the iloprost group than in the placebo group (5 vs. 0). Common adverse events that occur 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 PPH population mentioned above was identified.

Summary and discussion

- Two RCTs (AIR which was double-blind,[41] AIR-2 which was open-label[36]) comparing iloprost (added to supportive treatment) with supportive treatment alone were identified. The duration was 12 weeks for both studies.

- The trials appear to be well conducted, although whether [redacted] Intention-to-treat analysis was not used for change in functional class measure in the AIR study, and [redacted]. The potential bias is likely to be in favour of control group in the AIR study [redacted]. Despite this the AIR study demonstrated favourable outcomes for iloprost treatment [redacted] The results from AIR-2 study need to be interpreted with great caution particularly due to the potential bias in the exclusion of patients from analysis and the weakness of open-label study.

- The trials included populations of mixed PH including non-PAH (chronic thromboembolic pulmonary hypertension) and mixed FC. Patients had a mean 6MWD of 323 and [redacted] metres 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 were PPH in FCIII at baseline (licensed indication for iloprost).

- Few data for patients with PAH only (Category 1 of Venice classification) stratified by FC were available from published literature and industry submissions. Results were summarised mainly based on patient populations with mixed PH and FC.

- Given the cautions with respect to the AIR-2 study highlighted earlier, the following results were mainly based on findings from a single trial, the AIR study[41]. Compared to 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 patient population of mixed PH and FC. Significant improvements in PAH associated symptom (dyspnoea) and EuroQol visual analogue scale were also observed. The paucity of data prevents any inference being made specific to PPH, FCIII.

- Outcomes measured immediately after inhalation demonstrate acute effects of inhaled iloprost. Whether these represent overall treatment effects is debatable, as outcomes measured pre-inhalation showed much smaller effects (within the duration of the trials).

- No randomised comparison between iloprost and supportive treatment in PAH subcategories other than PPH population was identified.

5.2.3.3 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 were 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 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 where only one trial provided the data) are listed in Table 17. Results for individual outcomes are summarised in the following sub-sections.

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, FC III, licensed doses	Yes	Both 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 FC III 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 FC III 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 COMBI study[58] and IPAH subgroup data from STEP study[59] were included. This analysis matches closely with iloprost's licensed indication (PPH, FC III), as the vast majority of the participants in these two trials were in FC III.
H. Subgroup analysis – PAH/CTD	CTD/PAH, FC III, licensed dose(s)	No	Data were not available.

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)		**FC III**			**All FC (data mainly on FC III)**		**All FC (data mainly on FC III)**	
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)**		64[59]	**5.85 (1.41 to 24.34)**	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)
6-minute walk distance[a] (meters)	**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)[b] (mm	**WMD**	57[59]	**-8.0 (-11.4 to -4.6)**		57[59]	**-8.0 (-11.4 to -4.6)**	0	No data available

Hg)								
Right atrial pressure (RAP)[b] (mm Hg)	**WMD**	0	No data available		0	No data available	0	No data available
Pulmonary vascular resistance (PVR)[b] (dynes*sec*cm^{-5})	**WMD**	57[59]	**-245 (-373 to -117)**		57[59]	**-245 (-373 to -117)**	0	No data available
Cardiac index[a]	**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

[a] Mean change from baseline; positive value favours iloprost.

[b] Mean change from baseline; negative value favours iloprost

Survival

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

Time to clinical worsening

The pooled relative risk indicated a trend in favour of iloprost but this did not reach statistical significance (RR = 0.39, 95%CI 0.04 to 3.45) and showed moderate heterogeneity between the studies (I^2 =53%). Sensitivity analyses excluding the open labelled RCT (COMBI) increased the effect size but this was also not a statistically significant finding (see Table 17, analyses A & E).[iv]

Functional class (FC)

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 relative risks, and the results were 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 compared to the placebo group had their FC improved (11/31 versus 2/33, RR = 5.85, 1.41 to 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 in 6MWD (post-inhalation) for the two trials are shown in Figure 6. The mean 6WMD for iloprost group compared to placebo/control 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 pre-inhalation in the STEP trial[59].

[iv] 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.

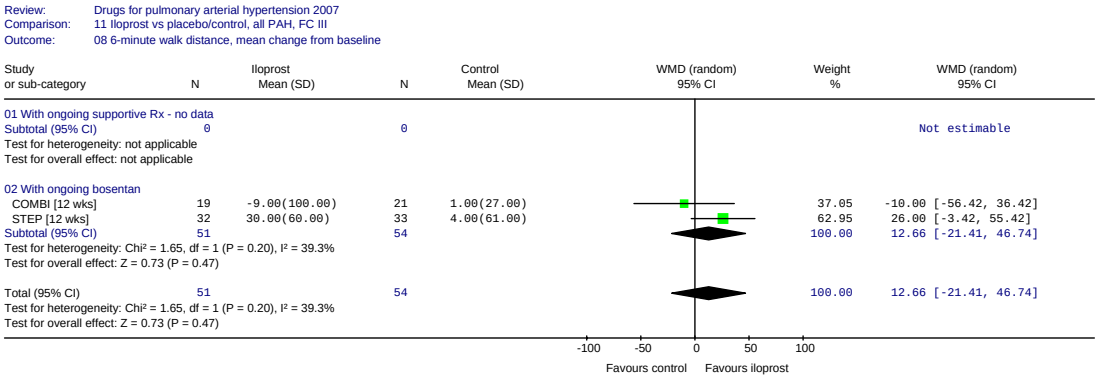


Figure 6 Iloprost added to ongoing bosentan and supportive treatment versus ongoing bosentan and supportive treatment – change in 6MWD

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 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 to placebo. When measured pre-inhalation, 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 due to 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 functional class 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, $\chi^2 = 0.18$, d.f.=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 to placebo/control with ongoing bosentan and supportive treatment. The duration of both trials was 12 weeks.

- Method of randomisation and serious adverse events were not clearly reported in the COMBI study[58]. The methodology and outcomes were well reported in the STEP study[59]. Intention-to-treat 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] while 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 difference between the iloprost group and the control group was observed for any of the outcome measures examined[58]. By contrast, the STEP study showed significant reduction in the risk of clinical worsening and increased likelihood of FC improvement for iloprost treated patients compared to placebo treated patients (with ongoing bosentan and supportive treatment), and also significant improvement in post-inhalation haemodynamic measures (mPAP and PVR) [59]. The changes in 6MWD between treatment groups were not statistically significant in both trials.

- The differences between treatment groups were generally smaller and not statistically significant for measures taken pre-inhalation. This is consistent with results from the AIR study (iloprost vs. placebo with ongoing supportive treatment).[41]

- Compared to the COMBI study, the STEP study had the advantage of being multicentre, double-blind 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 in the STEP study according to the mean 6MWD at baseline. It was not clear whether the inconsistent results between the two studies were attributed to any of these factors.

- No significant difference in the improvement in 6MWD and FC was observed in the STEP study between patients with IPAH and those with PAH of other causes[59].

5.2.4 Bosentan

5.2.4.1 Quantity and quality of included studies

Bosentan was investigated in six of the included RCTs. Four of these (Channick 2001,[15,43] BREATHE-1,[45,46] BREATHE-5,[47] STRIDE-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 to 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 in Section 5.2.7.

All 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 was 12 weeks for Channick 2001,[43] 18 weeks for STRIDE-2[48] and 16 weeks for BREATHE-1,[45] BREATHE-2[56] and BREATHE-5.[47] The bosentan dose of 125 mg twice daily was used in all 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 four weeks was used before patients were up-titrated 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 the trials included mixed population of IPAH (59-84% within each trial) and PAH/CTD (16-30% within each trial). STRIDE-2 also included 11% of patients with CHD. The submission to NICE by Actelion indicates that PAH associated with CHD (post-surgically 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 of the five trials (Channick 2001,[43] BREATHE-5[47]) 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 a 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 rest four trials (ranged from 334 to 358 metres) despite the differences in FC mix. The primary outcome measure was change in 6MWD for Channick 2001,[43] BREATHE-1[45] and STRIDE-2[48], and was 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 were summarised in Table 19. Method of randomisation was adequate in Channick 2001,[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 the five trials were double-blind studies, except that the bosentan arm in the STRIDE-2 trial was open-label (and was the only open-label arm in the trial). The investigators stated 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. Intention-to-treat (ITT) analysis was used in all trials for most outcomes but not for haemodynamic measures. The proportion of patients completing the studies was slightly lower in the placebo groups compared to the bosentan groups, except for BREATHE-2 in which a slightly lower

proportion of patients treated with bosentan (plus epoprostenol) completed the trial compared to those treated with placebo (plus epoprostenol).

Given the different nature of comparisons between the trials, the results of Channick 2001[43], BREATHE-1[45], BREATHE-5[47] and STRIDE-2 (bosentan vs. placebo only)[48] will be described separately from the results of BREATHE-2 in sections 5.2.4.2 and 5.2.4.3 respectively.

Table 18 Characteristics of included bosentan trials

Trial name/key paper (protocol number); location/centres	Duration; design; number of patients randomised	Intervention[a] (od: once daily; bd: twice daily; tid: three times daily)	Comparator[a]	Type of PAH[b]	Functional class	Age (years), mean (SD, range) % female	Baseline exercise capacity and haemodynamic measures,[c,d] mean (SD)			
Bosentan vs. placebo										
Channick 2001 (AC-052-351)[43]; USA & France, 6 centres	12 weeks; double-blind, parallel; n=32	Bosentan (oral) 125 mg bd [e] (n=21)	Placebo (n=11)	PPH (84%), scleroderma (16%)	III (100%)	51 (13) 88%	6MWD Cardiac index mPAP	358 (85) 2.4 (0.8) [n=30] 55 (12) [n=30]	PVR RAP SvO_2	912 (427) [n=29] 9.8 (5.1) [n=29] NR
BREATHE-1 / Rubin 2002[45]; International, 27 centres	16 weeks[f]; double-blind, parallel; n=213	Bosentan (oral) 125 mg bd [e] (n=74), 250 mg bd [e] (n=70)	Placebo (n=69)	PPH (70%), CTD (30%)	III (92%) IV (8%)	48 (16) 79%	6MWD Cardiac index mPAP	334 (75) 2.4 (0.8) [n=208] 54 (16)	PVR RAP SvO_2	970 (628) [n=200] 9.5 (5.7) [n=210] NR
BREATHE-5 / Galiè 2006[47]; international, 15 centres	16 weeks; double-blind, parallel; n=54	Bosentan (oral) 125 mg bd [e] (n=37)	Placebo (n=17)	Eisenmenger syndrome (100%)	III (100%)	39 (11) 61%	6MWD Cardiac index mPAP	343 (78) NR 76 (17)	PVR RAP SvO_2	3250 (1352) 5.8 (3.5) NR

Trial name/key paper (protocol number); location/centres	Duration; design; number of patients randomised	Intervention[a] (od: once daily; bd: twice daily; tid: three times daily)	Comparator[a]	Type of PAH[b]	Functional class	Age (years), mean (SD, range) % female	Baseline exercise capacity and haemodynamic measures,[c,d] mean (SD)			
STRIDE-2 (FPH02) / Barst 2006[48]; international, 55 centres	18 weeks; double-blind (open-label for bosentan), parallel; n=247	Bosentan (oral) 125 mg bd [e] (n=60); sitaxentan (oral) 50 mg od (n=62), 100 mg od (n=61)	Placebo (n=62)	IPAH (59%), CTD (30%), congenital heart disease (11%)	II (37%) III (59%) IV (4%)	54 (15) 78%	6MWD Cardiac index mPAP	337 (80) 2.4 (0.8) 48 (14)	PVR RAP SvO_2	880 (560) [g] NR NR
Bosentan + epoprostenol vs. epoprostenol										
BREATHE-2 / Humbert 2004[56]; USA & Europe, 7 centres	16 weeks; double-blind, parallel; n=33	Bosentan (oral) 125 mg bd [e] + epoprostenol (iv infusion) started with 2 ng/kg/min and increased to 12-16 ng/kg/min between week 14 and 16 (n=22)	Placebo + epoprostenol (iv infusion) started with 2 ng/kg/min and increased to 12-16 ng/kg/min between week 14 and 16 (n=11)	PPH (82%), CTD (18%)	III (76%) IV (24%)	46 (18, 15-69) 70%	6MWD Cardiac index mPAP	NR 1.7 (0.5) 60 (16)	PVR RAP SvO_2	1483 (537) 11.9 (5.9) NR

[a] With ongoing supportive treatment unless otherwise specified. [b] CTD: PAH associated with connective tissue disease; IPAH: idiopathic PAH; :PPH: primary pulmonary hypertension. [c] NR: not reported. [d] 6-MWD: 6-minute walk distance (metres); Cardiac index (litre/min/m^2); mPAP: mean pulmonary arterial pressure (mm Hg); PVR: pulmonary vascular resistance (dyn*sec*cm^{-5}); RAP: right atrial pressure; SvO_2: mixed venous

oxygen saturation (%). [e] 62.5 mg twice daily for the first four weeks. [f] Patients who were randomised within the first 2 months of the study (N=48) were treated and followed up for a further 12 weeks. [g] Converted from mm Hg/litre/min (Wood units).

Table 19 Quality assessment of included bosentan trials

Study	Truly random allocation (strata for randomisation)	Adequate allocation concealment	Blinding	Use of ITT analysis* (n included in analysis/N randomised)		% patient completed the trial	Comments
Bosentan vs. placebo							
Channick 2001[43] 12 wks	Yes	Unclear	Double-blind	Survival analysis – no death Clinical worsening – yes Functional class – yes	6-MWD – yes Haemodynamic – no (29-30/32) Quality of life – N/A	Placebo: 82% (9/11) Bosentan: 100% (21/21)	
BREATHE-1 / Rubin 2002[45] 16 wks	Unclear	Unclear	Double-blind	Survival analysis – N/A Clinical worsening – yes Functional class – yes	6-MWD – yes Haemodynamic – N/A Quality of life – N/A	Not reported	
BREATHE-5 / Galiè 2006[47] 16 wks	Yes	Yes	Double-blind	Survival analysis – no death Clinical worsening – N/A Functional class – yes	6-MWD – yes Haemodynamic – no (unclear[a]) Quality of life – N/A	Placebo: 88% (15/17) Bosentan: 95% (35/37)	

Study	Truly random allocation (strata for randomisation)	Adequate allocation concealment	Blinding	Use of ITT analysis* (n included in analysis/N randomised)		% patient completed the trial	Comments
STRIDE-2 / Barst 2006[48] 18 wks	Yes	Yes	Double-blind for placebo (and sitaxentan); open-label for bosentan	Survival analysis – N/A Clinical worsening – yes Functional class – no (120/122)	6-MWD – no (120/122) Haemodynamic – N/A Quality of life – N/A	Placebo: 82% (51/62) Bosentan: 87% (52/60)	Seven randomised patients (2 did not receive treatment, 5 did not have a valid post-baseline 6 MWT) were excluded from efficacy analyses.
Bosentan + epoprostenol vs. epoprostenol							
BREATHE-2 / Humbert 2004[56] 16 wks	Unclear	Unclear	Double-blind	Survival analysis – N/A Clinical worsening – yes Functional class – yes	6-MWD – no (29/33) Haemodynamic – yes except PVR Quality of life – N/A	Epoprostenol: 91% (10/11) Epoprostenol + bosentan: 82% (18/22)	

*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). Where analysis for the outcome was performed but the number of patients included was not reported, this was noted as 'unclear'. Where ITT analysis was not used, the number of patients included in the analysis (or a range of numbers where more than one outcome were analysed/more than one analysis were preformed with various numbers of patients used) over the number that should have been used in an ITT analysis is shown.

5.2.4.2 Bosentan added to supportive treatment versus supportive treatment alone

This comparison was investigated in Channick 2001[43], BREATHE-1[45], BREATHE-5[47] and STRIDE-2[48]. Planned meta-analyses for the comparison and those actually being carried out were 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 was change in FC, the planned primary analysis (all PAH, FCIII) included data only from Channick 2001[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 this analysis. However sensitivity analyses including populations of mixed FC from these two trials were carried out. The results of meta-analyses (or of individual trials where only one trial provided the data) are listed in Table 21. Results for individual outcomes are summarised in the following sub-sections. Given the relatively small number of patients included in the primary analysis, results presented were mainly drawn from data of mixed FC. Findings specifically for FCIII were stated separately where appropriate.

Where 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. Where STRIDE-2[48] is mentioned in this section, it is only referred to with regard to data from the placebo and bosentan arms.

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, FC III, licensed dose(s)	Yes	Data from Channick 2001[43] (n=32) and BREATHE5[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 2001[43] (n=32), BREATHE-1[45] (n=213), BREATHE5[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 2001[43] (n=32), BREATHE-1[45] (n=213) and BREATHE5[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 – PAH/CTD	PAH/CTD, all FC, licensed dose(s)	Yes	Subgroup analyses reported by Denton and colleagues[44] were included. See texts for detail.

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 – PAH/CTD**	
PAH population		**All PAH subcategories**			**All PAH subcategories**		**All PAH subcategories**		**PAH/CTD only**	
Functional class (FC)		**FC III**			**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)**	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)**	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
6-minute walk distance[a]	**WMD**	86 [43,47]	**59 (20 to 99)**		421 [43,45,47,48]	**41 (24 to 58)**	299 [43,45,47]	**49 (27 to 70)**	66[43,45]	22 (-32 to 76)
Haemodynamics										

Mean pulmonary arterial pressure (mPAP)[b]	**WMD**	84 [43,47]	**-5.9 (-9.3 to -2.5)**		84 [43,47]	**-5.9 (-9.3 to -2.5)**	84 [43,47]	**-5.9 (-9.3 to -2.5)**	0	Data not available
Right atrial pressure (RAP)[b]	**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)[b]	**WMD**	29 [43]	**-414 (-596 to -232)**		29 [43]	**-414 (-596 to -232)**	29 [43]	**-414 (-596 to -232)**	0	Data not available
Cardiac index[a]	**WMD**	30 [43]	**1.0 (0.7 to 1.3)**		30 [43]	**1.0 (0.7 to 1.3)**	30 [43]	**1.0 (0.7 to 1.3)**	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)**	54 [47]	0.77 (0.21 to 2.84)	0	Data not available

[a] Mean change from baseline; positive value favours bosentan.

[b] Mean change from baseline; negative value favours bosentan

Survival

A total of 5 deaths (1 from bosentan groups, 4 from placebo groups) were reported in the four trials.[43,45,47,48] An additional 3 deaths from the bosentan group (250 mg twice daily) occurred within four weeks after withdrawal from or completion of the BREATHE-1 trial. The number is too small to draw any firm conclusion.

Time to clinical worsening

Clinical worsening was not reported in BREATHE-5[47] and was defined differently in Channick 2001[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] (hospitalization for PAH, death, transplantation, atrial septostomy, initiation of new chronic PAH treatment, or combined WHO FC deterioration and ≥15% decrease in 6MW distance from baseline). Time-to-event analysis was carried out in all three trials although hazard ratios were not reported. Two of these reported significant increase in time to clinical worsening for bosentan group(s) compared to placebo (p=0.033 in Channick 2001[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 relative risk of clinical worsening for Channick 2001[43] and BREATHE-1[45] trials significantly favours bosentan (Analysis F; RR = 0.28, 0.13 to 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, 0.15 to 1.24, I^2 = 62%).

Functional class (FC)

Table 21 shows that the proportion of patients who maintained or improved FC was not significantly different between bosentan and placebo group. 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, 1.05 to 2.15, I^2 = 0%). The pooled result from three trials[43,47,48] (excluding BREATHE-1, data not available) specifically for FCIII also favours bosentan but just fails to reach statistical significance (RR = 2.08, 0.97 to 4.46, I^2 = 0%).

Exercise capacity

The mean changes from baseline in 6MWD for the four trials[43,45,47,48] (mixed FC) are shown in Figure 7. Significant increase in 6MWD for bosentan groups compared to placebo groups was observed in all trials, including Channick 2001[43] and BREATHE-5[47] which recruited only patients in FCIII. The pooled results from these two studies (Analysis A, Table 21) was 59 metres in favour of bosentan (95% CI 20 to 99, I^2 = 0%)

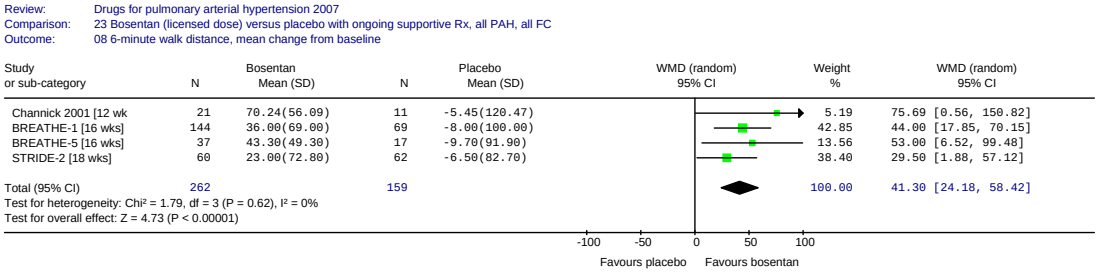


Figure 7 Forest plot: Bosentan added to supportive treatment versus supportive treatment – change in 6MWD

Quality of life

No trial reported QOL outcomes.

Haemodynamic measures

As post-treatment haemodynamic outcomes were measured only in Channick 2001[43] and BREATHE-5[47] which recruited exclusively patients in FCIII, the results shown in Table 21 for haemodynamic outcomes were identical for Analysis A, B and F. Compared to placebo, bosentan significantly reduced mPAP and PVR and increased cardiac index. Significant difference in the change of RAP between bosentan and placebo groups was observed in Channick 2001[43] (-6.2 mm Hg, 95% CI -9.6 to -2.8) but not in BREATHE-5 (-0.1, -2.1 to 1.9). In Channick 2001 the RAP reduced 1.3 mm Hg in the bosentan group while increased 4.9 mm Hg in the placebo group. RAP increased slightly in both bosentan and placebo groups (0.3 and 0.4 mm Hg respectively) in BREATHE-5.

Other effectiveness measures

A significant decrease (improvement) in Borg Dyspnoea Index for the bosentan groups compared to the placebo group was observed in BREATHE-1[45] (mean difference -0.6, -1.2 to -0.1) and Channick 2001[43] (-1.6, -3.1 to 0.0) but no significant difference between bosentan and placebo was observed in STRIDE-2[48].

Serious adverse events and other adverse events

The total number of patients who experienced at least one serious adverse event was not reported in Channick 2001[43] and BREATHE-1 [45]. Pooled result (mix FC) for BREATHE-5 and STRIDE-2 showed a significant decreased risk for bosentan treated patients compared to placebo (RR = 0.45, 0.23 to 0.89, I^2 = 0%). Common adverse events that occur 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 (Channick 2001[43] and BREATHE-1[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 PAH/CTD in Channick 2001 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 PAH/CTD patients (n=66) indicated that patients treated with bosentan may have more severe disease compared to those treated with placebo (6MWD 312 versus 361 metres, P=0.01). The change in 6MWD from baseline increased 19.5 metres in patients treated bosentan while deteriorated 3 metres in patients treated placebo. The difference between groups was not statistically significant (22 metres, 95%CI -32 to 76). The Kaplan-Meier estimates of the percentage of patients without experiencing clinical worsening also showed a non-significant trend in favour of bosentan compared to 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 to 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 all the outcomes examined in this review, with the exception of right atrial pressure. Significant treatment effect was found in Channick 2001[43] but not in BREATHE-5[47] (see Haemodynamic measures subsection above).

Summary and discussion

- Four RCTs comparing bosentan (added to supportive treatment) with supportive treatment alone were identified. Three of them (Channick 2001[43], BREATHE-1[45] and BREATHE-5[47] were double-blind studies while the bosentan arm in the STRIDE-2 trial[48] was open-label. The duration 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 in 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 due to its open-label design.

- There was heterogeneity with regard to the populations enrolled in the trials. For example BREATHE5 enrolled exclusively Eisenmenger syndrome whilst the others enrolled mixed IPAH and CTD-APAH. The mean 6MWD at baseline ranged from 334 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 2001 and BREATHE-5) provided some data specific to FCIII.

- Compared to supportive treatment alone, bosentan added to supportive treatment has demonstrated significant improvement in exercise capacity (6MWD) and haemodynamic outcomes (mPAP, PVR and cardiac index) both in PAH populations with mixed FC and specifically in FCIII. Significant increase in time to clinical worsening, improvement in FC and PAH symptom (dyspnoea), and decreased risk of serious adverse events were also observed among bosentan treated patients compared to placebo in PAH populations with mixed FC.

- Subgroup analysis of PAH/CTD patients in Channick 2001[43] and BREATHE-1[45] showed similar results to those of the whole trial population (mixed IPAH and PAH/CTD).

5.2.4.3 Bosentan plus epoprostenol versus epoprostenol

This comparison was investigated in the BREATHE-2 trial (Humbert et al 2004)[56]. This trial was the only study included in this review that genuinely compared the initiation of a drug combination versus 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 have been shown in Table 18 and Table 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 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 a 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 due to acute cardiopulmonary failure, the other due to anaemia, pneumonia with rapidly progressing right heart failure). A third patient died after being withdrawn from the study for PAH worsening. All the three patients received epoprostenol/bosentan combination. The number is however too small to make any firm conclusion. Worsening pulmonary hypertension was reported as adverse events in two patients in the epoprostenol group and one patient in the combination group. These figures obviously do not included deaths and thus were 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 combination and 5/11 for epoprostenol, RR = 1.30, 95%CI 0.62 to 2.71). Results specifically for patients in FCIII at baseline showed little difference (9/17 for combination and 4/8 for epoprostenol, RR = 1.06, 95%CI 0.46 to 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 the 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 % improvement) in the combination group than in the epoprostenol group. None of the differences between groups however were 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, 0.25 to 15.82).

Summary and discussion

- One double-blind, placebo-controlled trial (BREATHE-1)[56] compared the initiation of epoprostenol plus bosentan to epoprostenol alone in mixed PAH populations (IPAH and PAH/CTD) 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 difference between the group treated with epoprostenol/bosentan combination and the group treated with epoprostenol was observed for any of the outcomes assessed in the trial.

5.2.5 Sitaxentan

5.2.5.1 Quantity and quality of included studies

Sitaxentan was investigated in three of the included RCTs. All the three trials (STRIDE-1/Barst 2004[49], STRIDE-2/Barst 2006[48], STRIDE-4/Barst 2007[37] compared sitaxentan to 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 been included in Section 5.2.4.2; the bosentan-sitaxentan comparison will be described in section 5.2.7. This section focuses on the comparison of sitaxentan added to supportive treatment versus supportive treatment alone. The characteristics of the three studies are summarised in Table 22. The STRIDE-2 trial[48] has been listed in relevant tables in section 5.2.4 (bosentan) but is also listed in this section for the convenience of readers.

All three studies[37,48,49] were industry-sponsored multicentre trials which randomised between 98 to 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 Spain and Poland. The clinical study reports (commercial in confidence) for all the 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 relevant sensitivity analysis in this review) while STRIDE-2 [48] and STRIDE-4[37] included a sub-licensed dose of 50 mg once daily (not considered in this review).

All the three trials recruited mixed PAH populations of IPAH (ranged from 53% in STRIDE-1 to 68% in STRIDE-4), PAH/CTD (15% to 30% within each trial) and congenital heart disease (11% to 24% within each trial). The majority of patients in STRIDE-1 and STRIDE-2 were in FCIII at baseline (66% and 59% respectively), while in STRIDE-4 only 38% were in FCIII at baseline (the majority being in FCII, 61%). The primary endpoint was percent of predicted peak oxygen uptake (Vo_2) and was change in 6MWD in STRIDE-2 and STRIDE-4.

Table 22 Characteristics of included sitaxentan trials

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

[a] With ongoing conventional therapy unless otherwise specified. [b] IPAH: idiopathic PAH; CTD: PAH associated with connective tissue disease; S-P: systemic-to-pulmonary. [c] NR: not reported. [d] 6MWD: 6-minute walk distance (metres); Cardiac index (litre/min/m^2); mPAP: mean pulmonary arterial pressure (mm Hg); PVR: pulmonary vascular resistance (dyn*sec*cm^{-5}); RAP: right atrial pressure (mm Hg); SvO_2: mixed venous oxygen saturation (%). [e] 62.5 mg twice daily for the first four weeks.

Table 23 Quality assessment of included sitaxentan trials

Study	Truly random allocation (strata for randomisation)	Adequate allocation concealment	Blinding	Use of ITT analysis* (n included in analysis/N randomised)		% patient completed the trial	Comments
STRIDE-1 / Barst 2004[49] 12 wks	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 od: 100% (55/55) Sitaxentan 300 mg od: 89% (56/63)	
STRIDE-2 / Barst 2006[48] 18 wks	Yes	Yes	Double-blind (for sitaxentan and placebo; open-label for bosentan)	Survival analysis – N/A Clinical worsening – yes Functional class – no ([redacted])[a]	6MWD – no ([redacted])[a] Haemodynamic – not measured Quality of life – not measured	Placebo: 82% (51/62) Sitaxentan 50 mg od: 87% (54/62) Sitaxentan 100 mg: 93% (57/61)	Patients who did not have a valid post-baseline 6MWT were excluded from efficacy analysis.
STRIDE-4 / Barst 2007[37] 18 wks	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 od: 88% (28/32) Sitaxentan 100 mg: 91% (29/32)	

*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). Where analysis for the outcome was performed but the number of patients included was not reported, this was noted as 'unclear'. Where ITT analysis was not used, the number of patients included in the analysis (or a range of numbers where more than one outcomes were analysed/more than one analysis were preformed with various numbers of patients used) over the number that should have been used in an ITT analysis is shown. [a] numbers refer to placebo and sitaxentan 100 mg arm only.

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

5.2.5.2 Sitaxentan (added to supportive treatment) versus supportive treatment

This comparison was investigated in all the three trials (STRIDE-1[49], STRIDE-2[48], STRIDE-4[37]). Planned analyses and those actually carried out are summarised in Table 24. Results of meta-analysis are listed in Table 25 according to planned comparisons. Results for individual outcomes are described in the following sub-sections. As all the 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 were stated separately where appropriate.

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, FC III, 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 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 the 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] and were described in the texts.
H. Subgroup analysis – PAH/CTD	PAH/CTD, all FC, licensed dose and above	No	Only limited data were available from STRIDE-1[61] and were described in the texts.

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)		**FC III**			**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 to 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)**	367[37,48,49]	**0.32 (0.12 to 0.81)**	304[37,48,49]	**0.33 (0.12 to 0.87)**
FC improved	**RR**	95[37,48]	1.53 (0.74 to 3.17)		302[37,48,49]	**1.74 (1.12 to 2.70)**	365[37,48,49]	**1.76 (1.15 to 2.70)**	302[37,48,49]	**1.74 (1.12 to 2.70)**
FC maintained or improved	**RR**	95[37,48]	1.11 (1.00 to 1.23)		302[37,48,49]	**1.10 (1.04-1.16)**	365[37,48,49]	**1.09 (1.03 to 1.15)**	302[37,48,49]	**1.10 (1.04-1.16)**
Withdrawal for any reason	**RR**	0	Data not available		304[37,48,49]	**0.43 (0.19 to 0.98)**	367[37,48,49]	0.57 (0.29 to 1.12)	238[48,49]	**0.31 (0.11 to 0.87)**
6-minute walk distance[a]	**WMD**	0	Data not available		302[37,48,49]	**32 (18 to 47)**	365[37,48,49]	**32 (18 to 46)**	302[37,48,49]	**32 (18 to 47)**
Haemodynamics										
Mean pulmonary arterial pressure (mPAP)[b]	**WMD**	0	Data not available		115[49]	**-3.0 (-5.9 to -0.1)**	178[49]	**-4.0 (-6.7 to -1.3)**	115[49]	**-3.0 (-5.9 to -0.1)**

Right atrial pressure (RAP)[b]	**WMD**	0	Data not available		115[49]	-1.0 (-2.5 to 0.5)	178[49]	**-1.5 (-2.8 to -0.3)**	115[49]	-1.0 (-2.5 to 0.5)
Pulmonary vascular resistance (PVR)[b]	**WMD**	0	Data not available		115[49]	**-270 (-402 to -138)**	178[49]	**-256 (-349 to -163)**	115[49]	**-270 (-402 to -138)**
Cardiac index[a]	**WMD**	0	Data not available		115[49]	**0.3 (0.1 to 0.5)**	178[49]	**0.4 (0.2 o 0.5)**	115[49]	**0.3 (0.1 to 0.5)**
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)

[a] Mean change from baseline; positive value favours sitaxentan.

[b] Mean change from baseline; negative value favours sitaxentan

Survival

A total of three deaths were reported in the three trials[37,48,49]: 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 conclusion.

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 hospitalization 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 trial 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 relative risk (mixed FC) for experiencing one or more clinical worsening events was significantly in favour of sitaxentan at licensed dose (100 mg once daily) compared to placebo (RR = 0.33, 95% CI 0.12 to 0.87, I^2 = 0%). Inclusion of above licensed dose had little impact on the estimate.

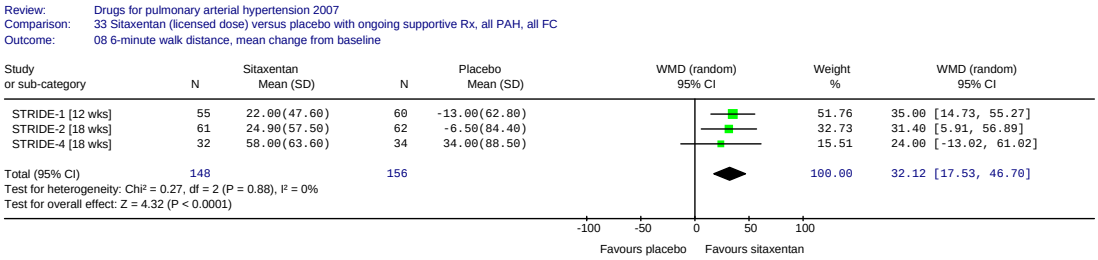
Functional class (FC)

Table 25 shows that the proportion of patients who maintained or improved FC was significantly higher among patients treated with sitaxentan (licensed dose) than those treated with placebo (RR = 1.10, 1.04 to 1.16, I^2 = 0%). The proportion of patients having FC improved was also significantly higher among sitaxentan (licensed dose) treated patients than placebo treated patients (RR = 1.74, 1.12 to 2.70, I^2 = 0%). Inclusion of above licensed dose had little impact on the estimates. The results specifically for FC III 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 in 6MWD for the three trials[37,48,49] are shown in Figure 8. Sitaxentan at licensed dose significantly increased 6MWD compared to placebo (32 metres, 18 to 47, I^2 = 0%) in patients with mixed FC. Data specifically for FCIII patients were not available.

Figure 8 Sitaxentan added to supportive treatment versus supportive treatment – change in 6MWD



Quality of life

QOL outcomes were measured only in the STRIDE-1 study[49] using the SF-36. No significant differences between treatment groups were found.

Haemodynamic measures

Haemodynamic outcomes were measure only in the STRIDE-1 study[49]. Results summarised in Table 25 show that sitaxentan at its licensed dose significantly reduced mPAP (-3.0 mm Hg, -5.9 to -0.1) and PVR (-270 dyn*sec*cm^{-5}, -402 to -138), and improved cardiac index (0.3, 0.1 to 0.5) compared to placebo in patients with mixed FC. Inclusion of above licensed dose appears to slightly increase the treatment effects (except PVR) and the reduction in RAP also reached statistical significance.

Other effectiveness measures

Borg Dyspnoea Index was measured in STRIDE-2[48] and STRIDE-4[37]. There was no significant difference between sitaxentan groups and 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 vs. 19/62) [48]. The pooled relative risk of three trials was not statistically significant (mixed FC, RR = 0.55, 0.27 to 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 occur more frequently in the sitaxentan groups include headache, peripheral oedema, nasal congestion, increased INR and/or prothrombin prolonged (interaction with warfarin).[48,49]

Subgroup analysis – PAH subcategories

Results for the subgroup of patients with connective tissue disease (PAH/CTD) within the STRIDE-1 study was reported by Grigis and colleagues[61]. Data from sitaxentan 100 mg and 300 mg arms were combined in this post-hoc analysis. The mean 6MWD increased 20 metres (SD=52) from baseline in the combined sitaxentan group (n=33) while decreased 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 to placebo treated patients were also observed in haemodynamic measures including RAP, PVR and cardiac index. More sitaxentan treated patients improved FC compared to placebo treated patients (8/33 vs. 1/9, P=0.14). In contrast to the overall trial results which showed a significant treatment effect in all the six domains of SF-36, significant improvements in the physical functioning and role physical domains were observed.

The authors also compared data from the PAH/CTD 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 to 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 duration of 12 to 18 weeks. The licensed dose for sitaxentan (100 mg once daily) was investigated in all the trials.

- Methods of randomisation and allocation concealment were adequate in all the three trials. Intention-to-treat 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 meta-analysis is likely to be small.

- All three trials included mixed populations of patients with IPAH, PAH/CTD and PAH associated with congenital heart disease. The mean 6MWD at baseline ranged from 337[48] to 398[49] metres. 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 patient population with mixed FC.

- Compared to 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 PAH/CTD was similar to those observed in the whole trial populations.[61] No significant differences were found between IPAH and PAH/CTD across various efficacy outcomes. 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.

5.2.6 Sildenafil

5.2.6.1 Quantity and quality of included studies

Sildenafil was investigated in six of the included RCTs. Four of these (SUPER-1/Galiè 2005[53], Bharani 2003[35], Sastry 2004[54], Singh 2006[55]) compared sildenafil to placebo in patients with ongoing supportive treatment (patients in Bharani 2003 appeared to have stopped previous vasodilator therapy before entering the study[35]). Another trial (PACES-1[38]), identified through industry submission, compared sildenafil to placebo in patients with ongoing epoprostenol and supportive treatment. The characteristics of these five studies are summarised in Table 26. Sildenafil was compared to bosentan in a further study by Wilkins and colleagues (SERAPH)[57], which will be described separately in Section 5.2.8.

The SUPER-1[53] and PACES-1[38] were industry-sponsored international studies which 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. Bharani 2003[35], Sastry 2004[54] and Singh 2006[55] were small (n=10, 22 and 20 respectively) single centre, cross-over trials conducted in India. The study by Sastry and colleagues was sponsored by a not-for-profit organisation[54] and the sponsorship for Bharain 2003[35] and Singh 2006[55] was not reported. The cross-over trials had duration of 2[35] to 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 up to 80 mg three times daily were also investigated in the SUPER-1[53] and were used in all the other trials (see Table 26).

Both SUPER-1[53] and PACES-1[38] trials recruited mixed PAH populations of IPAH and PAH/CTD. The SUPER-1 study also included 6% of patients with congenital heart disease. The majority of patients in both trials were in FCIII at baseline; there were 39% and 26% of patients in FCII at baseline for SUPER-1 and PACES-1 respectively. The primary endpoint was change in 6MWD for both trials. Bharani 2003 recruited patients in FC II to IV at baseline with various types of pulmonary hypertension including PPH, PAH associated with Eisenmenger syndrome and other forms of pulmonary hypertension[35]. Sastry 2004 recruited exclusively PPH patients, the majority of which were in FCII at baseline (82%)[54]. Singh 2006 recruited mixed PAH populations of IPAH and Eisenmenger syndrome[55]. The study however included significant proportion of children (as young as 3 years old). Given the large proportion of study populations being outside sildenafil's licensed indication in Bharani 2003[35], Sastry 2004[54] and Singh 2006[55] and their small sample sizes, the characteristics and study results of these three trials will only be briefly listed/mentioned in the following sections and data from these study are not meta-analysed.

Quality assessment of the five trials were 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 [redacted].

Because of the different nature of comparisons between the trials, the results of SUPER-1 and PACES-1 will be described separately in sections 5.2.7.2 and 5.2.7.3 respectively.

Table 26 Characteristics of included sildenafil trials

Trial name/key paper (protocol number); location/centres	Duration; design; number of patients randomised	Intervention[a] (od: once daily; bd: twice daily; tid: three times daily)	Comparator[a]	Type of PAH[b]	Functional class	Age (years), mean (SD, range)[c] % female	Baseline exercise capacity and haemodynamic measures,[c,d] mean (SD)			
Sildenafil vs. placebo with ongoing supportive treatment										
SUPER-1 (A1481140) / Galiè 2005[53]; international, 53 centres	12 weeks; double-blind, parallel; n=278	Sildenafil (oral) 20 mg tid (n=69), 40 mg tid (n=67), 80 mg tid (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 Cardiac index mPAP	344 (81) 2.4 (0.7) 53 (15)	PVR RAP SvO_2	957 (509) 9 (5) NR
Bharani 2003[35]	2 x 2 weeks (with washout period of ≥ 2 weeks); double-blind, cross-over; n=10	Sildenafil (oral) 25 mg tid	Placebo	PPH (30%), Eisenmenger syndrome (30%), non-PAH (30%)[e]	II (33%) III (56%) IV (11%)	32 (15, 18-60) 56%	6MWD Cardiac index mPAP	164 NR NR	PVR RAP SvO_2	NR NR NR
Sastry 2004[54]; India, single centre	2 x 6 weeks (no washout period); double-blind, cross-over; n=22	Sildenafil (oral) 25 – 100 mg tid depending on body weight[f] (n=10 receiving sildenafil first)	Placebo (n=12 receiving placebo first)	PPH (100%)	II (82%) III (18%)	NR (range 16-55) 55%	6MWD Cardiac index mPAP	NR 2.8 (1.1) NR	PVR RAP SvO_2	NR NR NR

Trial name/key paper (protocol number); location/centres	Duration; design; number of patients randomised	Intervention[a] (od: once daily; bd: twice daily; tid: three times daily)	Comparator[a]	Type of PAH[b]	Functional class	Age (years), mean (SD, range)[c] % female	Baseline exercise capacity and haemodynamic measures,[c,d] mean (SD)			
Singh 2006[55]; India, single centre	2 x 6 weeks with a 2-week washout; double-blind, cross-over; n=20	Sildenafil (oral) 25 – 100 mg tid depending on body weight	Placebo	IPAH (50%), Eisenmenger Syndrome (50%)	II (40%) III (55%) IV (5%)	NR (range 3 - 45) 75%	6MWD Cardiac index mPAP	262 (99) NR NR	PVR RAP SvO_2	NR NR NR
Sildenafil vs. placebo with ongoing epoprostenol and supportive treatment										
PACES-1[38] (A1481141), international, multicentre	16 weeks; double-blind, parallel; n=267	Sildenafil (oral) started 20 mg tid, up-titrated to 80 mg tid by week 8 if tolerated + ongoing epoprostenol (individualised optimal dose) (n=134)	Placebo + ongoing epoprostenol (individualised optimal dose) (n=133[g])	PPH (79%), CTD (21%)	N=257 I (1%) II (26%) III (67%) IV (5%)	48 (13, range 18 - 75) 80%	6MWD Cardiac index mPAP	NR NR NR	PVR RAP SvO_2	[redacted] n=164 [redacted] [redacted] [redacted] [redacted]

[a] With ongoing conventional therapy unless otherwise specified. [b] IPAH: idiopathic PAH; CTD: PAH associated with connective tissue disease; PPH: primary pulmonary hypertension; S-P: systemic-to-pulmonary. [c] NR: not reported. [d] 6MWD: 6-minute walk distance (metres); Cardiac index (litre/min/m^2); mPAP: mean pulmonary arterial pressure (mm Hg); PVR: pulmonary vascular resistance (dyn*sec*cm^{-5}); RAP: right atrial pressure; SvO_2: mixed venous oxygen saturation (%). [e] Including two patients with interstitial lung disease and one patient with PAH associated with thromboembolism; information regarding one patient who did not complete the report was not reported. [f] 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. [g] Two of these patients did not receive any study medication.

Table 27 Quality assessment of included sildenafil trials

Study	Truly random allocation (strata for randomisation)	Adequate allocation concealment	Blinding	Use of ITT analysis* (n included in analysis/N randomised)		% patient completed the trial	Comments
Sildenafil vs. placebo with ongoing supportive treatment							
SUPER-1 / Galiè 2005[53] 12 wks	Yes (baseline 6 MWD 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 tid: 97% (67/69) 40 mg tid: 97% (65/67) 80 mg tid: 92% (65/71)	*Primary analysis excluded patients without baseline and at least one post-baseline measurement (n=266), but ITT analysis was performed as a sensitivity analysis
Bharani 2003[35] 2 x 2 wks	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 2004[54] 2 x 6 wks	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 2006[55] 2 x 6 wks	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 wks	Yes (baseline 6MWD, PAH subcategory)	Yes	Double-blind	Survival – yes Clinical worsening – yes Functional class – no (257/265)	6MWD – no (250*-[redacted]/265) Haemodynamic – no ([redacted]/265) Quality of life – no (234-242/265)	Placebo: [redacted] Sildenafil: [redacted]	*Patients with missing baseline 6-MWT or no post baseline 6-MWT were excluded from the analysis

*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). Where analysis for the outcome was performed but the number of patients included was not reported, this was noted as 'unclear'. Where ITT analysis was not used, the number of patients included in the analysis (or a range of numbers where more than one outcomes were analysed/more than one analysis were preformed with various numbers of patients used) over the number that should have been used in an ITT analysis is shown.

5.2.6.2 Sildenafil added to supportive treatment versus supportive treatment alone

This comparison was investigated in SUPER-1[53], Bharani 2003[35], Sastry 2004[54] and Singh 2006[55]. As previously stated, results from the latter three trials will only be briefly mentioned and will not be combined with SUPER-1[53] due to 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 were 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 sub-sections. 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 were stated separately where appropriate.

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, FC III, 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 were 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 texts.
H. Subgroup analysis - PAH/CTD	PAH/CTD, all FC, licensed dose	No	Stratified data were not available. Data for mixed FC were available for 6MWD and were described in the texts.

Table 29 Results from SUPER-1: sildenafil added to supportive treatment versus 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)		**FC III**			**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 maintained or improved	**RR**	74[53]	[redacted]		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]	[redacted]	277[53]	[redacted]
6-minute walk distance[a]	**WMD**	0	Data not available		139[53]	**38 (12 to 64)**	141[c 53]	**42 (9 to 75)**[c]
Haemodynamics								
Mean pulmonary arterial pressure (mPAP)[b]	**WMD**	0	Data not available		130[53]	**-2.7 (-5.3 to -0.1)**	258[53]	**-3.7 (-5.5 to -1.9)**
Right atrial pressure (RAP)[b]	**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)[b]	**WMD**	0	Data not available		130[53]	**-171 (-311 to -31)**	258[53]	**-225 (-341 to -109)**
Cardiac index[a]	**WMD**	0	Data not available		130[53]	0.2 (0.0 to 0.5)	258[53]	**0.3 (0.1 to 0.5)**
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)

[a] Mean change from baseline; positive value favours sildenafil.

[b] Mean change from baseline; negative value favours sildenafil

[c] Data were insufficient for combining the three sildenafil doses; comparison between sildenafil 80 mg three times daily and placebo is shown.

Survival

A total of 4 deaths were reported in the SUPER-1 trial[53]. The number is too small to draw any conclusion.

Time to clinical worsening

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

Functional class (FC)

Table 29 shows that the difference in the proportion of patients who maintained or improved FC between placebo group and 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 (not shown in Table 29) was significantly higher in sildenafil 20 mg three times daily group compared to placebo group (mixed FC, RR = 3.91, 95% CI 1.55 to 9.88). The relative risk increased further when the two sildenafil groups of higher doses were included (mixed FC, RR = 4.97, 2.09 to 11.79). The result of having FC improved (not shown in Table 29) specifically for FCIII patients

[redacted]

Exercise capacity

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

Quality of life

QOL outcomes were not reported in the published paper for SUPER-1[53] but were reported in Pfizer's submission to NICE. It stated that improvement in all domains of the SF-36 (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health) was observed in the sildenafil groups

compared to placebo 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 were not performed according the study protocol but the differences may not have 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 effect on the various domains of SF-36. EQ-5D Utility Index was unchanged in placebo and sildenafil 40 mg three times daily groups (mean change from baseline 0.0, 0.0 to 0.1) and was slightly increased in sildenafil 20 mg and 80 mg three times daily groups (0.1, 0.1 to 0.2). Data specifically for FCIII patients were not available.

Haemodynamic measures

Table 29 shows sildenafil at its licensed dose significantly reduced mPAP (-2.7 mm Hg, -5.3 to -0.1) and PVR (-171 dyn*sec*cm^{-5}, -311 to -31) compared to 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 to the placebo group.

Serious adverse events and other adverse events

The risk of experiencing at least one serious adverse event was similar between treatment groups (mixed FC, RR = 0.82, 0.44 to 1.51 for sildenafil groups combined vs. placebo). Common adverse events that occur 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 that were defined according to demographic features, disease characteristics, and baseline variables were examined descriptively in the SUPER-1 study[53]. The treatment effect at licensed dose did not differ significantly between PPH and PAH/CTD subgroups: 40 metres (95% CI 14 to 66) versus 55 metres (25 to 85) respectively (test for heterogeneity, χ^2=0.55, d.f.=1, p=0.46).

Results from cross-over trials

All the three short-term cross-over trials[35,54,55] reported significant improvement in exercise capacity and haemodynamic measures for sildenafil (at above licensed doses) compared to 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 which investigated the licensed dose for sildenafil (20 mg three times daily). It was an international, double-blind study with duration of 12 weeks. Three further single centre, cross-over trials (Bharani 2003[35], Sastry 2004[54], Singh 2006[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 intention-to-treat (ITT) principle. However ITT analyses were performed as sensitivity analyses and the results were consistent with its primary analyses.

- The majority of patients included in the SUPER-1 study had IPAH. Patients with PAH/CTD and PAH associated with congenital heart disease were also included. The mean 6MWD at baseline was 344 metres. Patients were of mixed FC; 58% were in FC III 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 patient population with mixed FC.

- Compared to supportive treatment alone, sildenafil at its licensed dose (added to supportive treatment) has demonstrated significant improvement in exercise capacity (6MWD), haemodynamic outcomes (mPAP and PVR), 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 in 6MWD was similar between PPH and PAH/CTD.

5.3.3 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 when this report was completed. Data presented in this section were largely obtained from the Pfizer's submission to NICE for this technology appraisal. Additional data were sought from the clinical study report (commercial in confidence) of this study that was made available to the assessment group by Pfizer. The characteristics and quality assessment of the PACES-1 study have been shown in Table 26 and Table 27 respectively.

Since 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 license, only a narrative summary of the study findings will be provided below. Most of the findings were based on the whole trial population, which included mixed types of PAH (IPAH and PAH/CTD) and mixed FC (I to IV).

Findings

Seven deaths occurred in the placebo group and one death occurred in the sildenafil group. The difference between groups just failed to reach statistical significance (RR = 0.14, 95% CI 0.02 to 1.12). Clinical worsening was defined in this trial as death, or lung transplantation, or hospitalisation due to pulmonary arterial hypertension, or initiation of bosentan therapy, or change in epoprostenol dose due to clinical deterioration. Time-to-event analysis showed that a significantly lower proportion of patients treated with sildenafil 80 mg three times daily compared to 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, 0.16 to 0.77). Significantly fewer patients in the sildenafil group withdrew from the study compared to placebo group (RR = 0.51, 0.26 to 0.98).

The proportion of patients with FC improved or maintained was not significantly different between sildenafil group and placebo group (mixed FC, RR = 1.06, 0.98 to 1.15; FCIII only, RR = 1.04, 0.96 to 1.12), but significantly more patients treated with sildenafil had their FC improved (mixed FC, RR = 2.47, 1.52 to 4.02; FCIII only, RR = 1.95, 1.16 to 3.29). Patients treated with sildenafil also had greater improvement in 6MWD (mean difference 26 metres, 11 to 41) and in various domains (physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning and mental health) of SF-36

questionnaire except '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 EQ-5D Utility Index (increased 0.052 for the sildenafil group and 0.022 for the placebo group). Significant reductions in mPAP, RAP and PVR were also observed in the sildenafil group compared to placebo group. The analyses of all above outcomes (FC, 6MWD, Borg Dyspnoea Index, quality of life and haemodynamic measures) were not ITT and more patients in the placebo group than in the sildenafil group were excluded from the analyses.

Serious adverse events were experienced by 29/134 patients in the sildenafil group compared to 39/131 in the placebo group (RR = 0.73, 0.48 to 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, 14 to 49) than in the subgroup of patients with PAH/CTD (8 metres, -23 to 38). The difference was however not statistically significant (test for heterogeneity χ^2 =1.80, d.f. = 1, P=0.18).

Summary and discussion

- One double-blind RCT (PACES-1[38]) compared sildenafil 80 mg three times daily (above licensed dose) to placebo in patients who were receiving ongoing epoprostenol and supportive treatment.

- Methods of randomisation and allocation concealment were adequate in PACES-1. Intention to treat analysis was not used for most outcomes. More patients in the placebo group were excluded from analyses compared to the sildenafil group due to missing data. The potential bias would be in favour of placebo if the excluded patients had worse outcomes.

- Results from PACES-1 indicated patients treated with sildenafil 80 mg three times daily had significantly lower risk of clinical worsening and 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 sildenafil and placebo in changes in Borg Dyspnoea score, EQ-5D Utility Index and risk of serious adverse events.

- The trial included mixed PAH populations (IPAH and PAH/CTD) with mixed FC (67% FCIII). Changes in 6MWD were not significantly different between IPAH and PAH/CTD. Results of changes in FC for patients in FCIII at baseline were similar to results of the overall trial population.

5.2.7 Direct (Head to Head) Comparisons

5.2.7.1 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 to sitaxentan (both at licensed dose) in the STRIDE-2 study[48]. The comparison of both drugs with placebo from this trial has been included in the bosentan and sitaxentan sections respectively. Bosentan (licensed dose) was compared to 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] was listed again for the convenience of readers; only relevant treatment arms were 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.

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 which 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 four weeks and up-titrated 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 PAH/CTD. The mean 6MWD at baseline was 297 metres. The primary endpoint 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 intention to treat 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.

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] (od: once daily; bd: twice daily; tid: three times daily)	Comparator[a]	Type of PAH[b]	Functional class	Age (years), mean (SD, range)[c] % female	Baseline exercise capacity and haemodynamic measures,[c,d] mean (SD)			
STRIDE-2 (FPH02) / Barst 2006[48]; international, 55 centres	18 weeks; double-blind (open-label for bosentan), parallel; n=247	Bosentan (oral) 125 mg bd [e] (n=60);	Sitaxentan (oral) 100 mg od (n=61)	IPAH (59%), CTD (30%), congenital heart disease (11%)	II (37%) III (59%) IV (4%)	54 (15) 78%	6MWD Cardiac index mPAP	337 (80) 2.4 (0.8) 48 (14)	PVR RAP SvO_2	880 (560) [g] NR NR
SERAPH / Wilkins 2005[57]; UK, single centre	16 weeks; double-blind, parallel; n=26	Bosentan (oral) 125 mg bd [e] (n=12)	Sildenafil (oral) 50 mg tid [f] (n=14)	IPAH (88%), CTD (12%)	III (100%)	43 (NR, 27-62) 81%	6MWD Cardiac index mPAP	297 (82) 2.3 (0.1) NR	PVR RAP SvO_2	NR NR NR

[a] With ongoing conventional therapy unless otherwise specified. [b] IPAH: idiopathic PAH; CTD: PAH associated with connective tissue disease. [c] NR: not reported. [d] 6MWD: 6-minute walk distance (metres); Cardiac index (litre/min/m^2); mPAP: mean pulmonary arterial pressure (mm Hg); PVR: pulmonary vascular resistance (dyn*sec*cm^{-5}); RAP: right atrial pressure (mm Hg); SvO_2: mixed venous oxygen saturation (%). [e] 62.5 mg twice daily for the first four weeks. [f] 50 mg twice daily for the first four weeks. [g] Converted from mm Hg/litre/min (Wood units).

Table 31 Quality assessment of included head to head trials

Study	Truly random allocation (strata for randomisation)	Adequate allocation concealment	Blinding	Use of ITT analysis* (n included in analysis/N randomised)		% patient completed the trial	Comments
STRIDE-2 / Barst 2006[48] 18 wks	Yes	Yes	Double-blind for sitaxentan and open-label for bosentan (outcome assessor blinded)	Survival analysis – N/A Clinical worsening – yes Functional class – no ([redacted])[a]	6MWD – no ([redacted])[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 ([redacted]) .
SERAPH / Wilkins 2005[57] 16 wks	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 result table in the paper excluded the patient who died during the trial.

*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). Where analysis for the outcome was performed but the number of patients included was not reported, this was noted as 'unclear'. Where ITT analysis was not used, the number of patients included in the analysis (or a range of numbers where more than one outcome were analysed/more than one analysis were preformed with various numbers of patients used) over the number that should have been used in an ITT analysis is shown. [a] numbers refer to bosentan and sitaxentan 100 mg arms only.

5.2.7.2 Sitaxentan versus bosentan with ongoing supportive treatment

Results presented in this section were of those from STRIDE-2[48] rather than from meta-analysis, as it is the only trial investigating this comparison. Planned comparisons and those actually listed are summarised in Table 32. Results are listed in Table 33 according to the planned comparisons, following 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 below are mainly based on results of mixed PAH populations. Findings specifically for FCIII were stated separately where appropriate.

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, FC III, 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 were highlighted in Analysis A and B.
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, FC III, licensed dose(s)	No	No data specifically for patients with IPAH were available.
H. Subgroup analysis – PAH/CTD	PAH/CTD, FC III, licensed dose(s)	No	No data specifically for PAH/CTD were available.

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)		**FC III**			**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**				
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)		[redacted]	[redacted]
Withdrawal for any reason[a]	**RR**	0	Data not available		[redacted]	0.49 (0.16 to 1.55)
6-minute walk distance[c]	**WMD**	0	Data not available		[redacted]	2 (-22 to 26)
Borg's dyspnoea index[d]	**WMD**	0	Data not available		[redacted]	[redacted]
Haemodynamics						
Mean pulmonary arterial pressure (mPAP)[d]	**WMD**	0	Not measured		0	Not measured
Right atrial pressure (RAP)[d]	**WMD**	0	Not measured		0	Not measured
Pulmonary vascular resistance (PVR)[d]	**WMD**	0	Not measured		0	Not measured
Cardiac index[c]	**WMD**	0	Not measured		0	Not measured
Safety						
Serious adverse events[a]	**RR**	0	Data not available		122[48]	[redacted]

[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.

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 vs. 4/61), withdrawal for any reasons (8/60 vs. 4/61) and FC worsened (5/[redacted] vs. 1/[redacted]). However these numbers were small and the differences between groups were not statistically significant. The number of patients having FC improved, experiencing at least one serious adverse event, and the changes in 6MWD and Borg Dyspnoea Index were similar between the two groups. Change in FC did not differ significantly between groups for patients in FCIII at baseline. QOL and haemodynamic outcomes were not measured in STRIDE-2[48].

5.2.7.3 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 75 m) and the bosentan group (increased 59 m) 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). Total number of patients who experienced at least one serious adverse event was not reported. Hospital admissions or unscheduled visits were required for three patients in the bosentan group and one patient in the sildenafil group. Right ventricular (RV) mass (the primary endpoint) was reduced in both group but only significantly in sildenafil group compared to baseline. The differences between the two groups in RV mass and all other measures including haemodynamic, hormonal and quality of life (Kansas City Cardiomyopathy Quality-of-Life questionnaire) measures were not statistically significant.

5.2.7.4 Summary and discussion

- Two RCTs included direct comparison between the technologies under assessment in this report. The STRIDE-2[48] was an 18-week, international study sponsored by the manufacturer of sitaxentan and compared sitaxentan (licensed dose) to bosentan (licensed) 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) to bosentan (licensed dose) with ongoing supportive treatment. The bosentan arm in the STRIDE-2 was open-label whereas the SERAPH was a double-blind study.

- Methods of randomisation and allocation concealment were adequate in both trials. Intention-to-treat analysis was used SERAPH[57] 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 is likely to be small.

- STRIDE-2 included mixed populations of patients with IPAH, PAH/CTD and PAH associated with congenital heart disease with mixed FC (59% FCIII).[48] SERAPH included exclusively patients in FCIII and a population of predominantly IPAH.

- For the comparison between sitaxentan and bosentan at licensed doses, no significant difference 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 difference 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.

- 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.

5.2.8 Ongoing Studies

Several on-going studies were identified through the formal searches and scrutiny of the industry submissions. These are documented for information in Appendix 6, Table 74.

5.2.9 Long-term studies

Scrutiny of the industry submissions revealed a number of long-term follow up studies. These are documented in Appendix 7, Table 75 and Table 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 (section 6.3).

5.3 Overview and discussion of clinical effectiveness

5.3.1 Comparison of each of the five technologies to 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 (where only one trial provided relevant data) for each of the five technologies under assessment for selected key outcomes. The results show that significant improvement in FC, 6MWD and haemodynamic measures have been clearly demonstrated in PAH populations for each of the technologies compared to placebo/control, although the volume of evidence varied between technologies. The findings for the other outcomes were less clear-cut. The main findings for this comparison are discussed below.

5.3.1.1 Survival

All of the RCTs included in this review were of a duration of 18 weeks or shorter. 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] in the 1990s was an exception and was the only RCT that had demonstrated

significant survival benefit within a trial. The pooled relative risks 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 of treatments for PH (i.e. a wider population than just PAH) reported a relative risk of death of 0.70 (0.41 to 1.22) compared to control.[63] The analysis pooled all disease modifying technologies for pulmonary hypertension including those outside this technology assessment. The merits of this are debatable. However this estimated 30% non-significant reduction in mortality led the authors to question the survival benefit offered by the technologies for PH, in particular that the trials were neither powered nor of long enough duration to adequately measure survival. The findings of this assessment report are in agreement with this conclusion.

Despite some methodological issues within the above meta-analysis[63] (for example, the head-to-head trial SERAPH[57] was included in the analysis with the bosentan arm being treated as control), its finding is consistent with 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 due to 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 due to differences in patient populations, entry criteria, treatments offered and methods of follow up.

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

Drug & population [No of trials]		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) ; NNT 2.2 (1.6 to 3.6, I^2 =69%) [3]**	**81 (45 to 117) [3]**	Chronic Heart Failure Questionnaire (+) [1] Nottingham Health profile (+/-) [1]	mPAP: **-6.3 (-8.7 to -3.9) [3]** RAP: **-2.4 (-4.1 to -0.7) [2]** PVR: **-427 (-548 to -306) [3]** CI: **0.6 (0.4 to 0.8) [2]**
PPH	Mixed FC	0.18 (0.03 to 1.18) [1]	No data	**7.45 (2.55 to 21.77); NNT 1.9 (1.1 to 5.9, I^2 =82%) [2]**	**58 (6 to 110) [2]**	Same as above	mPAP: **-6.8 (-10.6 to -3.0) [2]** RAP: -2.3 (-5.1 to 0.5) [1] PVR: **-401 (-613 to -189) [2]** CI: **0.6 (0.2 to 0.9) [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
PAH/CTD	Mixed FC	0.79 (0.22 to 2.77) [1]	No data	**42.25 (2.62 to 680.61); NNT 2.6 (2.0 to 4.0) [1]**	**100 (55 to 144) [1]**	No data	mPAP: **-6.0 (-9.0 to -2.9) [1]** RAP: **-2.5 (-4.6 to -0.4) [1]** PVR: **-440 (-588 to -292) [1]** CI: **0.6 (0.4 to 0.8) [1]**
Iloprost							

Drug & population [No of trials]		**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)**
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); NNT 8.3 (4.5 to 33.3, I^2 =0%) [2]**	**36 (12 to 60) [1]**	EuroQol VAS (+) [2] EuroQol health state score (-) [1] SF-12 (-) [1] Minnesota Living with Heart Failure Questionnaire (-) [1]	mPAP: **-4.4 (-6.7 to -2.1) [1]** RAP: **-2.2 (-3.5 to -0.9) [1]** PVR: **-335 (-421 to -249) [1]** CI: no data
PPH	Mixed FC	0.52 (0.05 to 5.55) [1]	No stratified data	**3.19 (1.11 to 9.11); NNT 5.9 (3.1 to 33.3) [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
PAH/CTD	Mixed FC	No stratified data	No stratified data	No stratified data	No stratified data	No stratified data	No stratified data
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); NNT 7.1 (4.0 to 50.0, I^2 =46%) [4]**	**41 (24 to 58) [4]**	No data	mPAP: **-5.9 (-9.3 to -2.5) [2]** RAP: -3.0 (-9.0 to 3.0) [2] I^2 = 89% PVR: **-414 (-596 to -232) [1]** CI: **1.0 (0.7 to 1.3) [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
PAH/CTD	Mixed FC	No stratified data	No stratified data	No stratified data	22 (-32 to 76) [2]	No stratified data	No stratified data
Sitaxentan							

Drug & population [No of trials]		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)
Mixed PAH	Mixed FC	0.20 (0.01 to 4.15) [3]	**0.33 (0.12 to 0.87) [3]**	**1.74 (1.12 to 2.70); NNT 10 (5 to infinity, I^2 =21%) [3]**	**32 (18 to 47) [3]**	SF-36 (-) [1]	mPAP: **-3.0 (-5.9 to -0.1) [1]** RAP: -1.0 (-2.5 to 0.5) [1] PVR: **-270 (-402 to -138) [1]** CI: **0.3 (0.1 to 0.5) [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) [1][d]**	No stratified data	No stratified data
PAH/CTD	Mixed FC	No stratified data	No stratified data	2.18 (0.31 to 15.24) [1][a]	**58 (0 to 116) [1][d]**	No stratified data	No stratified data
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); NNT 4.8 (3.0 to 11.1) [1]**	**38 (12 to 64) [1]**	SF-36 (+/-) [1] EQ-5D current health state VAS (+) [1] EQ-5D Utility Index (?) [1]	mPAP: **-2.7 (-5.3 to -0.1) [1]** RAP: -1.1 (-2.7 to 0.5) [1] PVR: **-171 (-311 to -31) [1]** CI: 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) [1]**	No stratified data	No stratified data
PAH/CTD	Mixed FC	No stratified data	No stratified data	No stratified data	**55 (25 to 85) [1]**	No stratified data	No stratified data

[a] Weighted mean difference for change from baseline; metres.
[b] '+' indicates there was significant improvement versus placebo/control in all domains; '+/-' indicates significant improvement versus placebo/control was found only in some of the domains; '-' indicates no significant improvement was found in any of the domains; '?' indicates improvement was observed but statistical significance was unclear.
[c] Weighted mean difference for change from baseline; mPAP: mean pulmonary arterial pressure (mm Hg); RAP: right atrial pressure (mm Hg); PVR: pulmonary vascular resistance (dynes*sec*cm^{-5}); CI: cardiac index (litre/min/m^2).
[d] Includes above licensed dose

In addition to the small numbers of patients/events and short duration, 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 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 that including patients with mixed FC. It is worth pointing out from statistical point of view that a certain level of association between datasets is to be expected when one set of data (i.e. FCIII only) is compared to another set of data which include the former (i.e. data for the whole trial population including FCIII and other FC). Conclusive results with regard to whether 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 clinical effectiveness of the treatments outside their licensed indication (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.

Whilst there appears to be limited statistical heterogeneity within many of the pooled analysis, there was considerable clinical heterogeneity between some of the population 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 be 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 to 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 latter trials in terms of use baseline FC and 6MWD as an inclusion criterion. A common feature for nearly all trials was the requirement of patients to be stable on supportive treatment for a certain period 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 implication on 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 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 latter trials to demonstrate reduction in mortality since 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 affect the response in control groups due to placebo effect (where placebo was used) and possible bias in the provision of care and assessment of outcome (where 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 various treatments of PAH confer survival benefit, although it is difficult to quantify the treatment effects and to ascertain whether difference exists 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 = 5, 95% CI 3 to 14) would be replicated in subsequent or 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 comparator (supportive treatment) between trials and over time.

5.3.1.2 Clinical worsening

Clinical worsening events were not defined or reported in any of the epoprostenol trials. Significant reduction in clinical worsening events and/or increase in time to clinical worsening was demonstrated

in individual trials of bosentan[43,45], pooled results of sitaxentan trials and pooled results of bosentan trials (excluding STRIDE-2[48]. Fewer clinical worsening events occurred in the active treatment arms compared to 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 discussed above in relation to survival are also applicable to clinical worsening events. An additional issue for this outcome is that different definitions 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.

5.3.1.3 Changes in functional class (FC)

All the five technologies demonstrated significant benefit compared to placebo/control with regard to having FC improved 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 there was 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 calculating number needed to treat (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 was shown (I^2 ≥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 being 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.

5.3.1.4 6MWD

All the five technologies demonstrated significant effect on increasing exercise capacity as measured by 6MWT compared to placebo/control. The mean difference between treatment and placebo/control groups appeared to be greatest in two of the epoprostenol trials (Rubin 1990[39] and Badesch 2000[33], approximately 100 metres). The between group difference varied from approximately 30 to 75 metres in other trials, with wide confidence intervals due to high variability between individual patients. Again values from different trials are not directly comparable due to 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/larger 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 (for example, last-observation carried forward; assuming no change compared to baseline; assuming a 6MWD of 0 for missing observations) however could produce different results. Interpretation of trials results and comparison between studies therefore requires great caution.

5.3.1.5 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 have used different tools and the findings seemed inconclusive (see Table 34). Two studies had measured EQ-5D Utility Index (AIR study for iloprost[41]; SUPER-1 for sildenafil[53]): there was improvement of approximately 0.1 (on a scale of 0 to 1) compared to placebo in both trials.

5.3.1.6 Haemodynamic measures

All the five technologies demonstrated significant effects on haemodynamic measures that are important indicators of the disease progress of PAH 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 but the magnitude of the reported group means and differences may not be clinically useful.

5.3.1.7 Serious adverse events and withdrawal for any reasons

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

Data with regard to the total number of patients experiencing at least one SAE were not available for all 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 significant reduction in the risk of experiencing at least one SAE compared to placebo, but the pooled results (or result from the only trial) for other technologies have failed to demonstrate significant risk reduction. Significant reduction in the risk of withdrawal for any reason was observed in individual trials for epoprostenol[11], iloprost[41] and 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 difference between drugs in patients' maintenance on treatment and overall risk-benefit profile cannot be ruled out.

5.3.2 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 (see section 5.2.7.2). The main caution 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]) used above licensed dose for sildenafil versus 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 ten 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, speediness of action and potential adverse effects of different technologies (plus costs) on patients' and physicians' preference, 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 under-powered to detect clinically relevant differences due to their sample size and duration. Indeed [redacted] were reported in the long-term extension of the STRIDE-2 (which was not included in this review as the patients in each of the treatment groups had varied duration of exposure to the drugs due to the study design). Sufficiently powered, long-term head-to-head RCTs (preferably double-blind and independently funded) between 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.

5.3.3 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 to 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]) (section 5.2.3.3) compared iloprost to control/placebo in patients who were stable on bosentan and supportive treatment but 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 against supportive treatment in patients who had not received oral treatments. Inhaled iloprost demonstrated significant benefit compared to placebo in the STEP study[59] but failed to demonstrate such benefit compared to 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 significant benefit of adding sildenafil to patients who were stable on epoprostenol. However the dose used in this study was much higher than the licensed dose of sildenafil.

5.3.4 Specific issues related to this technology appraisal

Several potential problems that could affect this assessment report in addressing 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 section 4 of this report. The major difficulty was 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 where possible evidence that is directly applicable to the licensed indication and evidence for specific subcategories of PAH (IPAH and PAH/CTD) are also presented (see Table 34 and also results tables for individual technologies in section 5.2).

It can be seen that while the most inclusive (whole trial data) evidence is sufficiently robust for all the technologies, the volume of available evidence reduces dramatically when only evidence directly applicable to the licensed indications is included (PPH FCIII and IV for epoprostenol; PPH FCIII for iloprost; PAH FCIII for bosentan, sitaxentan and sildenafil). Where evidence is available, the confidence intervals tend to be wider compared to the inclusive evidence and the results may no longer be significant. There is few data for specific subcategories of PAH and little scope for comparison between them. In addition to the volume of evidence, all the data were restrictive to duration of 18 weeks or shorter. A possible lesson learned (amongst other explanations) from a one-year trial of beraprost (not included in this assessment) suggest that observations made at 3 months may not last beyond this time. [67]

Furthermore, there are specific issues related to evidence of individual technologies. For epoprostenol, all 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 current UK context. For inhaled iloprost, there is fluctuation of drug effects due to the method of administration. Whether some of the outcomes measured immediately after inhalation can present its overall treatment benefit is questionable. In addition, conflicting results between some of the iloprost trials have been observed. For bosentan, the exceptional high response in 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 related to doses higher than its license (this also applies to evidence from observational studies). Beyond all these, there is also a possible mismatch between the licensed indication of each drug and the actual use in clinical practice.

6. ASSESSMENT OF COST-EFFECTIVENESS

6.1 Systematic review of existing cost-effectiveness evidence

6.1.1 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 - Feb 2007, EMBASE (Ovid) 1980 - Feb 2007, CINAHL (EBSCO) 1982 – Feb 2007, Cochrane Library (DARE and NHS EED) 2007 Issue 1 and HEED (Feb 2007).
- Industry 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.

6.1.2 Study selection, data extraction and quality assessment strategy

Inclusion and exclusion criteria applied for economic searches are shown in Table 35.

Table 35 Inclusion 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	Iv epoprostenol, inhaled iloprost, bosentan, sitaxentan, sildenafil,
Comparator	Placebo, supportive therapy, any intervention drug
Outcome	Quality of life estimates, cost estimates, cost-effectiveness

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 pre-designed 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 assumption 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.

6.1.3 Results

6.1.3.1 Economic evaluations

A total of four economic evaluations meeting the inclusion criteria were identified, none of which were UK studies. All four evaluations met at least 8 of the 10 Drummond 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 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 paper[72], a US-based study, compared bosentan with treprostinil or epoprostenol, and Wlodarczyk and colleagues from Australia[73] also considered bosentan but in comparison with conventional therapy. Three out of the four studies had connections with industry with the exception of Highland et al[72] where no reference to funding or conflict of interests was stated.

All four studies were model-based analyses. The studies by Einarson and Narine conducted a cost-minimisation analysis as they assumed that treprostinil and epoprostenol were clinically

equivalent.[70,71]Wlodarczyk et al, 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 conducted a cost-utility analysis.[72] 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 IV, although the Narine and Einarson model only considered patients who were non-responders to oral therapy.

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 Inc (distributor of treprostinil in Canada)	Not stated	United Therapeutics Corp.	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	2 cohorts of patients of FCIII and IV	Cohort of 100 PAH patients	2 cohorts of 270 patients of FCIII and IV who have failed or are not candidates for bosentan	Patients of FCIII or IV
Form of analysis	Cost-minimisation	Cost-utility	Cost-minimisation	Cost-effectiveness (cost per life year gained)
Model used	Excel spreadsheet	Markov model	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 Aus $
Base case results	Treprostinil gave savings of CA$2,610,642 (60 patients over 3 years) (£ 1,364,959, 2006) and an average annual saving of $14,504 (per patient per year) (£ 7,583, 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 average cost saving per patient per year was $12,478. (£9,084, 2006)	ICER: AU$55,927 per life year gained (£23,657, 2006)

The model presented in the Einarson and Narine papers was a decision analytical spreadsheet model built in Microsoft Excel. This model followed a cohort of patients over a three year period and was built to represent a logical sequence of clinical practice for PAH patients. Highland et al presented a

Markov cohort model which followed patients over a one year period with a cycle length of three 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 six 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 from non-comparative studies. The two therapies in question were assumed to be clinically equivalent, based on results of a three 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 relative risk of improvement in the six minute walking test (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 data provided by industry. Mortality data for conventional therapy was 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 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 one 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 serious adverse events, 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 and Narine 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 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 were 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 functional state IV. 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 $37,433 over the three year time horizon, with an expected average cost-saving per patient per year of $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 $2,610,642 overall, with average annual saving of $14,504 from a health care perspective and $15,452 from a societal perspective. Again, savings were attributed to reduced hospitalisations. PSA presented in both analyses demonstrated almost 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 $3,631,900 with a QALY difference of 11. Sensitivity analyses included changing the relative risk 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 on conventional therapy, with the 6.7 discounted life years after 15 years for bosentan compared with 2.8 for conventional therapy. The discounted mean cost was $234,618 for bosentan and $18,287 for conventional therapy, giving an ICER of $55,927 per QALY gained. After five years the ICER was a much higher $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 as was the inclusion of epoprostenol for a small proportion of patients which reduced the ICER.

6.1.3.2 Quality of life

A total of sixteen potential quality of life studies (excluding the economic evaluation papers presenting quality of life) were identified, however two of these were subsequently found to be general commentary papers rather than presenting empirical data (Keogh et al.[74] Hoeper et al [75]). 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 was identified from the industry submissions giving health state valuations for NYHA FCI to IV.[76] The section will briefly list 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 from 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 twelve 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 IV 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 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 IV. 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 Visual Analogue Scale (VAS) and standard gamble (SG) 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 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 taken every 3 months from patients on the waiting list of a lung transplantation programme and after transplantation. However the values for different periods of time on the waiting list were not related to any health state e.g. FC or specific condition. Kirsch et al[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 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 presented in the paper by Highland et al presenting a decision model comparing three treatments. A description of this paper can be found earlier in the section. For completeness, the values used in the paper are presented in Table 37 alongside all the other the utility values presented in the 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 were not UK studies.[88] [89,90] The remaining study [91] concerned epoprostenol treatment in children alone, and presented costs in US $. This population group is outside the remit of the appraisal therefore this paper was also omitted.

Table 37 Utility values in published quality of life papers by FC

	Keogh (2007)[84]	**Kirsch (2000)[76]**		**Highland (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	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

Table 38 Utility values in published quality of life papers, non-FC related health states

	Olschewski (2002)[41]	**Sitbon (2004)[85]**	**Shafazand (2004)[86]**	**Groen (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,	-	-	SG: 0.72 (0.61-0.82)	-

epoprostenol			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)	-
Pre-transplantation *First 6 months* *6-9 months* *9-12 months* *1 year*	-	-		 0.55 0.50 0.45 0.40

6.1.4 Summary

The published economic evaluations used three different approaches to modelling, and none of the models produced results 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) 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.

6.2 Review of industry 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.

6.2.1 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 their technology. The submission states that the drug is available [redacted] for this indication.

[redacted]

6.2.2 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 iv epoprostenol, with no supportive therapy comparator included in this 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 three months. The patient group modelled was that with a diagnosis of primary pulmonary hypertension of FCIII who had failed or were unable to tolerate oral therapy, and would otherwise have required iv epoprostenol. Age on initiation of treatment was 52 years.

Health states were based on the NYHA functional classification, with the starting state of FCIII, with transitions to FCII or IV 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 iv 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 which followed patients for this time period. The base-case analysis use 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 was obtained from Barst et al[11] However as findings for the sub-group of patients in FCIII at baseline were not available, the percentage with improvement or deterioration from baseline in mixed population FCIII and IV was used. Additional analyses were undertaken using pooled data, using additional data from studies identified in their systematic review.

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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 Sitaxentan sodium (Thelin®)**	**Pfizer Sildenafil (Revatio®)**
Choice of therapy	Inhaled iloprost with switch to intravenous epoprostenol on reaching FC IV	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	▪ Historic care (30% iv prostaglandins, 70% supportive therapy) ▪ Supportive therapy alone ▪ iv prostaglandins	▪ Bosentan ▪ Supportive care	▪ Background therapy ▪ Each of the other 4 intervention therapies
Patient characteristics	Patients with Primary Pulmonary Hypertension, FC III, who are unable to tolerate oral therapy. Age on initiation 52.	FCIII, age sampled from distribution. Separate analyses for IPAH patients and those with connective tissue disease (CTD).	FCIII, age 18+ (STRIDE trial populations)	FCIII. Age 18+ with primary or secondary PAH from SUPER-1 and SUPER-2 studies. Age on initiation: 49.
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. 4 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 one week)	Markov model of 2 distinct parts: Year 1, Year 2 onwards (with cycle length of 12 weeks (x3) and 16 weeks (x1) 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: £348k, QALY difference: 0.04 per person)	IPAH: ▪ vs. historical care, £21,000 per QALY ▪ vs. epoprostenol, bosentan dominates ▪ vs. supportive therapy,	▪ 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

Submission features	**Schering Health Care Iloprost trometamol (Ventavis®)**	**Actelion Pharmaceuticals Bosentan (Tracleer®)**	**Encysive Sitaxentan sodium (Thelin®)**	**Pfizer Sildenafil (Revatio®)**
		£84,000 per QALY CTD: ▪ vs. historical care, £15,000 per QALY ▪ vs. epoprostenol, bosentan dominates ▪ vs. supportive therapy, £78,000 per QALY		

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 five 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, III and IV, 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 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 what conventional therapies they prescribed, the average dose and the proportion taking each therapy. Information was collected on NHS contacts such as 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 where iloprost is provided at a fixed cost irrespective of the dose, thus allowing for 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/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 iv epoprostenol in FCIV) compared to 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, with 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 above, iloprost is assumed to have a fixed price regardless of dose.

6.2.3 Actelion submission (bosentan)

The model presented in this submission was a Discrete Event Simulation (DES), constructed in Simul8 software, which compared bosentan (as first line treatment) with three comparators: "historic care", supportive therapy and iv prostaglandins. Historical care is defined as 30% of patients receiving the lowest cost iv 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 iv iloprost is historically the iv prostaglandin of choice but because epoprostenol is cheaper, this is used in the model. In addition, epoprostenol efficacy is also used for iv prostaglandins due to limited iv 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 – idiopathic PAH (IPAH) and PAH associated with connective tissue disease (CTD). 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 dataset of two pivotal RCTs[43,45], plus data on long term follow up and a dataset associated with additional papers by Williams and Denton et al.[44,93] 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 PAH associated with CTD. 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 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 over-estimate the utility of patient on supportive therapy alone. No disutility associated with taking iv 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 [redacted] in utility [redacted] 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 delivery costs were assumed to be 8% of the advanced therapy acquisition costs, based on input from one of the specialist centres. However, they state that this cost is negotiated centre by centre. A breakdown of the therapies forming the supportive care comparator is not given. In addition, it is not clear if the cost of a monthly liver function test is included in the costs for bosentan. Costs were for 2006, and discount rate of 3.5% was applied to both costs and QALYs. It is assumed the analysis was from an NHS/PSS perspective, although this is 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 iv 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 iv prostaglandins. Results of the PSA for IPAH patients showed bosentan to have a 40% chance of being cost-effective compared with historic care at £20,000 per QALY, and 90% at £30,000, but not being 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, but not cost-effective 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 not on active treatment was included. Additional sensitivity analyses considered the proportion of patients on iv 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 historic care as the comparator, the submission argues that bosentan is cost-effective in the IPAH and CTD sub-groups 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 iv 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.

6.2.4 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 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 five years, with a cycle length of one week. The model followed a population of PAH patients of FCIII over the age of 18, based on trial populations from STRIDE-2[48] and STRIDE 2X.[95] Patients started in a pre-deterioration 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 rate of FC deterioration and death of patients. Survival in the supportive care arm was obtained by using the NIH survival equation where mortality was related to haemodynamic measures.[5] This equation applied to IPAH and was derived from three years data. The rationale behind the short time horizon of five years was that the survival equation used for supportive care was derived from three years data, and so the authors did not consider it valid beyond five 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 for sitaxentan compared with supportive care was £94,631 per life year gained, and £19,531 per life year gained when compared with bosentan. PSA was also undertaken, with the results showing considerable uncertainty particularly versus supportive care where sitaxentan only had 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 connective tissue disease and this sub-group 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 suggests cost-effectiveness. Thus the submission therefore argues that sitaxentan is also likely to do so.

It is important to remember that the ICERs reported here relate to life years gained and not QALYs. This is the only economics 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) is not provided. The lack of comprehensiveness of the cost analysis (e.g. the failure to include costs of supportive care or adverse events) is 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.

6.2.5 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 conducted a cost-minimisation analysis (CMA) comparing all five interventions considered in the appraisal. The premise behind the CMA 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 two onwards, a yearly cycle was used. The model population was patients aged 18 and over with primary or secondary PAH in FCIII, conforming to the inclusions/exclusion criteria of the SUPER-1[53] and SUPER-2[96] studies. The start age of the patients in the model was 49, 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 age 79.

Patients received initial treatment and switched to alternative therapy when that treatment failed and the patient deteriorated. Alternative treatment was iloprost or epoprostenol and patients remained on that therapy even if they got worse. Events and health states were based on changes in six minute walking distance (6MWD), with states representing improvement, no change and deterioration in 6MWD and death. Improvement in 6MWD was more than 39m compared to baseline, no change in 6MWD between 0 and 39m greater than baseline and deterioration representing 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 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 interviews with PAH experts, and the data were validated by a clinical expert with the use of patient profiles for the average FCIII patient. 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 there were no robust data for PSS resource use.

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 sildenafil had an 84% probability of being cost-effective at £30,000 per QALY gained and 66% 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 one 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 newer treatments. However, 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.

6.2.6 Summary of industry submissions

The disparity in methods used between the different industry 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 industry submissions are, in effect, not all addressing the same policy question.

6.3 Independent economic assessment

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

6.3.1 Methods

6.3.1.1 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 pulmonary arterial hypertension (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 iv 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 was used to represent the average age of patients with the disease. The general mortality data were weighted to take into account a ratio of 1.5:1 women to men with the disease. 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 iv 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 iv 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 indication only, therefore this was the only option considered. Data on the effectiveness of combination therapies was not available 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 iv 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.

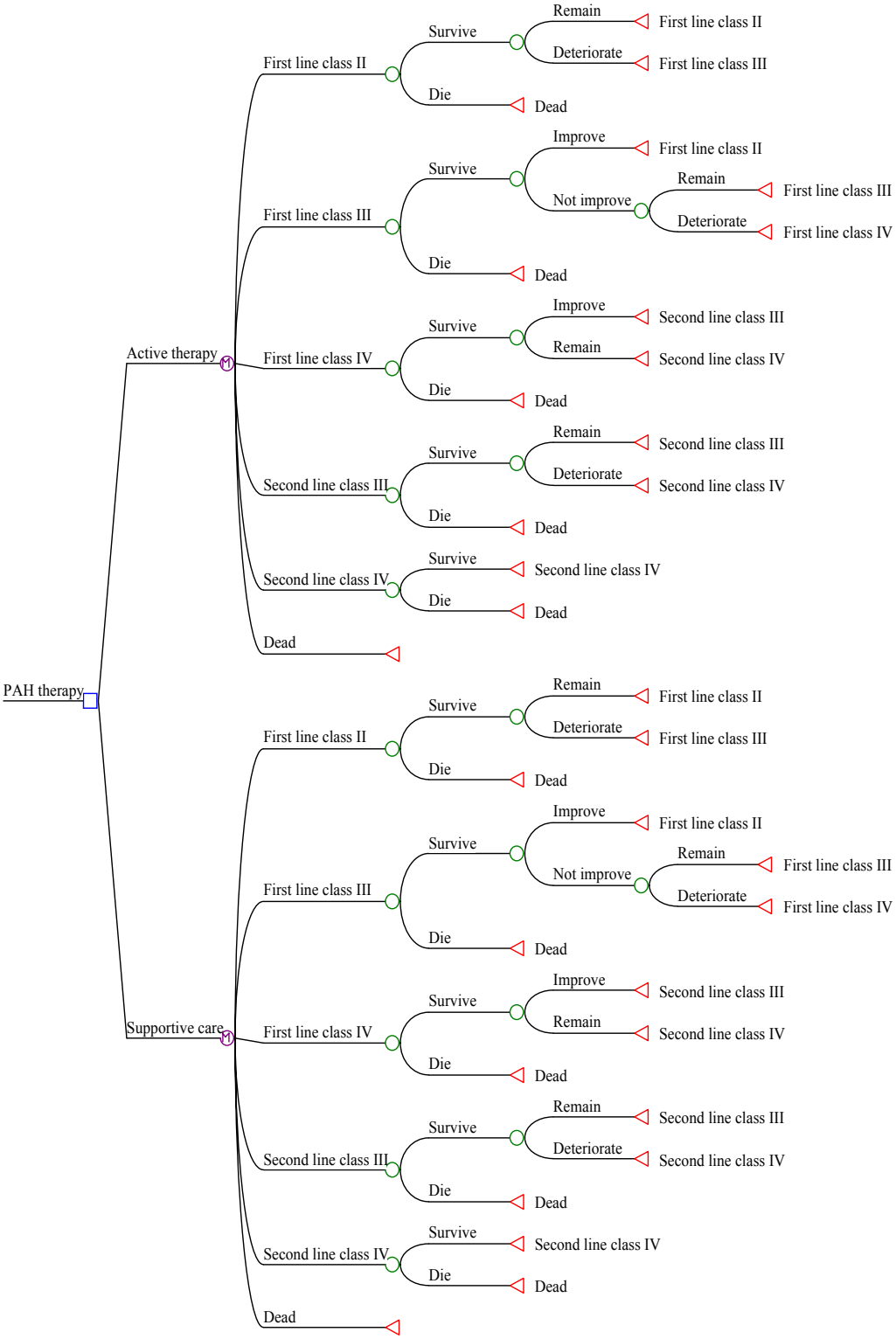

Figure 9 Diagram of decision model

6.3.1.2 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 industry submission. No appropriate transition data stratified by FC were available for epoprostenol. Of the three epoprostenol trials, data from Barst 1996[11] (PPH only, mixed FC) were regarded as the best option given that Rubin 1990[39] was only of 8 weeks duration and Badesch 2000[33] included exclusively PAH patients with scleroderma which is outside epoprostenol's license. Data from Barst 1996[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 IV (i.e. transition probabilities and odds ratios for improvement of at least one FC based on the whole trial population are used for both III to II and IV to III; the values for deterioration of at least one FC including deterioration to death based on the whole trial population are used for III to IV). Similar rules were applied for other drugs where FC-specific transition probabilities and odds ratios were not available (i.e. assuming same value for IV to III and III to II; for II to III and III to IV).

Transition probabilities for the supportive care for models of oral therapies were calculated using combined data from the placebo arms of Channick 2001[43] (study of bosentan), BREATHE-5[47] (study of bosentan), STRIDE-2[48] (study of sitaxentan and bosentan) and SUPER-1[53] (study of 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 III to II) 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 2001[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 was not available for bosentan arms). The odds ratios for sitaxentan were obtained from pooled analysis using data from STRIDE-2[48] and STRIDE-4[37] but excluding data from STRIDE-1[49] (data stratified by FC was not available). The odds ratios for sildenafil were available from the SUPER-1 trial.[53]

Due to 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 II to III beyond 12 weeks on supportive care.

Transition probabilities were entered into the model as beta distributions (Table 40, Table 42). Odds ratios were entered as log-normal distributions (Table 41, Table 43).

Table 40 Transition probabilities for supportive care for the first 12 weeks

	Functional class transition (r/n) (lower and upper confidence limits)		
Intervention	FCIII to II	FCIII to IV*	FCIV to III
Epoprostenol (Barst 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 2001[43], BREATHE-5[47], STRIDE-2[48] & SUPER-1[53])	0.125 [redacted] (0.067-0.198)	0.094 [redacted] (0.044-0.159)	-

*Including III to death (where occurred) except for STRIDE-2, for which it was unclear whether reported III to IV included death.

Table 41 Odds ratio by intervention for the first 12 weeks

	Functional class transition Odds ratio (lower and upper confidence limits)		
Intervention	FCIII to II	FCIII to IV*	FCIV to III
Epoprostenol (Barst 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 2001[43] & BREATHE-5[47])	5.02 (1.35-18.65)	0.21 (0.03-1.76)	-
Sitaxentan (Pooled data from STRIDE-2[48] & STRIDE-4[37])	2.08 (0.46-9.44)	0.18 (0.02-1.64)	-
Sildenafil (SUPER-1[53])	[redacted]	[redacted]	-

*Including III to death (where occurred) except for STRIDE-2, for which it was unclear whether reported III to IV included death.

Table 42 Transition probabilities for supportive care beyond 12 weeks (using 12 week data)

	Functional class transition (r/n) (lower and upper confidence limits)		
Intervention	FCII to III (using III to IV for epoprostenol & iloprost)	FCIII to IV	FCIV to III
Epoprostenol (Barst 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] & SUPER-1[53] for II to III; Channick 2001[43], BREATHE-5[47], STRIDE-2[48] & SUPER-1[53] for III to IV)	0.127 [redacted] (0.054-0.226)	0.094 [redacted] (0.044-0.159)	-

Table 43 Odds ratios (lower and upper confidence limits) by intervention beyond 12 weeks

	Functional class transition		
Intervention	FCII to III (using same as III to IV)	FCIII to IV	FCIV to III
Epoprostenol (Barst 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 2001[43] & BREATHE-5[47])	0.21 (0.03-1.76)	0.21 (0.03-1.76)	-
Sitaxentan (Pooled data from STRIDE-2[48] & STRIDE-4[37])	0.18 (0.02-1.64)	0.18 (0.02-1.64)	-
Sildenafil (SUPER-1[53])	[redacted]	[redacted]	-

6.3.1.3 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 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 44 Rates for additional PAH-related mortality for all therapies (per 12 weeks)

Treatments	FC	Per cycle mortality	Beta distribution
Epoprostenol, iloprost (Pooled data from Sitbon 2002 [66], Sitbon 2005 [98], McLaughlin 2002 [65])	III	0.021 (0.017-0.025)	*n*=5000, *r*=105
Epoprostenol (Pooled data from Sitbon 2002 [66], McLaughlin 2002 [65])	IV	0.056 (0.044-0.069)	*n*=1250, *r*=70
Bosentan (Sitbon 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

Table 45 Mortality on supportive care, by intervention therapy (per 12 weeks)

Treatments	FC	Mortality on supportive care	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

6.3.1.4 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 BNF prices for March 2007,[27] using the licensed dose (Table 46). In the first month of bosentan, it was assumed that the dose was 62.5mg twice a day, with a dose of 125mg twice a day for subsequent months. For inhaled iloprost and iv epoprostenol where the actual dose varies, estimates of average doses from clinical opinion were used. The amount of inhaled iloprost varies from patient to patient, however as one vial is 10µg and a patient opens a vial each time they nebulise, the cost of a 10µg 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 between 15 and 20 ng/kg/min at the end of the first year and an average of 17.5ng/kg/min was used for the first year. Although it was assumed the dose in the first months would be much lower (the iloprost industry submission uses values of 2.2ng/kg/min at baseline and 14.1ng/kg/min at 3 months), comparison with this industry data demonstrated that using this mean over the whole year would be not be inappropriate. An average dose of 40ng/kg/min was used for the second and subsequent years as the range was between 30 and 50ng/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 70kg was applied.

Further information was provided by the manufacturers with regards to the cost contract with the NHS. GlaxoSmithKline stated that epoprostenol was available [redacted] for this indication, [redacted]. Schering Health Care referred to a fixed fee system called VENTafee where 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 [redacted] per 4 weeks for the 1st and subsequent years of epoprostenol respectively.

Table 46 Costs of therapies

Therapy	Dose Mean (range)	Unit Cost (per 4 weeks) (£) (sd)
Epoprostenol Year 1 Year 2	 17.5 (15-20) ng/kg/min 40 (30-50) ng/kg/min	 4282.94 (305.92) 9789.59 (1223.70)
Iloprost	10µg vial 7 times/day	2773.40
Bosentan	125mg bd	1541.00
Sitaxentan	100mg od	1540.00
Sildenafil	20 mg tds	348.60

The therapies included in the definition of supportive care were warfarin, furosemide, digoxin and oxygen and it was assumed all patients would be on each therapy. This is likely to be an over-estimate, however, the costs of supportive therapies are small in comparison with the intervention therapies. In addition, where supportive care was not in conjunction with an active therapy, it was assumed 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 industry submission, with rates of 5%, 27% and 71% for FCII, III and IV respectively. An assumption was made that all patients in FCIV taking supportive therapies only would be on oxygen. The intensity of oral 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 regular monitoring to ensure the patient lies within their therapeutic international normalised ratio (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 very 4 weeks.

Table 47 Costs of supportive therapies

Therapy	Average dose per day	Cost per 4 weeks (£)
Warfarin	5mg od	1.47
Furosemide	100mg od	3.59
Digoxin	125mg od	2.40
Oxygen	ml	0.656125 per unit
FCII (5% uptake)	2	1.84
FCIII (27% uptake)	2	9.94
FCIV (71% uptake)	2.3	30.06
FCIV (100% uptake, supportive therapy only)	2.3	42.34

For each active therapy an initiation cost was required. In the case of the three oral therapies, the model assumed 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 iv 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 three days with a specialist nurse spending two hours a day with the patient to train them. Initiation costs for iv epoprostenol were higher as it was assumed that a patient would spend approximately 12 days in hospital. Much training is required to ensure 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 two hours a day, five days a week training the patient. In addition the cost of the insertion of a central venous catheter for iv administration of epoprostenol was also included. The unit cost used here was an elective inpatient stay for catheterisation of two 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. Due to the possibility of liver toxicity when taking bosentan or sitaxentan, it was assumed patients had a liver function test every four 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 whilst on iv 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 was 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 their own research. 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, 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 9. 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.

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

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).[27] 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 2005/2006.[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 49 Unit costs

Resource item	Unit cost	Source
Initiation costs		
Day ward	838	NHS Reference costs 2005/06[103] Day cases, Cardiac Catheterisation and Angiography without complications (HRG code E14)
Inpatient day	188	Curtis & Netten 2006[102] Patient rehabilitation, general inpatient cost, cost per bed day.
Specialist nurse (per hour)	37	Curtis & Netten 2006[102] Nurse advanced (including clinical nurse specialist) (including qualifications)
Central venous catheter insertion for iv therapy	1648	NHS Reference costs 2005/06 [103] Elective inpatient, Cardiac Catheterisation and Angiography without complications (2 day stay) (HRG code E14)
Additional costs		
Service contracts (per 4 weeks) - Epoprostenol - Iloprost - Bosentan, sitaxentan, sildenafil	[redacted]	Confidential
Liver function test	22.47	The London Clinic Pathology Pricelist 03-04 (from sildenafil submission)
Sepsis	2011	NHS Reference costs 2005/06[103] Non-elective inpatient. Septicaemia (HRG code S12)
Catheter site infection	1321	NHS Reference costs 2005/06[103] Non-elective inpatient. Other non-viral infections (HRG code S15)
Warfarin monitoring visit	10.39	Jowett (2006)[101]

6.3.1.5 Estimation of QALYs

As the model health states were based on FC, utility values also based on FC were sought from the literature and industry submissions. Valuations based on FC were available from two quality of life studies gave,[76,84] one economic evaluation[72] and data from the iloprost and bosentan industry 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 is from the simple pooling analysis. The data from Meads et al remains academic in confidence. The values used in the Highland 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 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 was comprised of 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

Table 51 Alternative utility values

	Meads[94]	***Kirsch 2 year TTO[76]***	***Kirsch 10 year TTO[76]***	***Olschewski[41]***
Health state	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
Functional class II	[redacted]	0.782 (0.031)	0.765 (0.023)	0.75 (0.193)
Functional class III	[redacted]	0.553 (0.045)	0.509 (0.044)	0.61 (0.254)
Functional class IV	[redacted]	0.371 (0.051)	0.284 (0.051)	0.44 (0.291)

6.3.1.6 Model assumptions

Odds ratios were calculated for the deterioration from FCIII to IV 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 125mg bd and 250mg bd, 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 bd dose, as liver toxicity is greater and no significant improvement is seen on the higher dose. Accordingly, the model assumed all patients were taking 125 mg bd.

6.3.1.7 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, where appropriate, an estimate of the incremental cost per QALY are shown. Cost-effectiveness acceptability curves 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.

6.3.1.8 Non-reference case analyses

Additional model runs were undertaken to consider the three main issues. Firstly, there was an investigation on the effect on results when running the model for shorter time horizons of 10 and 20 years. Alternative therapy costs supplied by the manufacturers for inhaled iloprost and iv 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.

6.3.2 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.

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, therefore shorter time horizons of 20 years and 10 years were also considered. The reference case analysis used the list price, 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 industry submission. Finally, four alternative sets of health states values were used, in order that values used in the industry models were also used in the assessment group model. The full results of these analyses can be found in Appendix 12.

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

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.

Table 52 Epoprostenol with supportive care versus supportive care alone, FCIII

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

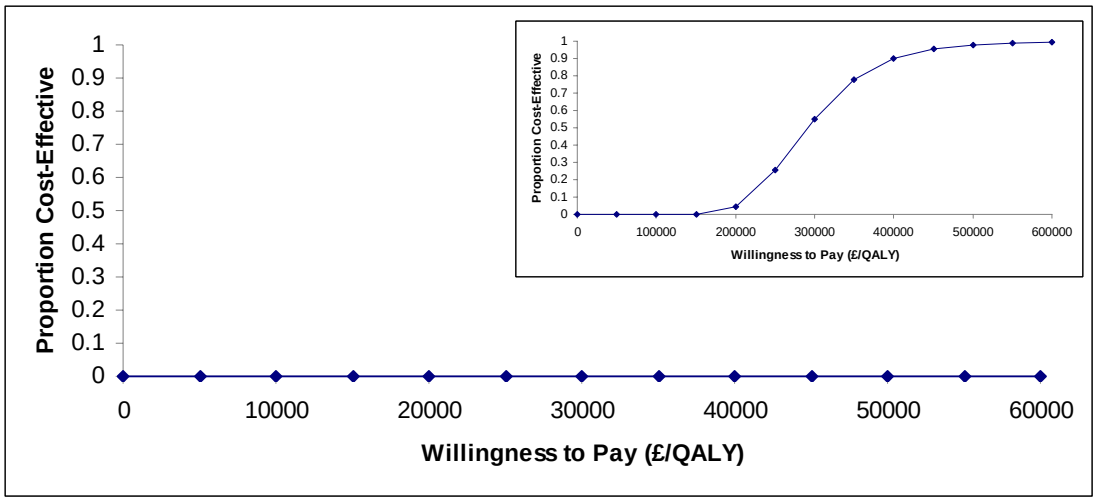

Figure 10 CEAC for epoprostenol with supportive care versus supportive care alone, FCIII

Inset graph shows larger X-axis scale

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 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 ([redacted]) epoprostenol price, which [redacted] the ICER from £277,000 per QALY to [redacted] per QALY.

Table 53 Non-reference case analyses for epoprostenol with supportive care versus supportive care alone, FCIII

Scenario	Cost difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective £20k/QALY	Probability cost-effective £30k/QALY
Reference case	218,000	0.787	277,000	0	0
20 years	216,000	0.779	277,000	0	0
10 years	189,000	0.683	277,000	0	0
Alternative epoprostenol price	[redacted]	0.787	[redacted]	[redacted]	[redacted]
Meads	218,000	[redacted]	[redacted]	0	0
Kirsch 2 year TTO	218,000	0.831	262,000	0	0
Kirsch 10 year TTO	218,000	0.799	272,000	0	0
Olschewski	218,000	0.853	256,000	0	0

6.3.2.2 Epoprostenol with supportive care versus supportive care alone, FCIV

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 quality 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).

Table 54 Epoprostenol with supportive care versus supportive care alone, FCIV

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

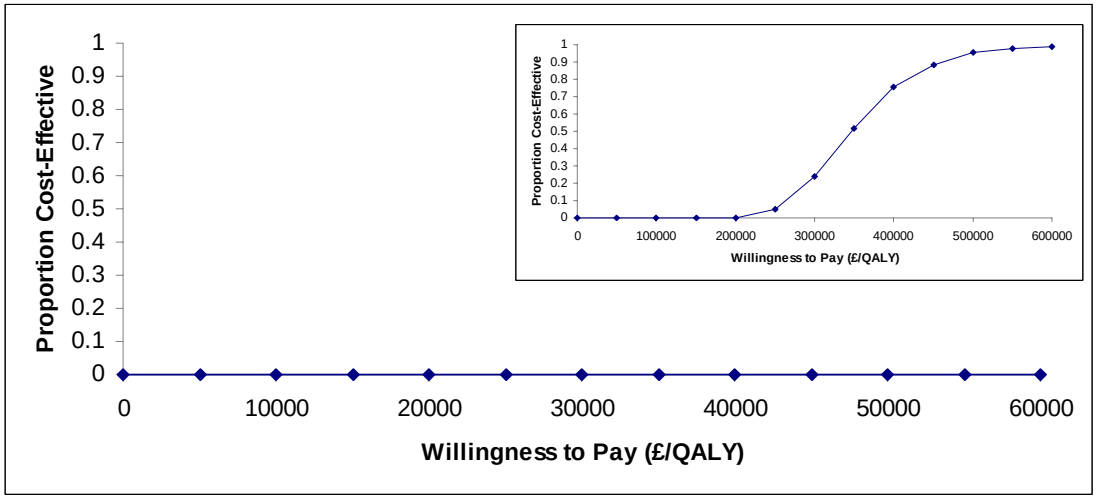

Figure 11 CEAC for epoprostenol with supportive care versus supportive care alone, FCIV

Inset graph shows larger X-axis scale

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 datasets presented in

Kirsch et al[76] gave a much higher ICER for epoprostenol in FCIV, and using the [redacted] price as stated by the manufacturer [redacted] the ICER to [redacted] per QALY gained.

Table 55 Non-reference case analyses for epoprostenol with supportive care versus supportive care alone, FC IV

Scenario	Cost difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective £20k/QALY	Probability cost-effective £30k/QALY
Reference case	403,000	1.174	343,000	0	0
20 years	401,000	1.167	344,000	0	0
10 years	368,000	1.058	348,000	0	0
Alternative epoprostenol price	[redacted]	1.174	[redacted]	[redacted]	[redacted]
Meads	403,000	[redacted]	[redacted]	0	0
Kirsch 2 year TTO *	402,000	0.895	449,000	0	0
Kirsch 10 year TTO *	402,000	0.726	554,000	0	0
Olschewski	403,000	1.049	384,000	0	0

* Small variations in the difference in cost are due to the use of different random number sets

6.3.2.3 Iloprost with supportive care versus supportive care alone, FCIII

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.

Table 56 Iloprost with supportive care versus supportive care alone, FCIII

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

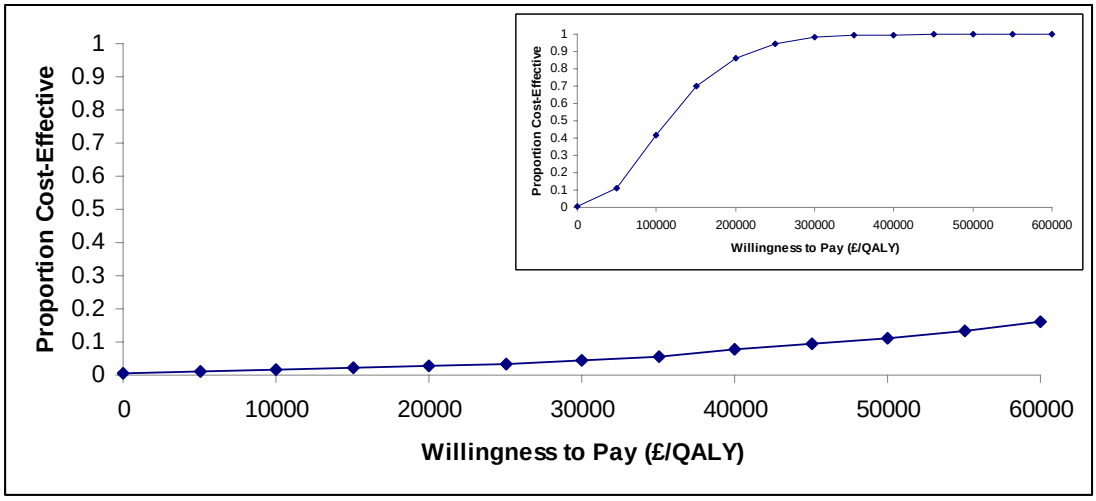

Figure 12 CEAC for iloprost with supportive care versus supportive care alone, FCIII

Inset graph shows larger X-axis scale

Analysis of the effect of single parameters in the reference case shows that the odds ratio for deterioration from III to IV 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/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 have 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.

Table 57 Non-reference case analyses for iloprost with supportive care versus supportive care alone, FCIII

Scenario	Cost difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective £20k/QALY	Probability cost-effective £30k/QALY
Reference case	103,000	1.017	101,000	0.03	0.05
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	[redacted]	1.017	[redacted]	[redacted]	[redacted]
Alternative iloprost price	87,000	1.017	85,000	0.06	0.10
Alternative iloprost and epoprostenol prices	[redacted]	1.017	[redacted]	[redacted]	[redacted]
Meads	103,000	[redacted]	[redacted]	0.03	0.04
Kirsch 2 year TTO*	102,000	1.030	99,000	0.03	0.05
Kirsch 10year TTO*	102,000	0.975	104,000	0.03	0.05
Olschewski	103,000	1.074	96,000	0.03	0.06

* Small variations in the difference in cost are due to the use of different random number sets

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

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 54% at £30,000 per QALY.

Table 58 Bosentan with supportive care versus supportive care alone, FCIII

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

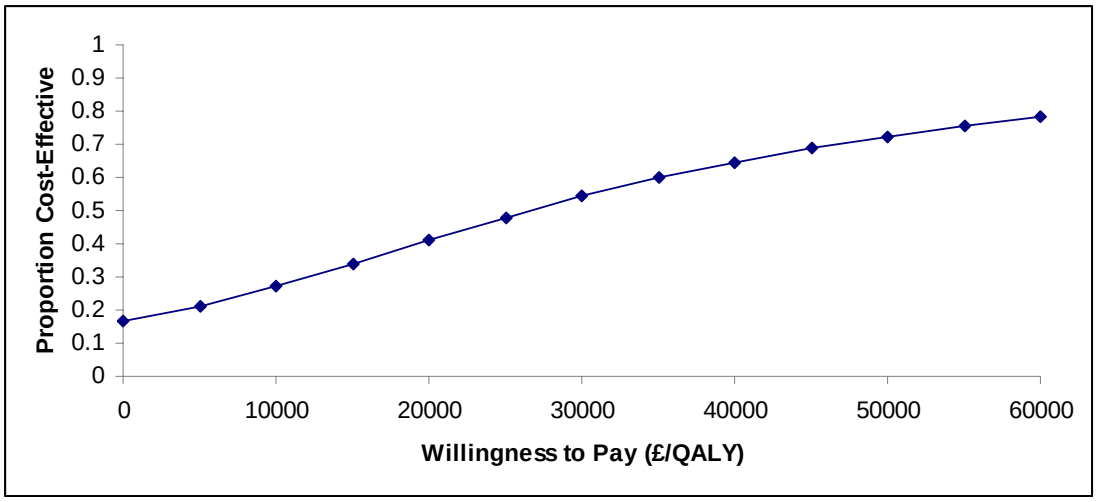

Figure 13 CEAC for bosentan with supportive care versus supportive care alone, FCIII

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 odds ratio for deterioration from III to IV after the first cycle vary from bosentan dominating the comparator in the most favourable decile group (in which the odds ratio is below 0.053) to an ICER of £90,000/QALY in the least favourable (OR>0.86). The ICER was over £30,000/QALY in the top five decile groups (OR>0.21).

The higher the mortality in class III on supportive care, the greater the difference in both costs and QALYs between bosentan and the comparator. The variation in cost difference is far higher than the variation in QALY difference. This is probably because, comparatively, more people are surviving to be treated with epoprostenol in FC IV in the bosentan arm. The higher the mortality 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 percent) up to £49,000/QALY in the least favourable group (annual mortality greater than 35.5 percent). The ICER was over £30,000/QALY in the top five decile groups (annual mortality greater than 21.3 percent).

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%. [redacted] the price of epoprostenol [redacted] the cost difference substantially therefore making bosentan [redacted] cost-effective at [redacted]. Changing the set of utility values used has very little impact on the overall result.

Table 59 Non-reference case analyses for bosentan with supportive care versus supportive care alone, FCIII

Scenario	Cost difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective £20k/QALY	Probability cost-effective £30k/QALY
Reference case	93,000	3.494	27,000	0.41	0.54
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	[redacted]	3.494	[redacted]	[redacted]	[redacted]
Meads	93,000	[redacted]	[redacted]	0.40	0.52
Kirsch 2 year TTO*	92,000	3.700	25,000	0.43	0.56
Kirsch 10 year TTO*	92,000	3.549	26,000	0.42	0.55
Olschewski	93,000	3.774	25,000	0.43	0.55

* Small variations in the difference in cost are due to the use of different random number sets

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

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 of being cost-effective is 45% and 56% respectively.

Table 60 Sitaxentan with supportive care versus supportive care alone, FCIII

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

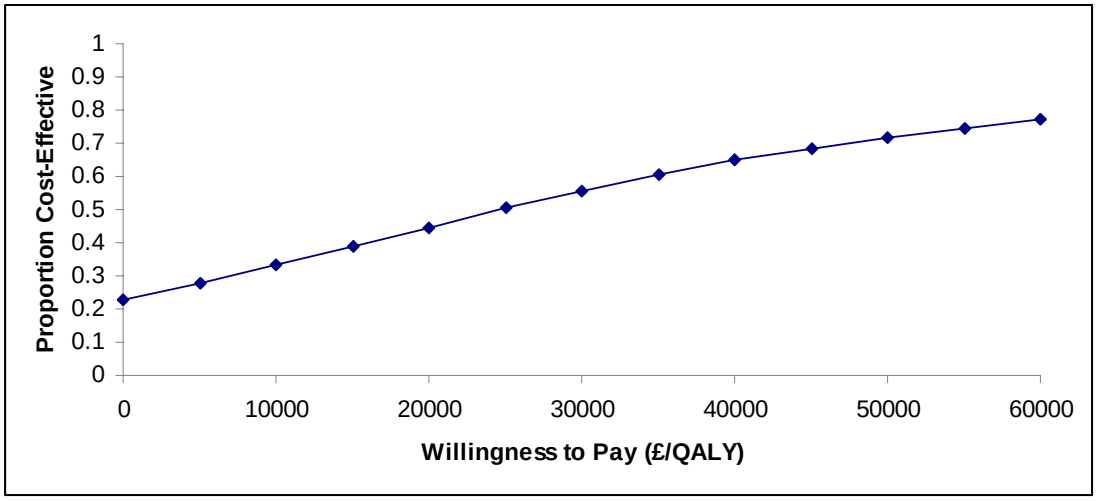

Figure 14 CEAC for sitaxentan with supportive care versus supportive care alone, FCIII

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 12.5.

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

The lower the mortality in FCIII on treatment, the greater the difference in both costs and QALYs between sitaxentan and the comparator. The variation in cost difference is far higher than the variation in QALY difference, with the effect that the results vary from an ICER of £2,500/QALY in the most favourable decile group (mortality per cycle greater than 0.0176, corresponding to annual mortality greater than 7.4 percent) up to £37,000/QALY in the least favourable group (annual mortality less than 2.3 percent). The ICER was over £30,000/QALY in the worst three decile groups (annual mortality less than 3.5 percent).

Similarly, the higher the mortality in FCIII on supportive care, the greater the difference in both costs and QALYs between sitaxentan and the comparator. The variation in cost difference is again far higher than the variation in QALY difference, 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 less than 10.5 percent) up to £50,000/QALY in the least favourable group (annual mortality greater than 35.5 percent). The ICER was over £30,000/QALY in the top four decile groups (annual mortality greater than 23.9 percent).

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 [redacted] price for epoprostenol resulted in a [redacted] ICER of [redacted] per QALY. Again, changing the set of utility values used has little impact on the ICER.

Table 61 Non-reference case analyses for sitaxentan with supportive care versus supportive care alone, FCIII

Scenario	Cost difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective £20k/QALY	Probability cost-effective £30k/QALY
Reference case	76,000	3.087	25,000	0.45	0.56
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	[redacted]	3.087	[redacted]	[redacted]	[redacted]
Meads	76,000	[redacted]	[redacted]	0.44	0.54
Kirsch 2 year TTO *	75,000	3.700	24,000	0.45	0.56
Kirsch 10 year TTO*	75,000	2.997	25,000	0.44	0.54
Olschewski	76,000	3.294	23,000	0.46	0.56

* Small variations in the difference in cost are due to the use of different random number sets

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

Reference case

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

Table 62 Sildenafil with supportive care versus supportive care alone, FCIII

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

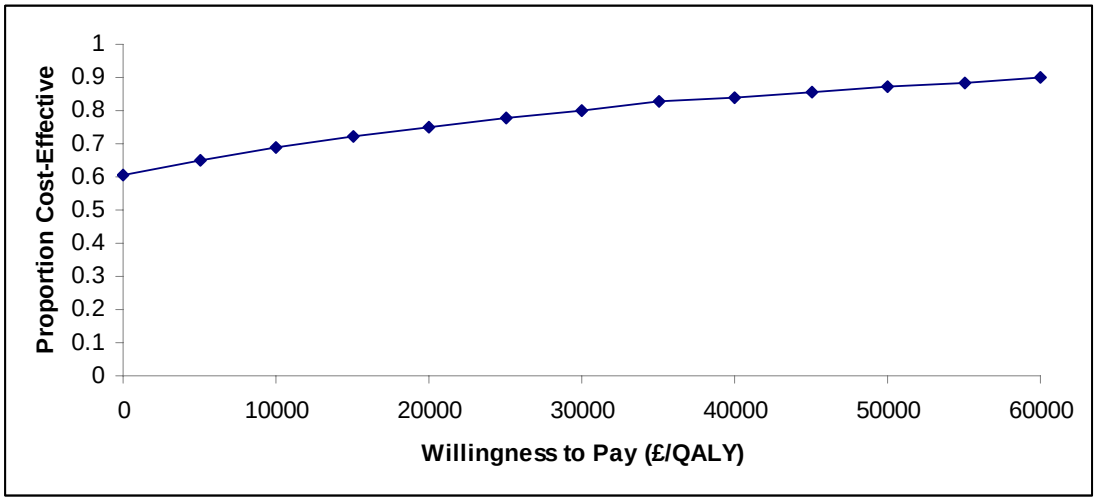

Figure 15 CEAC for sildenafil with supportive care versus supportive care alone, FCIII

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 odds ratio for deterioration from III to IV after the first cycle, sildenafil remained dominant in six decile groups (in which the odds ratio is below 0.26) but the ICER reached £70,000/QALY in the least favourable decile group (OR>0.83). The ICER was over £30,000/QALY in the top two decile groups (OR>0.50).

The lower the mortality 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 £2,000/QALY.

Similarly, the higher the mortality 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/QALY in all groups.

Non-reference case analyses

The results of the additional analyses including in Table 63 show that for almost all scenarios, sildenafil remains dominant over supportive care alone. Reducing the time horizon to 20 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 [redacted] price for epoprostenol gave an ICER of [redacted].

Table 63 Non-reference case analyses for sildenafil with supportive care versus supportive care alone, FCIII

Scenario	Cost difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective £20k/QALY	Probability cost-effective £30k/QALY
Reference case	-36,000	3.235	Dominates	0.75	0.78
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	[redacted]	3.235	[redacted]	[redacted]	[redacted]
Meads	-36,000	[redacted]	[redacted]	0.75	0.80
Kirsch 2 year TTO*	-34,000	3.376	Dominates	0.76	0.81
Kirsch 10 year TTO*	-34,000	3.227	Dominates	0.75	0.80
Olschewski	-36,000	3.480	Dominates	0.75	0.81

* Small variations in the difference in cost are due to the use of different random number sets

6.3.3 Discussion

All intervention therapies alongside supportive care led to a QALY improvement compared with supportive care alone, however the cost-effectiveness ratios vary considerably. It should be emphasised that as the interventions are largely used in different populations, comparison between therapies is not appropriate.

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, where 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 in the supportive care arm when compared with a technology for FCIII. If the technology were effective (delaying transition to FCIV) and much cheaper, 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 in price but much less so (as less patients are going to FCIV). Iloprost is a lot more expensive than the oral drugs and results in a much reduced QALY difference - patient are getting to FCIV quicker than on oral therapies, but slightly less so than supportive care. Therefore the price of epoprostenol is having quite an impact on the cost of the technology arm and supportive care arm, thus the cost in both arms is being [redacted] quite a lot, but there is little overall impact on the difference in cost.

The transition probabilities for supportive care and the odds ratios for 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 value for FCII to III and FCIII to IV; for FCIV to III and III to II; 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 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 the trials of the technologies under assessment. Separate data for FCIII and IV were not

available for epoprostenol and data from a trial with mixed FC III and IV 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 2001[43] (bosentan) to [redacted] in the 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. Different mix of subcategories of PAH within each trial and the relative small numbers upon which the proportions were based may also contribute to the apparent variation. However, it is likely that the exceptionally high response observed in the BREATHE-1 and STRIDE-4 was partly attributable to the Hawthorne effect (patients who entered a trial would perform better irrespective of treatment received due to 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. However, sensitivity analysis shows that the results are not sensitive to the overall response rate: it is the odds ratio between treatment and comparator that is critical.

The model used in the independent assessment is based on the use of functional class alone as the description of the 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 six-minute walking distance. This would, however, require the collection of appropriate data. Such data was 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 probabilistic sensitivity analysis 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 which would not be meaningful.

7. 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 NSCAG centres. As most PAH patients are already seen at these centres and that the technologies of this assessment are already in used for PAH patients, there should be limited impact on the centres.

PCTs

Apart from services for children, drug costs are not funded by the NSCAG services but locally by, for example, application to patient's PCT. National guidance recommending the use or 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 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 oppose to distant from a centre.

National Guidelines

There are no up to date UK or EU guidelines on the management and treatment of PAH. New guidelines drawn up by leading clinical expert groups are due to be published shortly. These new guidelines should take into account the same evidence of effectiveness of the technologies as this assessment in the treatment of PAH, but will almost certainly have a wider scope and include drugs outside this assessment. It is to be seen whether the guidelines are in accord with the evidence presented in this report and any guidance based on it.

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

Budget impact of each technology is difficult to accurately assess due to the absence of information on the number of PAH patients in England and Wales, the number in each functional class (FC), the numbers in each FC likely to be administered a given intervention, doses given and also 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 11 (Figure 116, Figure 117 and Figure 118). The values presented do take drug (licensed doses) and administration cost into consideration but not additional monitoring and underlying supportive care as these were considered to be of relatively minimal cost compared the technologies.

The data on current English (including Welsh) usage of the technologies (see section 3.3.6 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 budgetary impacts for each technology per annum is:

Epoprostenol – [redacted] patients – [redacted] to [redacted] million

Iloprost – [redacted] patients - [redacted] to [redacted] million

Bosentan – [redacted] patients - [redacted] million

Sitaxentan – [redacted] patients - [redacted] million

Sildenafil – [redacted] patients - [redacted] million

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 [redacted] 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.

8. DISCUSSION

8.1 Statement of principle findings

8.1.1 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 to 18 weeks and compared one of the technologies (intravenous epoprostenol, inhaled iloprost, bosentan, sitaxentan and sildenafil) added to supportive treatment versus supportive treatment alone. Only a small number of trials had 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 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 they are likely to be under-powered 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 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 to supportive treatment alone was demonstrated in open-label RCTs that included patients of mixed

FC (mainly III and IV)[11,33,39]. Effectiveness has been shown in both patients with PPH (Rubin 1990[39], Barst 1996[11]) and patients with scleroderma (Badesch 2000)[33].

- The clinical effectiveness of inhaled iloprost (added to supportive treatment) compared to supportive treatment alone was shown in a double-blind RCT (AIR[41]) that included patients of mixed FC (III and IV) with mixed types of pulmonary hypertension including non-PAH. An additional open-label RCT (AIR-2[36]) also demonstrated effectiveness but only for some of the measured outcomes.

- The clinical effectiveness of bosentan (added to supportive treatment) compared to supportive treatment alone was demonstrated in double-blind RCTs [43,45,47] that included patients predominantly of FCIII and an additional sitaxentan RCT that included open-label bosentan[48]. Effectiveness of bosentan has been shown in mixed PAH populations of IPAH and PAH/CTD (Channick 2001[43], BREATHE-1[45]), and in patients with PAH associated with Eisenmenger syndrome (BREATHE-5)[47].

- The clinical effectiveness of sitaxentan (added to supportive treatment) compared to supportive treatment alone was demonstrated in double-blind RCTs (STRIDE-1[49], STRIDE-2[48], STRIDE-4[37] that included patients of mixed FC (predominantly II and III) with mixed PAH populations including IPAH, PAH/CTD and PAH associated with congenital heart disease.

- The clinical effectiveness of sildenafil (added to supportive treatment) compared to supportive treatment alone was demonstrated in a double-blind RCT (SUPER-1[53] that included patients of mixed FC (predominantly II and III) with mixed PAH populations including IPAH, PAH/CTD and PAH associated with congenital heart disease. For sildenafil in particular there is more data for above licensed doses than for the license dose.

Direct comparison

- Only two RCTs have directly compared the technologies against each other. The STRIDE-2 study[48] compared sitaxentan to bosentan (both at licensed dose) for 18 weeks. The SERAPH study[57] compared sildenafil (above licensed dose) to 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 the combinations of the technologies (including adding one to another) was investigated in four RCTs.[38,56,58,59]

- A double-blind RCT (BREATHE-5)[56] showed no benefit for using the combination of bosentan plus intravenous epoprostenol compared to intravenous epoprostenol alone in patients of mixed FC (III and IV) with mixed types of PAH (IPAH, PAH/CTD).

- A double-blind RCT (STEP) 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.[41] However a further open-label RCT (COMBI) that included patients of FCIII with IPAH failed to demonstrate this.[58]

- A double-blinded RCT (PACES-1) 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 II and III) with mixed types of PAH (IPAH and PAH/CTD).

8.1.2 Cost-effectiveness

- None of the four published economics evaluations produced results generalisable to the NHS, as none were UK-based, only one considered QALYs, and only one study compared the intervention with supportive care alone.

- There was no consensus in the industry 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.

- 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 iv epoprostenol with supportive care versus supportive care alone in FCIII and £343,000 in FCIV. For FCIII only, the

ICER for inhaled iloprost was £101,000 per QALY, £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. 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 dominates supportive care when the cost for epoprostenol was lowered. Comparison between intervention therapies is not appropriate due to different target populations.

- The reference case represents the [redacted] drug cost of epoprostenol. Sensitivity analyses using a [redacted] epoprostenol cost [redacted] the ICERs for bosentan, sitaxentan and sildenafil compared to the reference case. This [redacted] epoprostenol cost appears to be the price paid by the designated centres.

- 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 from trials of short duration containing few patients. Therefore a longitudinal dataset of a sufficient number of patients would be of great benefit to future modelling in this clinical condition.

8.2 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 that 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 their licensed indication. Evidence in relation to use of these technologies outside their current licensed indication such as treating patients with milder disease (FCII) was not assessed.

- This assessment focused on evidence from RCTs, which were considered to be most robust and least subject to bias.

- A comprehensive literature search was performed. Submissions from the industry were scrutinised and several unpublished trials were included. Additional data were obtained from clinical study reports. The assessment is likely to be most up to date and comprehensive compared to the existing literature.

- Extensive reporting of the RCTs was undertaken and comprehensive analyses were carried out to highlight the mismatch between the licensed indication (the scope of the technology appraisal) and the available evidence.

- There was considerable clinical input into the model.

- Evidence from meta-analysis of RCTs (or individual RCTs where only one trial was available) was used to inform the parameters of treatment effects in economic modelling.

- Trials included in the assessment were of short duration. Long-term observational studies were not systematically reviewed due to time/resource constraint, however data were sought from all such studies cited in industry submissions to inform the economic evaluation. In part clinicians often make treatment decision based on available long term date rather than solely on the RCTs. 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 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.

8.3 Uncertainties

- Whether the improvement in FC, exercise capacity and haemodynamic measures on treatment shown in the RCTs lasts beyond the duration of these trials, and whether these improvements translate into long-term benefit in survival and quality of life remains uncertain. Although an increasing volume of evidence from observational studies supports the possibility of long-term benefit 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 where data were not available. These include assuming the same treatment effects (odds ratios) for patients in different FC in terms of FC improvement and deterioration, and assuming the treatment effect in preventing FC deterioration (III to IV) 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 patient's 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 burning need for head to head comparisons for patients in FCIII and in particular for the three oral technologies (bosentan, sitaxentan and sildenafil).

8.4 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 cost 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 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 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 only considers 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 e.g. such as bridging treatment for those patients who are awaiting a heart /lung transplantation but deteriorating on other treatment(s).

8.5 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 due to the differences in trial design and study population between the technologies, and their different places in the treatment pathway.

9. CONCLUSIONS

All the five technologies (intravenous epoprostenol, inhaled iloprost, bosentan, sitaxentan and sildenafil), 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.

9.1 Implications for service provision

Given the uncertainties listed above, there is evidence from the clinical and cost-effectiveness analysis which may be sufficiently robust to allow a decision on whether to recommend the use or otherwise of each of the five technologies as an adjunct to supportive care (compared to supportive care alone). There is insufficient evidence due to 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 a 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, on the effectiveness of combination of technologies, the benefit of which cannot be assumed without being adequately tested in RCTs.

The findings of the cost-effectiveness of these technologies may require further confirmation as substantial uncertainty exists due to the paucity of data and consequently the large number of assumptions needed 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 generally accepted threshold were to be withdrawn, it would have 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 treatment after failing oral therapies. Furthermore, as the findings suggested the cost-effectiveness of oral treatments is highly dependent upon the costs of epoprostenol, any changes in the costs and/or availability of epoprostenol and licensing of new treatments that occupy a similar place in the treatment pathway (i.e. if cheaper treatment with similar effectiveness to epoprostenol were licensed for patients in FCIV) would have knock-on effects on the cost-effectiveness of the other technologies.

9.2 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. 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 included in this assessment.
- Trials are required of the comparative effectiveness of the technologies. This seems most pressing for the three oral drugs (bosentan, sitaxentan and sildenafil) given their similar places in the treatment pathway and the possibility of differential clinical/cost-effectiveness between them. Such trials would allow for direct clinical and cost effectiveness analyses.
- Trials are required of mono versus dual and tri-therapy across all the technologies. Some of these are already in progress.
- Any future RCTs should ideally have 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 maybe difficult and raises ethical issues. Ethical issues should not be a problem though for well designed head to head comparisons.
- In addition 6MWT and other parameters routinely measured in the trials as the key end points have not been adequately evaluated and how clinically meaningful any change in them is, is unclear. Further work is required in this area including the exploration and validation of existing and new endpoint.

- Trials should report data in a disaggregated manner. Many trials report only aggregate data for change in parameters, usually for whole trial population and often mixed FC. The availability of baseline, end point, change in outcome data stratified by sub-population of PAH and by FC or the availability of individual patient data would greatly help future analyses. Data from existing trials in this format was requested for this assessment report but for the most part was not provided/available.
- There is a great deal of variability between some of the existing trials with regard to improvement whilst receiving supportive care alone. Such variability needs to be explored to ascertain the underlying cause and this then fed into the design of future studies.
- There is no information currently available on sequencing of technologies. Whilst probably a lower priority than the above this is still an important research question. So studies assessing 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.
- An evidence based guideline for the treatment of PAH using the technologies of this assessment (and others) is 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, long term response to treatment and survival.

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10. APPENDICES

Appendix 1. National Pulmonary Hypertension Service Census. Distribution of Patients and Current UK Usage of the Technologies

Current usage data is taken from the National Pulmonary Hypertension Service Census submitted as part of the submission for this technology appraisal by the Royal College of Physicians.[31] 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 PH not just PAH and therefore figures may be greater than that 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 section 3.3.6.

Figure 16 details the total number of patients seen at designated PH centres in England and Scotland by year since 2004.

ACADEMIC IN CONFIDENCE – FIGURE REMOVED

Figure 16 Total numbers of patients under the care of Pulmonary Hypertension Service.[v].

Key summary data (Table 64), and data on mono, dual and triple therapy utilisation in England, Scotland, Adults and Children
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Table 65, **********
Table 66, **********
Table 67) are selectively reproduced below for the year 2006-7.

[v] Data from [redacted] UK Centres. [redacted].
Data was collected to the 31 March each year and excluded patients who have been discharged, died or not seen since 1 April of the previous year.

Table 64 Summary Data of patients, their location and type of treatment in the National PH Service 2006-7

Summary Data	English Patients[a]	Scottish Patients	UK Children	Total UK Patients[a]
Patients attending PH Service	[redacted]	[redacted]	[redacted]	[redacted]
Patients on disease-targeted mono therapy	[redacted]	[redacted]	[redacted]	[redacted]
Patients on disease-targeted dual / triple therapy	[redacted]	[redacted]	[redacted]	[redacted]
Patients on any disease-targeted therapy	[redacted]	[redacted]	[redacted]	[redacted]
Transplants	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 65 Patients receiving mono-therapy, their location and specific treatment in the National PH Service 2006-7

Name of Therapy	English Patients*	Scottish Patients	UK Children	Total UK Patients
Epoprostenol (iv)	[redacted]	[redacted]	[redacted]	[redacted]
Treprostinil (sc)	[redacted]	[redacted]	[redacted]	[redacted]
Treprostinil (iv)	[redacted]	[redacted]	[redacted]	[redacted]
Iloprost (iv)	[redacted]	[redacted]	[redacted]	[redacted]
Iloprost (nebulised)	[redacted]	[redacted]	[redacted]	[redacted]
Bosentan	[redacted]	[redacted]	[redacted]	[redacted]
Sitaxentan	[redacted]	[redacted]	[redacted]	[redacted]
Sildenafil	[redacted]	[redacted]	[redacted]	[redacted]
Trial Drug[b]	[redacted]	[redacted]	[redacted]	[redacted]
Totals	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 66 Patients receiving dual therapy, their location and specific treatment in the National PH Service 2006-7

Name of Therapy	Total English Patients[a]	Total Scottish Patients	UK Children	Total UK Patients[a]
Bosentan & Sildenafil	[redacted]	[redacted]	[redacted]	[redacted]
Sitaxentan and Sildenafil	[redacted]	[redacted]	[redacted]	[redacted]
Bosentan + Epoprostenol (iv)	[redacted]	[redacted]	[redacted]	[redacted]

Bosentan + Iloprost (iv or neb)	[redacted]	[redacted]	[redacted]	[redacted]
Bosentan + Treprostinil (sc or iv)	[redacted]	[redacted]	[redacted]	[redacted]
Sildenafil + Iloprost (iv or neb)	[redacted]	[redacted]	[redacted]	[redacted]
Sildenafil + Treprostinil (sc or iv)	[redacted]	[redacted]	[redacted]	[redacted]
Sildenafil + Epoprostenol (iv)	[redacted]	[redacted]	[redacted]	[redacted]
Trial Drug[b]	[redacted]	[redacted]	[redacted]	[redacted]
Totals	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 67 Patients receiving triple therapy, their location and specific treatment in the National PH Service 2006-7

Name of Therapy	**English Patients[a]**	**Scottish Patients**	**UK Children**	**Total UK Patients[a]**
Bosentan + Sildenafil + Epoprostenol (iv)	[redacted]	[redacted]	[redacted]	[redacted]
Bosentan + Sildenafil + Iloprost (iv or neb)	[redacted]	[redacted]	[redacted]	[redacted]
Bosentan + Sildenafil + Treprostinil (sc or iv)	[redacted]	[redacted]	[redacted]	[redacted]
Treprostinil (sc) & bosentan & sildenafil & iloprost (neb)	[redacted]	[redacted]	[redacted]	[redacted]
Totals	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

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[vi]

[vi] 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 08

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 08[vii]

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
#2 pah
#3 pulmonary next hypertension
#4 pulmonary next artery next hypertension

[vii] Additional search to account for alternative spelling of sitaxentan/sitaxsentan

#5 MeSH descriptor Hypertension, Pulmonary, this term only
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 epoprostenol or prostacyclin or flolan
#8 iloprost or ventavis
#9 bosentan or tracleer
#10 sitaxentan or thelin or sitaxsentan
#11 sildenafil or revatio
#12 (#7 OR #8 OR #9 OR #10 OR #11)
#13 (#6 AND #12)

Source - Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations February 27, 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 February 27, 2007[viii]

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)

[viii] Additional search to account for alternative spelling of sitaxentan/sitaxsentan

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 Feb 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 which included pulmonary artery hypertension or pulmonary hypertension.

Source – EMBASE (Ovid) 1980 to 2007 Week 09

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 – Feb 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 where they also included 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[104]	Study design/Narrative review
Battistini 2006[105]	Study design/Narrative review
Bell 2006[106]	Study design/Narrative review
Benza 2007[107]	Comparator/Comparison of two doses of sitaxentan without placebo or other active control
Castro 2001[108]	Study design/Spanish commentary on Channick 2001[43]
Galiè 2004[109]	Study design/Narrative review
Ghofrani 2002a[110]	Study design/ < 1 week duration
Ghofrani 2002b[111]	Study design/ < 1 week duration
Goldsmith 2004[112]	Study design/Narrative review
Hughes 2006[113]	Study design/Uncontrolled study
Keogh 2007[84]	Study design/Uncontrolled study
McLaughlin 2005[114]	Comparator/Comparison of survival data from RCT with predicted survival using mathematical equation
Oudiz 2004[115]	Intervention/Treprostinil not included in this review
Ricachinevsky 2006[116]	Population/Review of treatment of PAH in children.
Simonneau 2002[117]	Intervention/Treprostinil not included in this review
Voswinckel 2006[118]	Intervention/Treprostinil not included in this review

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 below.

Table 69 List of included systematic reviews

Study	Description
Kenyon 2003[119]	Bosentan for the treatment of PAH
Fung 2004[120]	Sildenafil for the treatment of PAH
Kanthapillai 2004[121]	Sildenafil for pulmonary hypertension (Cochrane review)
Baker 2005[122]	Inhaled iloprost in PAH
Lee 2005[123]	Sildenafil for pulmonary hypertension
Paramothayan 2005[60]	Prostacyclin for pulmonary hypertension in adults (Cochrane review)
Liu 2006[124]	Endothelin receptor antagonists for PAH (Cochrane review)
Wittbrodt 2007[125]	Sitaxentan for treatment of pulmonary hypertension

Appendix 5. Extracted data from included RCTs for outcomes included in meta-analysis

Table 70 Extracted data for death/survival, clinical worsening, withdrawal for any reasons, changes in FC, and serious adverse events

	Death		Clinical worsening		Withdrawal for any reasons	Change in functional class				Serious adverse events
	n/N	Life table estimates: proportion died, 95% CI	n/N	Life table estimates: proportion worsened, 95% CI	n/N	N	Improved	Unchanged	Worsened	n/N
Epoprostenol										
Rubin 1990[39] 8 wks										
Control	3/12	NR	NR	NR	NR	9	2	NR	NR	NR
Epoprostenol	1/11	NR	NR	NR	NR	10	10	0	0	NR
Barst 1996[11] 12 wks										
Control	8/40	0.2*	NR	NR	10[a]/40	31	1	27	3	NR
Epoprostenol	0/41	0	NR	NR	3[a]/41	40	16	19	5	NR
ITT population (used in analysis) assuming worsening FC for patients who died or had transplantation										
Control	NR	NR	NR	NR	NR	40	1	27	12	NR
Epoprostenol	NR	NR	NR	NR	NR	41	16	19	6	NR
Badesch 2000[33] 12 wks										
Control	5/55	NR	NR	NR	NR	55	0	NR	NR	NR
Epoprostenol	4/56	NR	NR	NR	NR	56	21	NR	NR	NR
Iloprost										

	Death		**Clinical worsening**		**Withdrawal for any reasons**	**Change in functional class**				**Serious adverse events**
AIR-1 / Olschewski 2002 [41] 12 wks										
Placebo	4/102	NR	12/102[b]	NR	14/102	92	13	67	12[c]	25/102
Iloprost	1/101	NR	5/101[b]	NR	4/101	97	25	65	7[c]	28/101
PPH, all FC										
Placebo	2/55	NR	NR	NR	7/55	50	4	38	8[d]	NR
Iloprost	1/53	NR	NR	NR	2/53	51	13	35	3[d]	NR
PPH, FC III (from industry submission)										
Placebo	NR	NR	NR	NR	NR	36	2	25	9	NR
Iloprost	NR	NR	NR	NR	NR	34	7	24	3	NR
AIR-2[36] 12 wks										
Data from industry submission or unpublished manuscript (Academic in confidence)										
Control	2[e]/33	NR	NR	NR	[redacted]	[redacted]	2/33[f]	[redacted]	[redacted]	7/33
Iloprost	2/30	NR	NR	NR	[redacted]	[redacted]	6/30[f]	[redacted]	[redacted]	8[g]/30
COMBI / Hoeper 2006[58] 12 wks										
Ongoing bosentan	0/21	Not applicable	4/21	NR	0/21	NR	NR	NR	NR	NR
Iloprost + ongoing bosentan	0/19	Not applicable	3/19	NR	1[h]/19	NR	NR	NR	NR	NR
STEP / McLaughlin 2006[59] 12 wks										
Placebo + ongoing bosentan	0/33	Not applicable	5/33	0.16*	5/33	33	2	30	1	7/32
Iloprost + ongoing	0/34	Not applicable	0/32	0	4/34	31	11	20	0	5/35

	Death		**Clinical worsening**		**Withdrawal for any reasons**	**Change in functional class**				**Serious adverse events**
bosentan										
IPAH only, mixed FC										
Placebo + ongoing bosentan	0/20	Not applicable	NR	NR	NR	20	1	NR	NR	NR
Iloprost + ongoing bosentan	0/17	Not applicable	NR	NR	NR	16	6	NR	NR	NR
Bosentan										
Channick 2001[43] 12 wks										
Placebo	0/11	Not applicable	3/11	NR	2/11	11	1	8	2	NR
Bosentan 125 mg bd	0/21	Not applicable	0/21	NR	0/21	21	9	12	0	NR
BREATHE-1 / Rubin 2002[45] 16 wks										
Placebo	2/69	NR	14/69	0.15*	NR	69	21	NR	NR	NR
Bosentan 125 mg bd	1/74	NR	5/74	0.06*	NR	74		NR	NR	NR
Bosentan 250 mg bd	0 (3?)/70	NR	4/70	0.06*	NR	70	60	NR	NR	NR
BREATHE-2 / Humbert 2004[56] 16 wks										
Placebo + epoprostenol	0/11	NR	NR	NR	1/11	11	5	NR	NR	NR
Bosentan + epoprostenol	2 (3?)/22	NR	NR	NR	4/22	22	13	NR	NR	NR
BREATHE-5 / Galiè										

	Death		**Clinical worsening**		**Withdrawal for any reasons**	**Change in functional class**				**Serious adverse events**
2006[47] 16 wks										
Placebo	0/17	Not applicable	NR	NR	2/17	17	2	14	1	3/17
Bosentan 125 mg bd	0/37	Not applicable	NR	NR	2/37	37	13	23	1	5/37
Sitaxentan										
STRIDE-1 / Barst 2004[49] 12 wks										
Placebo	0/60	NR	3/60	Proportion with no event [redacted]	5/60	60	9	47	4	9/59
Sitaxentan 100 mg od	0/55	NR	0/55	[redacted]	0/55	55	16	39	0	3/56
Sitaxentan 300 mg od	1/63	NR	1/63	[redacted]	7/63	63	19	43	1	10/63
IPAH, mixed FC[61]										
Placebo	NR	NR	NR	NR	NR	37	6	28	3	NR
Sitaxentan 100 mg & 300 mg	NR	NR	NR	NR	NR	55	18	36	1	NR
PAH/CTD, mixed FC[61]										
Placebo	NR	NR	NR	NR	NR	9	1	7	1	NR
Sitaxentan 100 mg & 300 mg	NR	NR	NR	NR	NR	33	8	25	0	NR
STRIDE-2 / Barst 2006[48] 18 wks										
Placebo	2/62	NR	10/62	NR	11/62	[redacted]	6	[redacted]	8	19/62
Bosentan 125 mg bd	0/60	NR	9/60	P = 0.80 vs. placebo	8/60	[redacted]	[redacted]	[redacted]	5	[redacted]

	Death		**Clinical worsening**		**Withdrawal for any reasons**	**Change in functional class**				**Serious adverse events**
Sitaxentan 50 mg od	0/62	NR	6/62	P = 0.27 vs. placebo	8/62	[redacted]	[redacted]	[redacted]	8	[redacted]
Sitaxentan 100 mg od	0/61	NR	4/61	P = 0.08 vs. placebo	4/61	[redacted]	8	[redacted]	1	8/61
FCIII only, mixed PAH										
Placebo	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR
Bosentan 125 mg bd	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR
Sitaxentan 50 mg od	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR
Sitaxentan 100 mg od	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR
STRIDE-4 / Barst 2007[37] 18 wks										
Placebo	0/34	NR	3/34	NR	[redacted]	34	9	21	4	[redacted]
Sitaxentan 50 mg od	0/32	NR	1/32	[redacted]	[redacted]	32	8	22	2	[redacted]
Sitaxentan 100 mg od	0/32	NR	0/32	P = 0.0898 vs. placebo	[redacted]	32	15	17	0	[redacted]
FCIII only, mixed PAH										
Placebo	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR
Sitaxentan 50 mg od	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR
Sitaxentan 100 mg od	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR
Sildenafil										
SUPER-1 / Galiè 2005[53] 12 wks										
Placebo	1/70	NR	7/70	0.100 (0.03 to 0.17)	[redacted]	70	5	58	7	12/70
Sildenafil 20 mg tid	1/69	NR	3/69	0.044 (0 to 0.093)	[redacted]	68	19	47	2	10/69
Sildenafil 40 mg tid	0/67	NR	2/67	0.030 (0 to 0.071)	[redacted]	66	24	40	2	10/67

	Death		**Clinical worsening**		**Withdrawal for any reasons**	**Change in functional class**				**Serious adverse events**
Sildenafil 80 mg tid	2/71	NR	5/71	0.071 (0.011 to 0.132)	[redacted]	69	29	38	2	9/71
FCIII only, mixed PAH										
Placebo	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR
Sildenafil 20 mg tid	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR
Sildenafil 40 mg tid	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR
Sildenafil 80 mg tid	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR
PACES-1[38] 16 wks										
Placebo + ongoing epoprostenol	7/131	NR	22/131	0.180 (0.110 to 0.249)	[redacted]/131	125	18	92	15	39/131
Sildenafil + ongoing epoprostenol	1/134	NR	8/134	0.062 (0.020 to 0.104)	[redacted]/134	132	47	76	9	29/134
FCIII only, mixed PAH										
Placebo + ongoing epoprostenol	NR	NR	NR	NR	NR	85	16	62	7	NR
Sildenafil + ongoing epoprostenol	NR	NR	NR	NR	NR	87	32	51	4	NR
Head to head trial										
SERAPH[57] 16 wks										
Bosentan 125 mg bd	0/12	NR	NR	NR	0/12	NR	NR	NR	NR	NR
Sildenafil 50 mg tid	1/14	NR	NR	NR	1/14	NR	NR	NR	NR	NR

*Estimated from figures

[a] Including death and lung transplantation.

[b] Defined as 'died or deteriorated' in the study.
[c] 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.
[d] 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.
[e] [redacted]
[f] From industry submission. The denominators (total number of patients included in the analysis) were different from those reported in the unpublished manuscript.
[g] [redacted]
[h] Stated in the paper 'all patients finished the study'. However, one patient stopped inhaling iloprost after 6 weeks due to intractable coughing.

Table 71 Extracted data for 6-minute walk distance and Borg dyspnoea index

	6MWD									Borg dyspnoea index									
	Baseline n	mean	SD	Post-Rx n	mean	SD	Change n	mean	SD	Baseline n	mean	SD	Post-Rx n	mean	SD	Change n	mean	SD
Epoprostenol																		
Rubin 1990[39] 8 wks																		
Control	9	205	NR	9	292	NR	9	79[c]	87.3[c]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Epoprostenol	10	246	NR	10	378	NR	10	131[c]	131.3[c]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Additional data from Cochrane review[60] & used in analysis																		
Control	NR	NR	NR	NR	NR	NR	11	35.70	143.94	NR	NR	NR	NR	NR	NR	NR	NR	NR
Epoprostenol	NR	NR	NR	NR	NR	NR	10	141.20	136.29	NR	NR	NR	NR	NR	NR	NR	NR	NR
Barst 1996[11] 12 wks																		
Control	40	272	145.5^	40	257	151.8^	40	-15	148.7[e]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Epoprostenol	41	316	115.3^	41	348	108.9^	41	32	112.1[e]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Badesch 2000[33] 12 wks																		
Control	55	240.0 (median)	NR	44[d]	233.6[d]	107.3[d]	55	-36.0	NR	NR	NR	NR	NR	NR	NR	NR	1.0 (median)	NR
Epoprostenol	56	271.5 (median)	NR	50[d]	317.0[d]	133.0[d]	56	63.5	NR	NR	NR	NR	NR	NR	NR	NR	-2.0 (median)	NR

	6MWD									Borg dyspnoea index									
	Baseline n	mean	SD	Post-Rx n	mean	SD	Change n	mean	SD	Baseline n	mean	SD	Post-Rx n	mean	SD	Change n	mean	SD
Iloprost																		
AIR / Olschewski 2002[41] 12 wks																		
Placebo	102	315	96	NR	NR	NR	102	-19*	81*^	NR	NR	NR	NR	NR	NR	NR	NR	NR
Iloprost	101	332	93	NR	NR	NR	101	17*	90*^	NR	NR	NR	NR	NR	NR	NR	NR	NR
AIR-2[36] 12 wks																		
Control	[redacted]																	
Iloprost	[redacted]																	
COMBI / Hoeper 2006[58] 12 wks																		
Ongoing bosentan	21	296	79	21	297	94	21	1	27	NR	NR	NR	NR	NR	NR	NR	NR	NR
Iloprost + ongoing bosentan	19	317	74	19	309	124	19	-9	100	NR	NR	NR	NR	NR	NR	NR	NR	NR
STEP / McLaughlin 2006[59] 12 wks																		
Placebo + ongoing bosentan	33	340	73	33	343[b]	99[b]	33	4[b]	61[b]	33	3.5	2.1	33	3.6[b]	2.5[b]	33	0.0[b]	1.5[b]
Iloprost + ongoing bosentan	34	331	64	32	367[b]	84[b]	32	30[b]	60[b]	32	3.9	1.7	32	3.4[b]	1.7[b]	32	-0.5[b]	1.2[b]

	6MWD									Borg dyspnoea index									
	Baseline n	mean	SD	Post-Rx n	mean	SD	Change n	mean	SD	Baseline n	mean	SD	Post-Rx n	mean	SD	Change n	mean	SD
Bosentan																		
Channick 2001[15] 12 wks																		
Placebo	11	355.09	81.96	11	349.64	147.12	11	-5.45	120.47	11	3.82	1.72	11	4.91	2.91	11	1.09	2.66
Bosentan 125 mg bd	21	360.29	86.05	21	430.52	66.43	21	70.24	56.09	21	4.38	1.80	21	4.19	2.42	21	-0.19	1.66
BREATHE-1 / Rubin 2002[45] 16 wks																		
Placebo	69	344	76	NR	NR	NR	69	-8	100*^	69	3.8	2.0	69	4.2	2.5^	69	0.3	1.7^
Bosentan 125 mg bd	74	326	73	NR	NR	NR	74	27	77*^	74	3.3	2.2	74	3.2	2.6^	74	-0.1	1.7^
Bosentan 250 mg bd	70	333	75	NR	NR	NR	70	46	59*^	70	3.8	1.9	70	3.3	2.5^	70	-0.6	1.7^
BREATHE-2 / Humbert 2004[56] 16 wks																		
Placebo + epoprostenol	11	NR	NR	NR	NR	NR	10	74 (median)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bosentan + epoprostenol	22	NR	NR	NR	NR	NR	19	68 (median)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
BREATHE-5 / Galiè 2006[47] 16 wks																		

	6MWD									Borg dyspnoea index									
	Baseline n	**mean**	**SD**	**Post-Rx n**	**mean**	**SD**	**Change n**	**mean**	**SD**	**Baseline n**	**mean**	**SD**	**Post-Rx n**	**mean**	**SD**	**Change n**	**mean**	**SD**
Placebo	17	366.4	67.5	NR	NR	NR	17	-9.7	91.9^	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bosentan 125 mg bd	37	331.9	82.8	NR	NR	NR	37	43.3	49.3^	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sitaxentan																		
STRIDE-1 / Barst 2004[49] 12 wks																		
Placebo	60	413	105	NR	NR	NR	60	-13	62.8	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sitaxentan 100 mg od	55	394	114	NR	NR	NR	55	22	47.6	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sitaxentan 300 mg od	63	387	110	NR	NR	NR	63	20	67.8	NR	NR	NR	NR	NR	NR	NR	NR	NR
IPAH, mixed FC[61]																		
Placebo	NR	NR	NR	NR	NR	NR	37	-10	65	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sitaxentan 100 mg & 300 mg	NR	NR	NR	NR	NR	NR	57	24	68	NR	NR	NR	NR	NR	NR	NR	NR	NR
PAH/CTD, mixed FC[61]																		
Placebo	NR	NR	NR	NR	NR	NR	9	-38	84	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sitaxentan 100 mg & 300 mg	NR	NR	NR	NR	NR	NR	33	20	52	NR	NR	NR	NR	NR	NR	NR	NR	NR
STRIDE-2 / Barst 2006[48] 18 wks																		
Placebo	62	321	85	NR	NR	NR	[redacted]	-6.5	84.4	NR	NR	NR	NR	NR	NR	[redacted]	0.19	2.15

	6MWD									Borg dyspnoea index									
	Baseline n	mean	SD	Post-Rx n	mean	SD	Change n	mean	SD	Baseline n	mean	SD	Post-Rx n	mean	SD	Change n	mean	SD
Bosentan 125 mg bd	60	337	78	NR	NR	NR	[redacted]	23.0	76.4	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
Sitaxentan 50 mg od	62	328	80	NR	NR	NR	[redacted]	17.8	58.3	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
Sitaxentan 100 mg od	61	360	72	NR	NR	NR	[redacted]	24.9	57.5	NR	NR	NR	NR	NR	NR	[redacted]	-0.01	1.91
STRIDE-4 / Barst 2007 [37] 18 wks																		
Placebo	34	342	82	NR	NR	NR	34	34	88.5	34	[redacted]	[redacted]	NR	NR	NR	34	[redacted]	[redacted]
Sitaxentan 50 mg od	32	350	73	NR	NR	NR	32	22	48.6	32	[redacted]	[redacted]	NR	NR	NR	32	[redacted]	[redacted]
Sitaxentan 100 mg od	32	344	83	NR	NR	NR	32	58	63.6	32	[redacted]	[redacted]	NR	NR	NR	32	[redacted]	[redacted]
Sildenafil																		
SUPER-1 / Galiè 2005[53] 12 wks																		
Placebo	70	344	79	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sildenafil 20 mg tid	69	347	90	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	-1 (median)	NR
Sildenafil 40 mg tid	67	345	77	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0 (median)	NR
Sildenafil 80 mg tid	71	339	79	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	-1	NR

	6MWD									**Borg dyspnoea index**								
	Baseline n	**mean**	**SD**	**Post-Rx n**	**mean**	**SD**	**Change n**	**mean**	**SD**	**Baseline n**	**mean**	**SD**	**Post-Rx n**	**mean**	**SD**	**Change n**	**mean**	**SD**
																	(median)	
PACES-1[38] 16 wks																		
Placebo + ongoing epoprostenol	119	NR	NR	NR	NR	NR	119	4.1	NR	119	3 (median)	NR	119	3 (median)	NR	NR	NR	NR
Sildenafil + ongoing epoprostenol	131	NR	NR	NR	NR	NR	131	30.1	NR	131	3 (median)	NR	131	3 (median)	NR	NR	NR	NR

*****Estimated from figures
^Estimated from standard errors
[a] Measured pre-inhalation (trough drug level/effect)
[b] Measured post-inhalation (peak drug level/effect)
[c] Estimated from 95% confidence interval
[d] Data from Paramothayan 2005[60] (Cochrane review)
[e] Imputed from standard deviations of baseline and post-treatment values assuming an intercorrelation coefficient of 0.5.

Table 72 Extracted data for mean pulmonary arterial pressure and right atrial pressure

	Mean pulmonary arterial pressure (mPAP)									Right atrial pressure (RAP)								
	Baseline n	mean	SD	Post-Rx n	mean	SD	Change n	mean	SD	Baseline n	mean	SD	Post-Rx n	mean	SD	Change n	mean	SD
Epoprostenol																		
Rubin 1990[39] 8 wks																		
Control	9	62.2	NR	9	62.2	NR	9	0[c]	13.6[c]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Epoprostenol	10	58.6	NR	10	49.3	NR	10	-8.4[c]	15.0[c]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Additional data from Cochrane review[60] & used in analysis																		
Control	NR	NR	NR	NR	NR	NR	11	0.30	13.50	NR	NR	NR	NR	NR	NR	NR	NR	NR
Epoprostenol	NR	NR	NR	NR	NR	NR	10	-7.57	14.14	NR	NR	NR	NR	NR	NR	NR	NR	NR
Barst 1996[11] 12 wks																		
Control	40	59	12.6^	NR	NR	NR	30	[redacted]	[redacted]	40	12	6.3	NR	NR	NR	[redacted]	[redacted]	[redacted]
Epoprostenol	41	61	12.8^	NR	NR	NR	38	[redacted]	[redacted]	41	13	6.4	NR	NR	NR	[redacted]	[redacted]	[redacted]
Badesch 2000[33] 12 wks																		
Control	55	49.1	10.2	NR	NR	NR	NR	0.94	8.16^	55	11.1	5.5	NR	NR	NR	NR	1.20	5.12^
Epoprostenol	56	50.9	10.6	NR	NR	NR	NR	-5.03	8.16^	56	13.1	5.0	NR	NR	NR	NR	-1.26	6.14^
Iloprost																		
AIR-1 / Olschewski																		

2002 12 wks																		
Placebo	101	53.8	14.1	NR	NR	NR	NR	-0.2	6.9	NR	NR	NR	NR	NR	NR	NR	1.4	4.8
Iloprost (post-inhalation)	100	52.8	11.5	NR	NR	NR	NR	-4.6[b]	9.3[b]	NR	NR	NR	NR	NR	NR	NR	-0.8[b]	4.6[b]
Iloprost (pre-inhalation)	NR	NR	NR	NR	NR	NR	NR	-0.1[a]	7.3[a]	NR	NR	NR	NR	NR	NR	NR	0.5[a]	4.6[a]
AIR-2[36] 12 wks																		
Control	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Iloprost	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR	NR	NR	NR
COMBI / Hoeper 2006[58] 12 wks																		
Ongoing bosentan	59	19	NR	NR	NR	NR	NR	NR	NR	9	5	NR	NR	NR	NR	NR	NR	NR
Iloprost + ongoing bosentan	54	12	NR	NR	NR	NR	NR	NR	NR	9	6	NR	NR	NR	NR	NR	NR	NR
STEP / McLaughlin 2006[59] 12 wks																		
Placebo + ongoing bosentan	28	52	13	28	55[b]	16[b]	28	2[b]	6[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Iloprost + ongoing bosentan	29	51	11	29	46[b]	13[b]	29	-6[b]	7[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bosentan																		
Channick 2001[43] 12 wks																		

Placebo	10	56	10	NR	NR	NR	10	5.1	8.9	10	9.9	4.1	NR	NR	NR	10	4.9	4.7
Bosentan 125 mg bd	20	54	13	NR	NR	NR	20	-1.6	5.4	19	9.7	5.6	NR	NR	NR	19	-1.3	3.9
BREATHE-1 / Rubin 2002[45] 16 wks																		
Placebo	69	53	17	NR	NR	NR	NR	NR	NR	67	8.9	5.1	NR	NR	NR	NR	NR	NR
Bosentan 125 mg bd	74	53	14	NR	NR	NR	NR	NR	NR	74	9.7	5.4	NR	NR	NR	NR	NR	NR
Bosentan 250 mg bd	70	57	17	NR	NR	NR	NR	NR	NR	69	9.9	6.5	NR	NR	NR	NR	NR	NR
BREATHE-2 / Humbert 2004[56] 16 wks																		
Placebo + epoprostenol	11	60.9	9.6^	11	59.2	10.6^	11	-2.2%	SE=3.6%	11	11.9	7.3^	11	12.2	6.0^	11	0.3	4.3^
Bosentan + epoprostenol	22	59.2	18.8^	22	52.5	11.3^	22	-9.0%	SE=6.0%	22	11.9	5.2^	22	10.0	5.6^	22	-1.9	6.6^
BREATHE-5 / Galiè 2006[47] 16 wks																		
Placebo	17	72.1	19.4	NR	NR	NR	17	0.5	5.8^	17	5.0	3.7	NR	NR	NR	17	0.4	3.7^
Bosentan 125 mg bd	37	77.8	15.2	NR	NR	NR	37	-5.0	9.7^	37	6.1	3.4	NR	NR	NR	37	0.3	3.0^
Sitaxentan																		
STRIDE-1 / Barst 2004[49] 12 wks																		
Placebo	60	52	16	60	53	15	60	0	8	60	8	5	NR	NR	NR	60	1	4
Sitaxentan 100 mg od	55	54	17	55	51	16	55	-3	8	55	7	5	NR	NR	NR	55	0	4
Sitaxentan 300 mg od	63	54	14	63	49	15	63	-5	11	63	9	5	NR	NR	NR	63	-1	4

STRIDE-2 / Barst 2006[48] 18 wks																		
Placebo	62	49	14	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bosentan 125 mg bd	60	50	15	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sitaxentan 50 mg od	62	48	15	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sitaxentan 100 mg od	61	45	12	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
STRIDE-4 / Barst 2007 [37] 18 wks																		
Placebo	34	64	14	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sitaxentan 50 mg od	32	56	17	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sitaxentan 100 mg od	32	63	23	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sildenafil																		
SUPER-1 / Galiè 2005[53] 12 wks																		
Placebo	70	56	16	NR	NR	NR	65	0.6	5.8[c]	70	9	4	NR	NR	NR	65	0.3	4.9[c]
Sildenafil 20 mg tid	69	54	13	NR	NR	NR	65	-2.1	8.8[c]	69	8	5	NR	NR	NR	65	-0.8	4.5[c]
Sildenafil 40 mg tid	67	49	13	NR	NR	NR	63	-2.6	7.1[c]	67	9	6	NR	NR	NR	63	-1.1	5.3[c]
Sildenafil 80 mg tid	71	52	16	NR	NR	NR	65	-4.7	8.0[c]	71	9	5	NR	NR	NR	65	-1.0	4.5[c]
PACES-1[38] 16 wks																		
Placebo + ongoing epoprostenol	NR	NR	NR	NR	NR	NR	102	0.2	NR	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
Sildenafil + ongoing epoprostenol	NR	NR	NR	NR	NR	NR	117	-3.6	NR	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR

^Estimated from standard errors
[a] Measured pre-inhalation (at trough drug level/effect)
[b] Measured post-inhalation (at peak drug level/effect)
[c] Estimated from 95% confidence interval

Table 73 Extracted data for cardiac index and pulmonary vascular resistance

	Cardiac Index									**Pulmonary Vascular Resistance (dyn*sec*cm^{-5})**								
	Baseline n	mean	SD	Post-Rx n	mean	SD	Change n	mean	SD	Baseline n	mean	SD	Post-Rx n	mean	SD	Change n	mean	SD
Epoprostenol																		
Rubin 1990[39] 8 wks																		
Data from Cochrane review[60]																		
Control	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	11	-23.2[b]	878.4[b]
Epoprostenol	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	10	-473.6[b]	680.8[b]
Barst 1996[11] 12 wks																		
Control	40	2.1	1.3^	NR	NR	NR	30	[redacted]	[redacted]	40	1280[b]	504^[b]	NR	NR	NR	[redacted]	[redacted]	[redacted]
Epoprostenol	41	2.0	0.6^	NR	NR	NR	38	[redacted]	[redacted]	41	1280[b]	512^[b]	NR	NR	NR	[redacted]	[redacted]	[redacted]
Badesch 2000[33] 12 wks																		
Control	55	2.2	0.7	NR	NR	NR	NR	-0.10	0.59^	55	896[b]	424[b]	NR	NR	NR	NR	73.6[b]	332.0^[b]
Epoprostenol	56	1.9	0.6	NR	NR	NR	NR	0.50	0.60^	56	1136[b]	568[b]	NR	NR	NR	NR	-366.4[b]	455.2[b^]
Iloprost																		
AIR / Olschewski																		

	Cardiac Index									**Pulmonary Vascular Resistance (dyn*sec*cm^{-5})**								
2002[41] 12 wks																		
Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR	96	1041	493	NR	NR	NR	NR	96	322
Iloprost (post-inhalation)	NR	NR	NR	NR	NR	NR	NR	NR	NR	91	1029	390	NR	NR	NR	NR	-239	279
Iloprost (pre-inhalation)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	-9	275
AIR-2[36] 12 wks																		
Control	NR	NR	NR	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]
Iloprost	NR	NR	NR	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]
COMBI / Hoeper 2006[58] 12 wks																		
Ongoing bosentan	21	2.1	0.5	NR	NR	NR	NR	NR	NR	21	12.9[b]	6.7[b]	NR	NR	NR	NR	NR	NR
Iloprost + ongoing bosentan	19	2.1	0.7	NR	NR	NR	NR	NR	NR	19	13.5[b]	6.6[b]	NR	NR	NR	NR	NR	NR
STEP / McLaughlin 2006[59] 12 wks																		
Placebo + ongoing bosentan	NR	NR	NR	NR	NR	NR	NR	NR	NR	28	783	378	28	867[d]	496[d]	28	81[d]	267[d]
Iloprost + ongoing bosentan	NR	NR	NR	NR	NR	NR	NR	NR	NR	29	821	389	29	676[d]	404[d]	29	-164[d]	223[d]
Bosentan																		
Channick 2001[43] 12																		

	Cardiac Index									**Pulmonary Vascular Resistance (dyn*sec*cm^{-5})**								
wks																		
Placebo	10	2.5	1.0	NR	NR	NR	10	-0.5	0.3	10	942	430	NR	NR	NR	10	191	234
Bosentan 125 mg bd	20	2.4	0.7	NR	NR	NR	20	0.5	0.4	19	896	425	NR	NR	NR	19	-223	244
BREATHE-1 / Rubin 2002[45] 16 wks																		
Placebo	68	2.4	0.7	NR	NR	NR	NR	NR	NR	66	880	540	NR	NR	NR	NR	NR	NR
Bosentan 125 mg bd	70	2.5	0.8	NR	NR	NR	NR	NR	NR	73	884	412	NR	NR	NR	NR	NR	NR
Bosentan 250 mg bd	70	2.2	0.8	NR	NR	NR	NR	NR	NR	62	1167	875	NR	NR	NR	NR	NR	NR
BREATHE-2 / Humbert 2004[56] 16 wks																		
Placebo + epoprostenol	11	1.7	0.7^	11	2.3	0.7^	11	37.9%	SE=13.3%	10	1426	443^	10	1050	487^	10	-25.7%	SE=7.2 %
Bosentan + epoprostenol	22	1.7	0.5^	22	2.5	0.5^	22	48.7%	SE=11.0%	20	1511	577^	20	947	465^	20	-35.2%	SE=5.4 %
BREATHE-5 / Galiè 2006[47] 16 wks																		
Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR	17	2870.0[a]	1209.3[a]	NR	NR	NR	17	155.1[a]	552.5^[a]
Bosentan 125 mg bd	NR	NR	NR	NR	NR	NR	NR	NR	NR	37	3425.1[a]	1410.5[a]	NR	NR	NR	37	-316.9[a]	841.3^[a]

	Cardiac Index									**Pulmonary Vascular Resistance (dyn*sec*cm^{-5})**								
Sitaxentan																		
STRIDE-1 / Barst 2004[49] 12 wks																		
Placebo	60	2.4	0.8	60	2.4	0.9	60	0.0	0.5	60	911	504 (484 in text)	60	960	535	60	49	244
Sitaxentan 100 mg od	55	2.4	0.8	55	2.7	0.8	55	0.3	0.6	55	1026 (1025 in text)	694	55	805	553	55	-221	442
Sitaxentan 300 mg od	63	2.3	0.7	63	2.7	0.9	63	0.4	0.6	63	946	484	63	753	524	63	-194	330
STRIDE-2 / Barst 2006[48] 18 wks																		
Placebo	62	2.4	0.7	NR	NR	NR	NR	NR	NR	62	11[b]	8[b]	NR	NR	NR	NR	NR	NR
Bosentan 125 mg bd	60	2.4	0.6	NR	NR	NR	NR	NR	NR	60	11[b]	5[b]	NR	NR	NR	NR	NR	NR
Sitaxentan 50 mg od	62	2.7	1.0	NR	NR	NR	NR	NR	NR	62	10[b]	7[b]	NR	NR	NR	NR	NR	NR
Sitaxentan 100 mg od	61	2.4	0.6	NR	NR	NR	NR	NR	NR	61	10[b]	7[b]	NR	NR	NR	NR	NR	NR
STRIDE-4 / Barst 2007 [37] 18 wks																		
Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR	34	1200[b]	800[b]	NR	NR	NR	NR	NR	NR
Sitaxentan 50 mg od	NR	NR	NR	NR	NR	NR	NR	NR	NR	32	1120[b]	800[b]	NR	NR	NR	NR	NR	NR

	Cardiac Index									**Pulmonary Vascular Resistance (dyn*sec*cm^{-5})**								
Sitaxentan 100 mg od	NR	NR	NR	NR	NR	NR	NR	NR	NR	32	1129[b]	640[b]	NR	NR	NR	NR	NR	NR
Sildenafil																		
SUPER-1 / Galiè 2005[53] 12 wks																		
Placebo	70	2.2	0.6	NR	NR	NR	65	-0.02	0.62[e]	70	1051	512	NR	NR	NR	65	49	425.7[e]
Sildenafil 20 mg tid	69	2.4	0.7	NR	NR	NR	65	0.21	0.70[e]	69	987	464	NR	NR	NR	65	-122	390.8[e]
Sildenafil 40 mg tid	67	2.3	0.7	NR	NR	NR	63	0.24	0.75[e]	67	869	438	NR	NR	NR	63	-143	301.7[e]
Sildenafil 80 mg tid	71	2.5	0.8	NR	NR	NR	65	0.37	0.72[e]	71	918	601	NR	NR	NR	65	-261	427.8[e]
PACES-1[38] 16 wks																		
Placebo + ongoing epoprostenol	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sildenafil + ongoing epoprostenol	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

^Estimated from standard errors.
[a]Pulmonary vascular resistance index (dynes*sec*cm^{-5})
[b] Converted from mmHg/litre/min (Wood unit).
[c]Measured pre-inhalation (at trough drug level/effect)
[d] Measured post-inhalation (at peak drug level/effect)
[e] Estimated from confidence intervals

Appendix 6. Ongoing trials of the technologies in PAH patients

A number of ongoing studies were identified. These are tabulated below 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 1 dose-limiting effect occurs
NCT00250640; multicentre (international)	P: NYHA FCIII familial or IPAH, no prior 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 (US)	P: PAH; NYHA FCIII-IV; receiving conventional therapy and bosentan; **I: inhaled iloprost at frequency of 6-9 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**)
NCT00302211; multicentre (US)	P: IPAH or familial PAH, age: 12-80; 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

clinical trial identifier; location (centres)	PICO	(expected) enrolment	study design	time frame	status	sponsor	comments
NCT00266162; multicentre (Germany)	P:PAH secondary to Eisenmenger syndrome; age >= 18; **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	
NCT00091715; multicentre (international)	P: PAH; NYHA FC II; age >= 12; **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 FC I; age >= 12; on sildenafil; **I: bosentan added to sildenafil;** C: placebo added to sildenafil; O: morbidity/mortality events, 6MWT, WHO FC, Borg dyspnoea index, EuroQol, 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 till end of study; time to death of all causes from baseline till 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, US)	P: idiopathic pulmonary fibrosis and pulmonary hypertension; age>= 19; **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	

clinical trial identifier; location (centres)	PICO	(expected) enrolment	study design	time frame	status	sponsor	comments
NCT00323297; multicentre (international)	P: PAH, age >=18, 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

Appendix 7. Long term follow up studies

Long term follow up studies on the technologies in this assessment were identified from the industry submissions for the purpose of providing further information and in particular for the independent economic evaluation (section 6.3). The identified studies are documented below and in Table 75. The key requirement was for data to be provided by FC for the outcomes: 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 functional class was extracted on change in NYHA/WHO functional class and on survival. As a rule summary data was used, but for STRIDE-1X and STRIDE-2X it was necessary to use individual patient data. Description of included studies can be found in Table 76.

Supportive Care/Standard treatment

One study, D'Alonzo 1991,[5] on patients treated only with supportive care was identified. No information applicable to the economic model was found as data on deterioration in FC were not presented. Although data on survival was provided, it was also not stratified by FC and 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 change in FC and survival. These were the studies by Barst 1994, McLaughlin 2002, Sitbon 2002 and Kuhn 2003.[65,66,126,127] Barst 1994[126] had a prospective design and all the others were retrospective.

Iloprost

Four long term studies were identified. Only one of these, Hoeper 2000,[128] 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 9 studies were identified three of which (Sitbon 2005, Williams 2006 and Sitbon 2007) were used to obtain data for the model. Also data from STRIDE-2X, which compared sitaxentan and bosentan were included for the long-term analysis of bosentan. Although Koegh 2007 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 Sitbon 2005 is an analysis of an IPAH subgroup of patients from the same population that was analysed in Sitbon 2007.

Sitaxentan

For sitaxentan two long-term extensions of randomised controlled trials were identified: *STRIDE-1X* and *STRIDE-2X*. An article describing the Canadian subpopulation of the *STRIDE-1X* (Langleben 2004[129]) was also found. Both *STRIDE-1X* and *STRIDE-2X* contained data stratified down by FC.

Sildenafil

The industry submission for sildenafil mentioned 2 long-term studies on treatment of PAH with sildenafil: *SUPER-2* and *PACES-2*. Both studies were described as ongoing and no data stratified by FC was provided.

Table 75 Long term studies on new drugs for pulmonary arterial hypertension supplied in industry submissions

Name of study	Duration/ follow-up; number of participants	Type of PAH	FC	Design	FC assessed (FC specific)	Survival assessed (FC specific)	6MWT assessed	Data on adverse events	Comments
Conventional treatment									
D'Alonzo 1991[5]	up to 5 years; 194 patients	IPAH	I, II, III, IV (% not stated)	registry with prospective follow-up	no	yes*	no	no	*median survival for III and IV FC; D'Alonzo equation
Epoprostenol									
Barst 1994[126]	3 years; 18 patients	IPAH	II (6%), III (72%), IV (22%)	open-label multicentre extension to Rubin 1990; matched with historic controls for survival	no	yes	yes	yes	time to transplantation
Shapiro 1997[130]	330-700 days; 69 patients (18 followed up > 330 days)	IPAH	III, IV*	open-label, prospective	no	yes (no)	no	no	mainly haemodynamic variables; *% in FC not stated;
McLaughlin 1998[131]	2 years (16.7 +/- 5.2 months); 27 patients	IPAH	III (63%), IV (37%)*	open-label, retrospective	yes (no)	no	no	yes	treadmill exercise; *unclear if the % applies to 27 included patients or 38 treated;
McLaughlin 2002[65]	5 years (36.3 months); 162 patients	IPAH	III (46%), IV (54%)	open-label, retrospective	yes (yes)	yes (yes)	no	yes	treadmill exercise
Sitbon 2002[66]	5 years (26 +/- 21 months); 178 epoprostenol, 135 control	IPAH	epoprostenol: III (67%), IV (33%)	open-label, retrospective	yes (no)	yes (yes)	yes	yes	control used for survival only, FC not stated;

Name of study	Duration/ follow-up; number of participants	Type of PAH	FC	Design	FC assessed (FC specific)	Survival assessed (FC specific)	6MWT assessed	Data on adverse events	Comments
Kuhn 2003[127]	3 years; 91 patients	IPAH, scleroderma, CHD, HIV, systemic lupus erythematous, portopulmonary, pulmonary venooclussive disease;	III (52%), IV (48%)	retrospective cohort	yes (yes)	yes (yes)*	yes	no	* 1 year
Iloprost									
Hoeper 2000[128]	1 year; 24 patients	IPAH	III (83%), IV (17%)	open-label, prospective	no	yes (yes)	yes	yes	
Opitz 2005[132]	5 years (median 535 +/- 61 days); 76 patients	IPAH	II, III, IV	prospective	no	yes (no)	no	no	cardiopulmonary exercise test;
AIR follow-up, **study report 303045**[133]	up to 5 years; 71 patients		III, IV (no % given)	open-label extension of AIR	yes (no)	yes (no)	-	yes	based on submission; data not stratified by FC;
AIR-2; academic in confidence manuscript;[36] Nikkho 2001[134], Nikkho 2003[135], Olschewski 2003[136], Olschewski 2005[137]	2 years; 52 patients	IPAH, secondary	II (33.3%), III (47.6%), IV (19%)*	prospective, open-label, active- controlled;	yes [redacted]	yes [redacted]	yes	yes	[redacted] *at baseline of RCT
Bosentan									

Name of study	Duration/ follow-up; number of participants	Type of PAH	FC	Design	FC assessed (FC specific)	Survival assessed (FC specific)	6MWT assessed	Data on adverse events	Comments
Sitbon 2003[138]	1 year; 29 patients	IPAH, scleroderma	-	open-label extension to Channick 2001	yes	-	yes	-	no article
McLaughlin 2005[114]	2.1 +/- 0,5 years; 169 patients	IPAH	I (1%), II (8%), III (82%), IV (9%);	prospective extension of 2 RCTs: BREATHE-1 and Channick 2001	no	yes (no)	no	yes	
Sitbon 2005[98] (bosentan vs. epoprostenol)	3 years; 485 patients (139 bosentan; 346 epoprostenol)	IPAH	III (100%)	prospective extension of 2 RCTs: BREATHE-1 and Channick 2001 matched with historic controls	no	yes (yes)	no	yes	includes subgroup survival analysis for 83 + 83 matched patients from both cohorts;
Denton 2006[44]	2 years (1.8 +/- 0.2); 64 patients	CTD	III (95.5%)*, IV (4.5%)*	prospective extension of 2 RCTs: BREATHE-1 and Channick 2001; subgroup	yes	yes (no)	yes	no	data on time to clinical worsening; *data on beginning of RCTs, 2 did not enter extensions
Gatzoulis 2006[139]	6-10 months (6-month results reported); 37 patients	Eisenmenger syndrome	II (30%), III (70%)	open-label extension of BREATHE-5	yes (yes)	yes	yes	yes	based on industry submission and conference abstract;
Provencher 2006[140]	1 year; 103 patients	IPAH	III (88%), IV (12%)	retrospective single centre	yes (yes)*	yes (no)	yes	yes	*4 months
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 controls	yes (yes)	yes (no)	no	no	

Name of study	Duration/ follow-up; number of participants	Type of PAH	FC	Design	FC assessed (FC specific)	Survival assessed (FC specific)	6MWT assessed	Data on adverse events	Comments
Koegh 2007[141]	Follow-up: up to 21 months 177 patients	IPAH, CTD	III, IV (% not stated)	multi-centre, prospective, open-label study	yes (no)	yes (yes)	no	yes	QOL; FC and survival data provided for end of study - patients followed up for different periods
Sitbon 2007[142]	[redacted]	IPAH, CTD	[redacted]	prospective extension of 2 RCTs: BREATHE-1 and Channick 2001	[redacted]	yes [redacted]	[redacted]	[redacted]	
Denton (unpublished)[143]	48 weeks; 53 patients	CTD	III (100%)	open-label prospective	yes	yes	no	yes	QOL data, time to clinical worsening
Sitaxentan **STRIDE-1X**[99]	58 weeks [redacted]	[redacted]	[redacted]	randomised, double-blind prospective extension of STRIDE-1 (2 doses)	yes (yes)	[redacted]	[redacted]	[redacted]	[redacted]
STRIDE-1X Langleben 2004[129]	1 year; 11 (10) patients	IPAH, CTD, CHD	II (10%), III (90%)*	open-label prospective extension of STRIDE-1 (Canadian)	yes (yes)	yes (yes)	yes	yes	1 patient discontinued due to deterioration at 7 months not included later; *for 10 patients
STRIDE-2X[100] (sitaxentan vs. bosentan)	1 year; [redacted]	[redacted]	[redacted]	prospective, randomised, multi-centre, open label extension study of STRIDE-2	yes (yes)	yes (yes)	[redacted]	yes	[redacted]

Name of study	Duration/ follow-up; number of participants	Type of PAH	FC	Design	FC assessed (FC specific)	Survival assessed (FC specific)	6MWT assessed	Data on adverse events	Comments
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%)*	prospective extension of SUPER-1	yes (no)	yes (no)	yes	yes	based on industry submission; data for 1 year survival; QOL; *RCT baseline
PACES-2[144]**;** (sildenafil + epoprostenol)	ongoing (design: 3 years); 242 patients	IPAH, CTD	(I-IV?); mostly II and III	open-label prospective extension of PACES-1	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	Functional class	Age (years), mean (SD, range); % female	Baseline exercise capacity and haemodynamic measures, mean (SD)	Comments (inclusion criteria)
D'Alonzo 1991[5]; 32 clinical centres in US	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%)	I, II, III, IV (% not stated)	no data on age; 56%	no data	**inclusion:** PPH, criteria described in Rich S. 1987
Barst 1994[126]; 4 referral centres	up to 70 months; open, multicentre, uncontrolled; 18 patients	**epoprostenol** started at 2 ng/kg per min and increased by 2 ng/kg/min every 10 to 15 minutes; dose no further increased 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; 5 patients oral vasodilator therapy;	IPAH (100%)	II (6%), III (72%), IV (22%)	35.9 (13.4); 67%	6MWT = 264 (160); mPAP = 60.9 (15); 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;
McLaughlin 2002[65]; The 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 per 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%)	III 46%, IV 54%	42.2; 75%	mean treadmill exercise time = 192 +/- 183 sec (127 patients); mPAP = 61 (13); PVR = 17.5 (8.1) Wood units	**inclusion:** III or IV FC; treated with calcium channel blockers previously and failed to improve or with limited response (predicting failure of calcium channel blockers therapy)

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	Functional class	Age (years), mean (SD, range); % female	Baseline exercise capacity and haemodynamic measures, mean (SD)	Comments (inclusion criteria)
Sitbon 2002[66]; Clamart, France	5 years (26 +/- 21 months); retrospective; 178 epoprostenol patients; 135 historic controls matched for NYHA FC for survival analysis - not FC stratified;	**epoprostenol** started at 1 ng/kg per min and increased every 12 hours by 1 ng/kg per min up to 10 ng/kg per min; dose adjustments made systematically to reach mean level of 14 ± 4 ng/kg per min at 3 months; **background:** (according to patient state and needs) warfarin, diuretics, digoxin, continuous nasal oxygen	IPAH (100%)	III 67%, IV 33%	43 (13); 76%	6MWT = 240 (146); mPAP = 67 (14); PVR - no data	**inclusion:** age > 15, PPH diagnosis based on NIH registry criteria; **exclusion:** (1) CTD, CHD, portal hypertension, HIV; (2) distal chronic thromboembolic PH, (3) chronic pulmonary disease; (4) acute pulmonary vasodilator response that predicted response to calcium channel blockers
Kuhn 2003[127]; 1 centre; Vanderbilt University Medical Center, US	follow-up: up to 3 years; 1 year for FC; retrospective cohort study; 91 patients;	**epoprostenol** on discharge from hospital at 4 to 6 ng/kg/minute as limited by side effects with a goal of 20 ng/kg/minute at 4 to 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 venoocclussive disease (2%)	III (52%); III (48%);	43 (15); 70%	6MWD = 296 (111)*; 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
Hoeper 2000[128]; 1 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%)	III (83%), IV (17%)	38 (12, range 22-65); 63%	6MWT = 278 (96); mPAP = 59 (10); PVR = 1205 (467) [preinhalation data]	**inclusion:** PPH according to NIH Registry criteria; III or IV FC, non-responders to conventional treatment; **exclusion:** secondary PH, severe right heart failure who were receiving catecholamines at time of presentation, lost to follow up;

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	Functional class	Age (years), mean (SD, range); % female	Baseline exercise capacity and haemodynamic measures, mean (SD)	Comments (inclusion criteria)
Sitbon 2005[98]; multicentre, international; records from referral centres: Clamart, France; Chicago; Denver; New York; San Diego;	36 months; prospective extension of 2 RCTs BREATHE-1 and Channick 2001 (subgroup); matched with historic controls; 485 (139 bosentan; 346 control);	**intervention:** bosentan as first line treatment; **control:** epoprostenol	IPAH (100%)	III 100%	**experimental:** 46 (16, range: 13 - 80); 80%; **control**: 41 (14, range 10 - 75); 74%	**experimental:** 6MWT = 351 (80); mPAP = 56 (15); PVR = 12 (6) Wood units; **control:** 6MWT = 335 (106); mPAP = 66 (18); PVR = 18 (10) Wood units	**inclusion BOS:** age: at least 12; symptomatic III FC IPAH; primary or secondary to CTD; resting mPAP > 25; PVR > 3 Wood units; pulmonary capillary wedge pressure < 15 mm Hg; 6MWT 150 - 450; **inclusion EPO:** III FC IPAH at start of EPO; more than zero survival time; known survival status; started EPO on or after January 1995;
Williams 2006[93]; Royal Free Hospital, London	up to 6 years; data for 2 years; prospective experimental, historic controls; 92 patients (45 bosentan, 47 control: 27 prostanoids)	**intervention:** bosentan 62.5 mg 2 x day for 4 weeks, increased to 125 mg 2 x 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 hrs in every 24) 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%)	**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); mPAP = 40 (11.8); PVR = 613 (345); **control:** 6MWT - median = 179; range (0 - 471)*; mPAP = 40 (11.4); PVR = 613 (345)	**inclusion:** mPAP > 25; pulmonary capillary wedge pressure < 15 mm Hg; PVR > 240; III or IV FC, conventional treatment; 6MWT < 450; **exclusion:** I or II FC; interstitial pulmonary fibrosis resulting in total lung capacity of < 60% and either mPAP < 35 or oxygen saturation at rest on air of < 85% or both; substitutes for 6MWT < 150: cardiac index < 2.1 l/min/m^2; right arterial pressure > 11 mm Hg; mixed venous oxygen saturation < 63%; *data on 30 patients of whom majority in IV 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	Functional class	Age (years), mean (SD, range); % female	Baseline exercise capacity and haemodynamic measures, mean (SD)	Comments (inclusion criteria)
Sitbon 2007[142]; multicentre, international;	prospective extension of 2 RCTs (BREATHE-1 and Channick 2001);						
STRIDE-1X (FPH01-X)[99];							

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	Functional class	Age (years), mean (SD, range); % female	Baseline exercise capacity and haemodynamic measures, mean (SD)	Comments (inclusion criteria)
STRIDE-2X (FPH02-X)[100];							

Appendix 8. Review of economic evaluations

Table 77 Drummond Adapted Criteria

After Drummond et al [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 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 Concensus on Health Economic Criteria List

After Evers et al, 2005[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	Yes	No	No	Yes

patient/client groups?				
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 and a ratio of women to men of 1.5:1. Annual survival figures were based on actuarial data (source: 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 PAH

This was assumed to be an independent competing risk, dependent on functional class and treatment but not age (such data as 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 class III. The same method was used for other treatments. It was assumed that there was no additional mortality in functional class II.

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 to 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 times 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 confidence interval of 0.017 to 0.025. These numbers fit to a beta distribution with n= 5000, r=105.

Applying the same method to all other treatments gave the following results:

Treatments	FC	time	Survival	Per cycle mortality	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

Mortality when on supportive care

In the absence of better data, we have used the odds ratios for deterioration from state III to IV to give us the effect of treatment on reducing mortality. Again using epoprostenol in functional class III as the example, the odds ratio of 0.4 in favour of epoprostenol gives us per cycle mortality on supportive care of 0.051 (0.041-0.069). Beta distributions were fitted to the correct mean and width of confidence interval. In this case this gives n=950, 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 as shown in the following table:

Treatments	FC	Mortality on treatment	Odds Ratio	Mortality on supportive care	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

Appendix 10. Resource Use

Resource use information provided by Schering Health Care Ltd.

NYHA Class II

Table 79 NHS Contacts & Personal and Social Services – NYHA Class II

NHS contacts - frequency per year	mean # pa	sd	freq/3 mo	% rec	mean	Costs/ 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 nonspecialist centre	2.500	1.1	0.6	100%	£45.6	
Nurse at nonspecialist 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 - NYHA II	**mean days pw**	**sd**	**freq/3 mo**	**% rec**	**mean**	**£16.0**
Residential care	1.750	3.5	21.0	0%	£0.0	
Day care	1.250	2.5	15.0	2%	£5.6	
Home care	0.500	1.0	6.0	10%	£10.3	

Table 80 Hospitalizations – NYHA Class II

Hospitalizations	mean # per annum	sd	avg LOS	sd	% rec	Costs/ 3 months
	0.8	0.447214	6.500	6.311	18%	**£62**
General ward					96%	£185
ICU					3%	£31
CCU					1%	£16
A&E					50%	£16

NYHA CLASS III

Table 81 NHS Contacts & Personal and Social Services – NYHA Class III

NHS contacts - frequency per year	mean # pa	sd	freq/3 mo	% rec	mean	Costs/ 3 months
Physician at specialist PAH centre	4.200	1.1	1.1	100%	£76.7	**£224.6**
Specialist nurse at PAH centre	5.500	4.4	1.4	100%	£39.9	
Physician at nonspecialist centre	2.300	1.1	0.6	100%	£42.0	
Nurse at nonspecialist 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 - NYHA III	**mean days pw**	**sd**	**freq/3 mo**	**% rec**	**mean**	**£178.8**
Residential care	3.500	4.0	42.0	6%	£50.5	
Day care	3.750	2.5	45.0	8%	£67.4	
Home care	1.400	0.9	16.8	28%	£60.8	
Hospice						

Table 82 Hospitalizations – NYHA Class III

Hospitalizations	mean # per annum	sd	avg LOS	sd	% rec	Costs/ 3 months
	1.40	0.22	7.60	5.19	38%	**£280**
General ward					97%	£796
ICU					4%	£213
CCU					1%	£53
A&E					43%	£57

NYHA CLASS IV

Table 83 NHS Contacts & Personal and Social Services – NYHA Class IV

NHS contacts - frequency per year	mean # pa	sd	freq/3 mo	% rec	mean	Costs/ 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 nonspecialist centre	1.900	1.5	0.5	100%	£34.7	
Nurse at nonspecialist 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 - NYHA IV	**mean days pw**	**sd**	**freq/3 mo**	**% rec**	**mean**	**£2,313.4**
Residential care	7.000	0.0	84.0	13%	£529.6	
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	

Table 84 Hospitalizations – NYHA Class IV

Hospitalizations	mean # per annum	sd	avg LOS	sd	% rec	Costs/ 3 months
	2.6	1.24499	9.500	4.108	70%	**£1,963**
general ward					86%	£3,019
ICU					16%	£3,638
CCU					4%	£909
A&E					50%	£285

Appendix 11. Effects of single parameter values on model outputs

The graphs shown below were obtained as follows. The results from the 10,000 replications of the model used for the reference case probabilistic sensitivity analysis were sorted in order by 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 then 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.

Where 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. Since 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 the cases where all ICERs are negative.

Appendix 11.1 Epoprostenol starting in functional class III

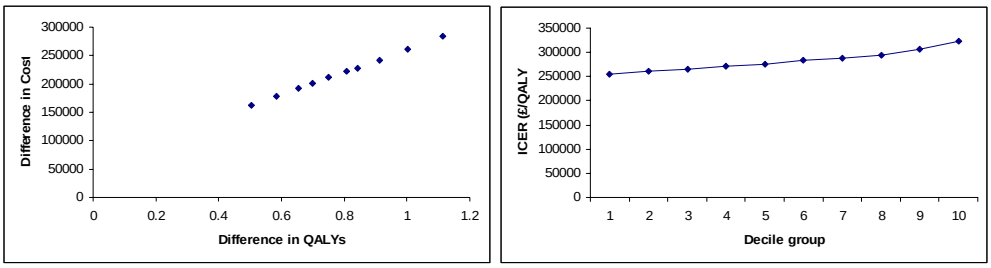

Figure 17 Epoprostenol class III variation by odds ratio of improvement from III to II

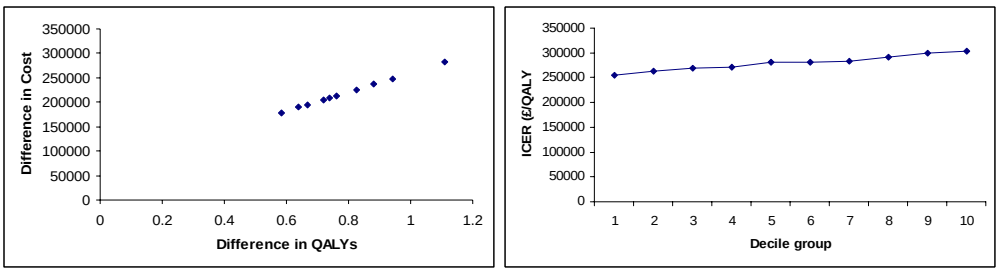

Figure 18 Epoprostenol class III variation by odds ratio of deterioration from II to III

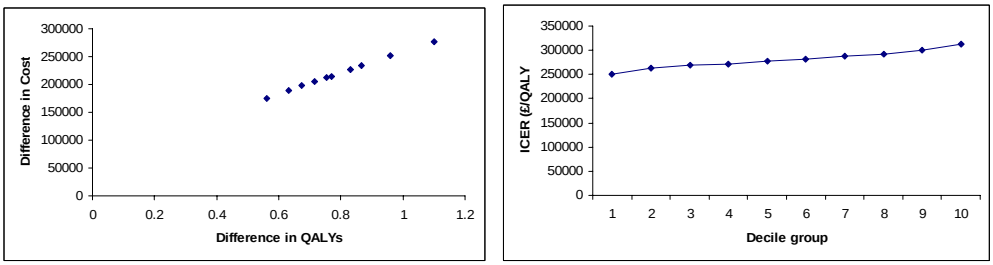

Figure 19Epoprostenol class III variation by odds ratio of deterioration from III to IV

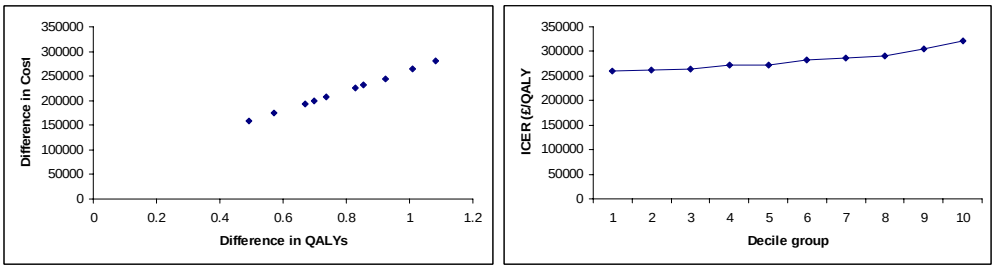

Figure 20 Epoprostenol class III variation by probability of improvement from III to II on supportive care

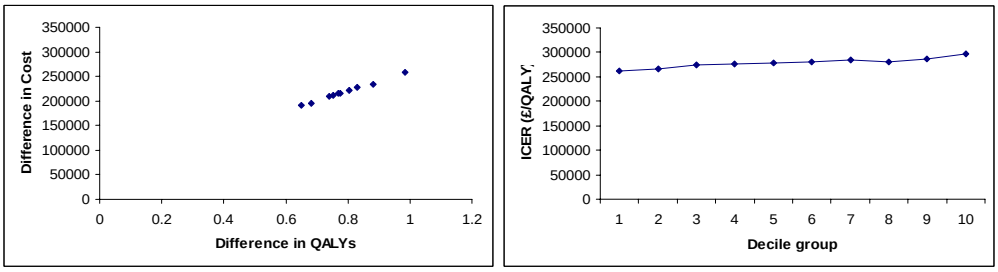

Figure 21 Epoprostenol class III variation by probability of deterioration from II to III on supportive care

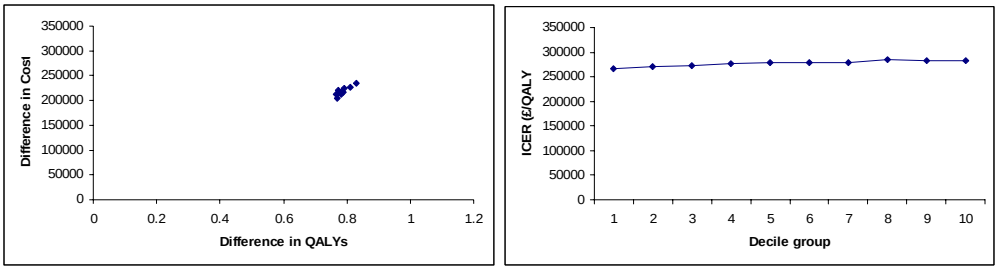

Figure 22 Epoprostenol class III variation by probability of deterioration from III to IV in first cycle on supportive care

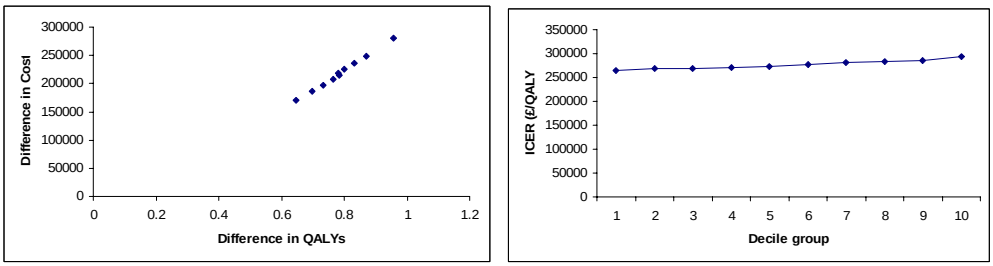

Figure 23 Epoprostenol class III variation by probability of deterioration from III to IV after first cycle on supportive care

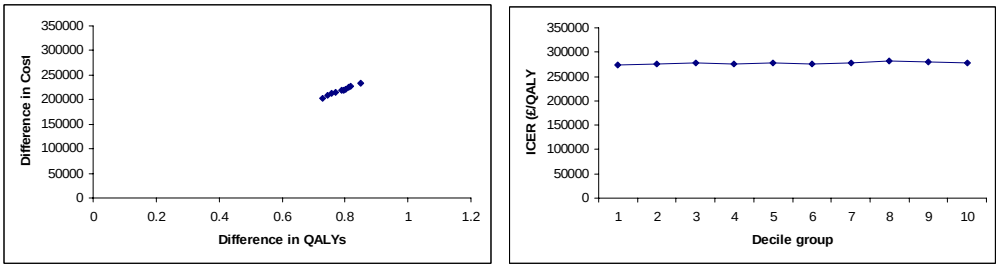

Figure 24 Epoprostenol class III variation by mortality in class III on treatment

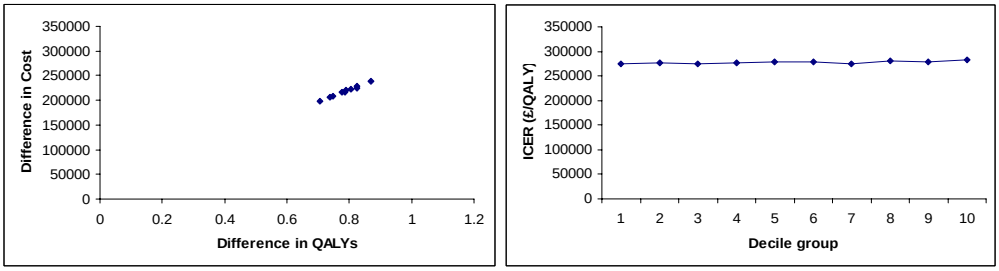

Figure 25 Epoprostenol class III variation by mortality in class III on supportive care

Appendix 11.2 Epoprostenol starting in functional class IV

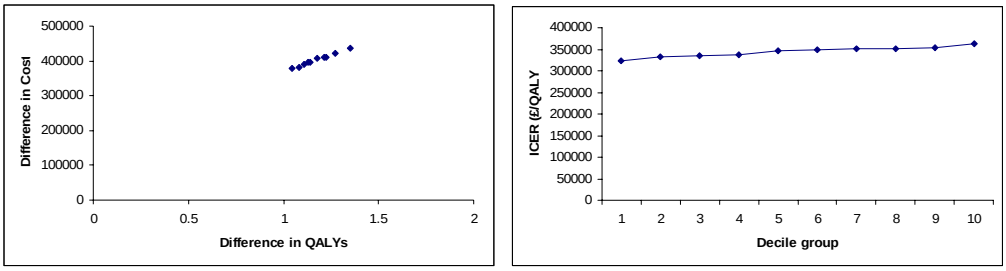

Figure 26 Epoprostenol class IV variation by odds ratio of improvement from IV to III

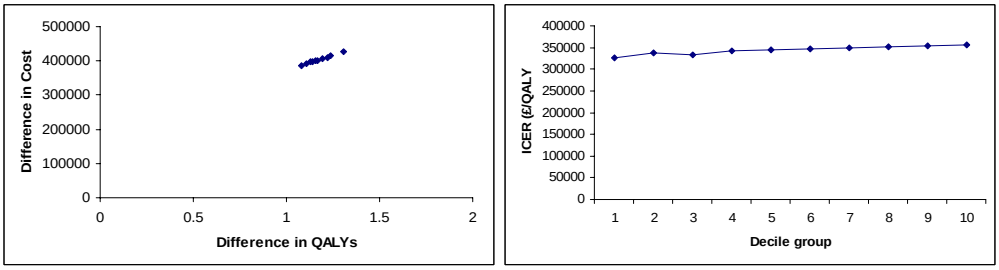

Figure 27 Epoprostenol class IV variation by odds ratio of deterioration from III to IV

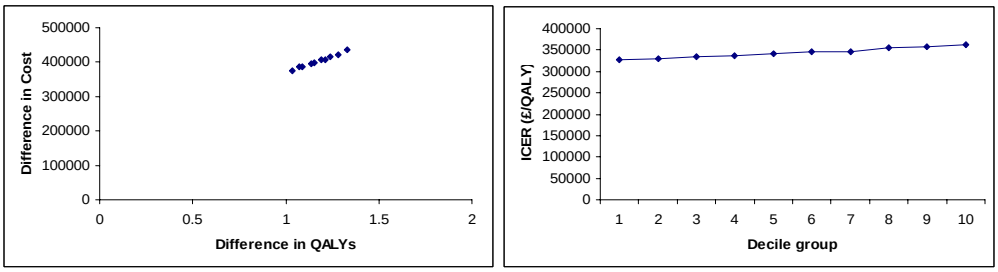

Figure 28 Epoprostenol class IV variation by probability of improvement from IV to III on supportive care

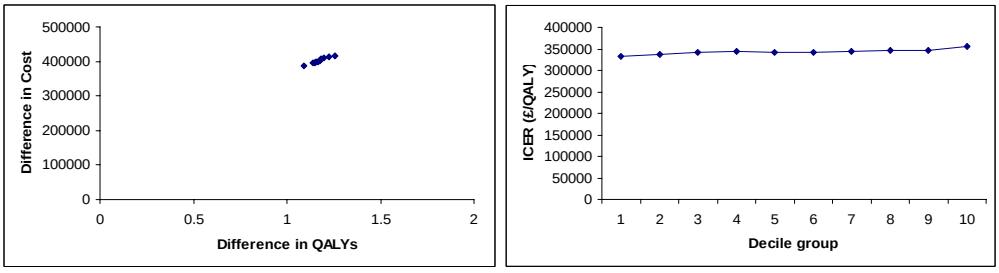

Figure 29 Epoprostenol class IV variation by probability of deterioration from III to IV on supportive care

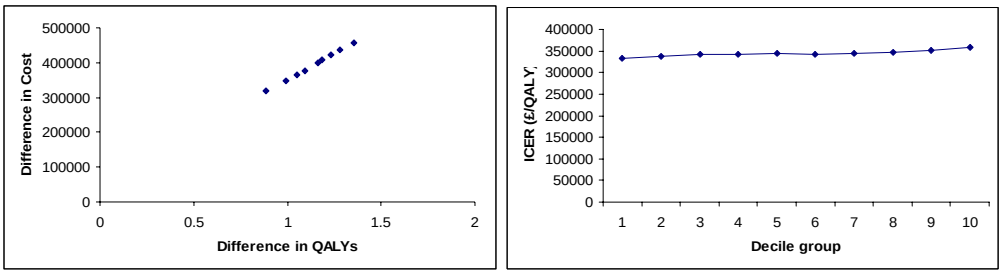

Figure 30 Epoprostenol class IV variation by mortality in class IV on treatment

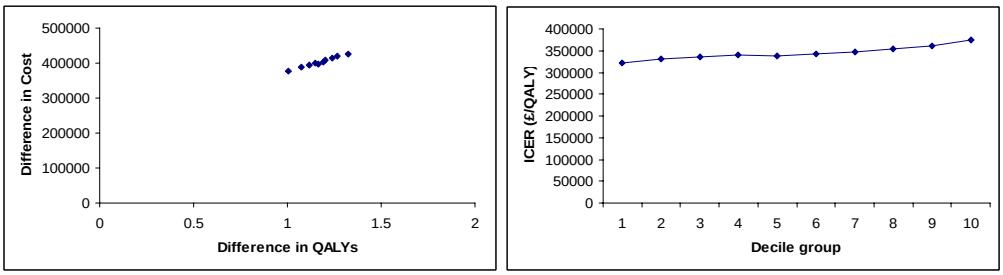

Figure 31 Epoprostenol class IV variation by mortality in class IV on supportive care

Appendix 11.3 Iloprost

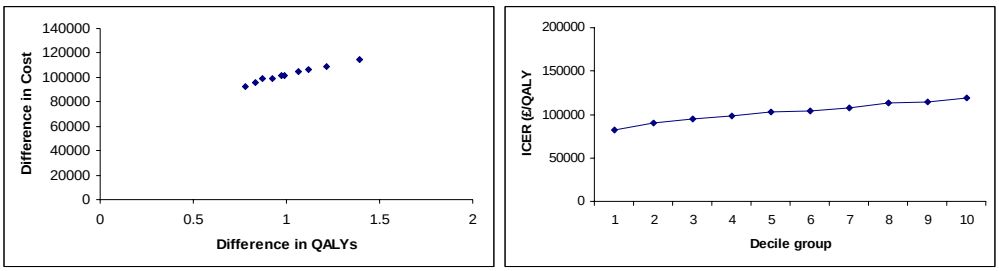

Figure 32 Iloprost variation by odds ratio of improvement from III to II

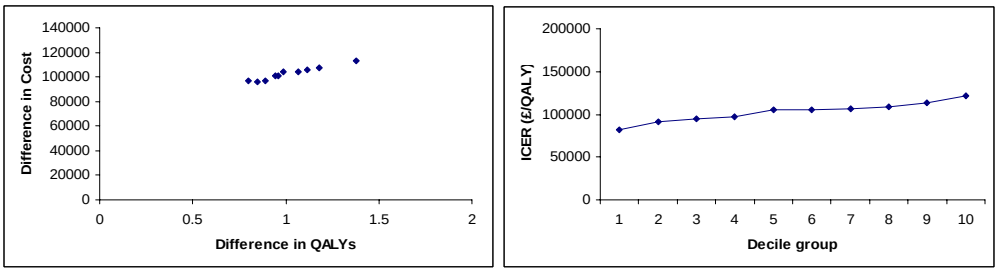

Figure 33 Iloprost variation by odds ratio of deterioration from II to III

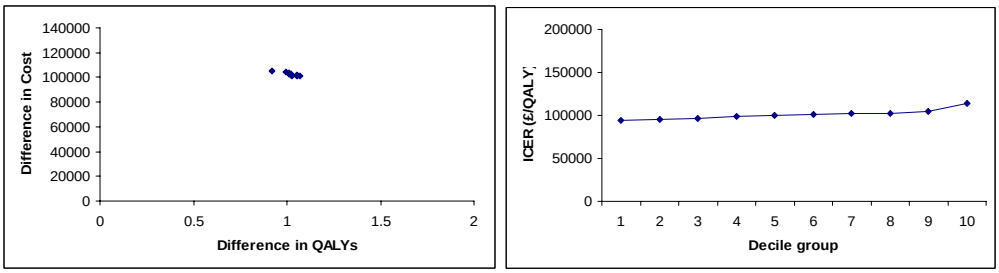

Figure 34 Iloprost variation by odds ratio of deterioration from III to IV in first cycle

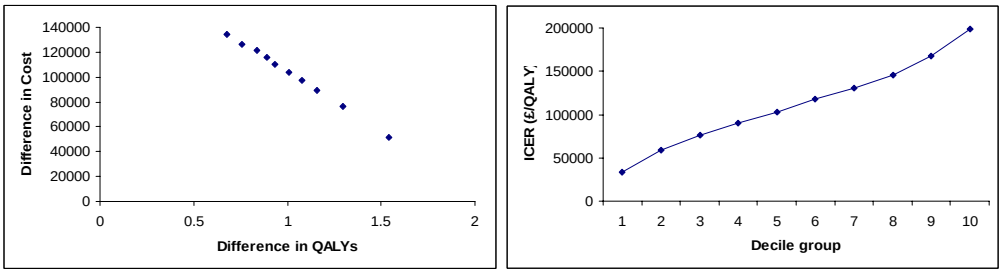

Figure 35 Iloprost variation by odds ratio of deterioration from III to IV after first cycle

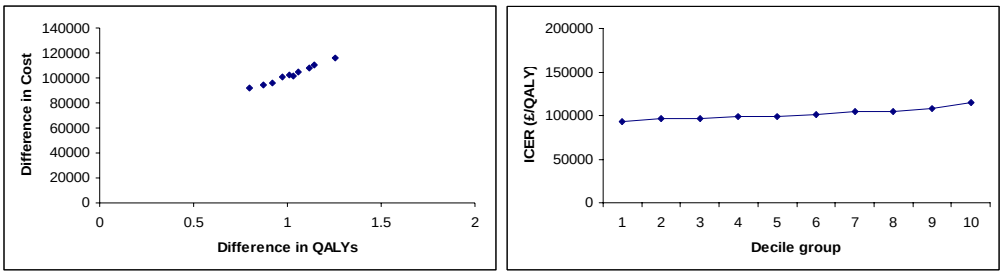

Figure 36 Iloprost variation by probability of improvement from III to II on supportive care

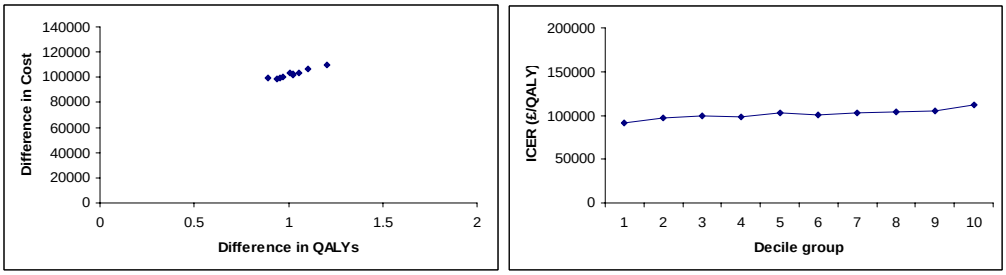

Figure 37 Iloprost variation by probability of deterioration from II to III on supportive care

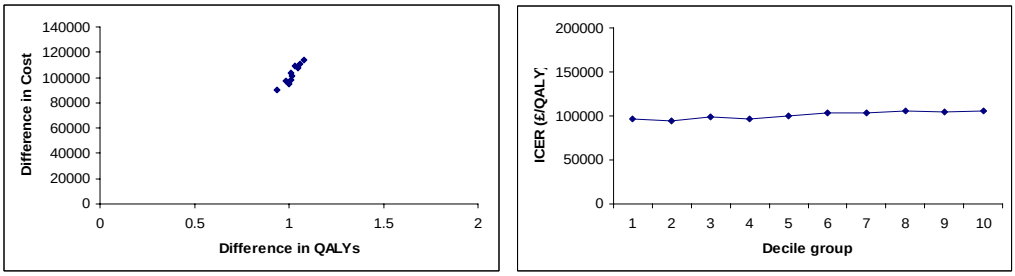

Figure 38 Iloprost variation by probability of deterioration from III to IV in first cycle on supportive care

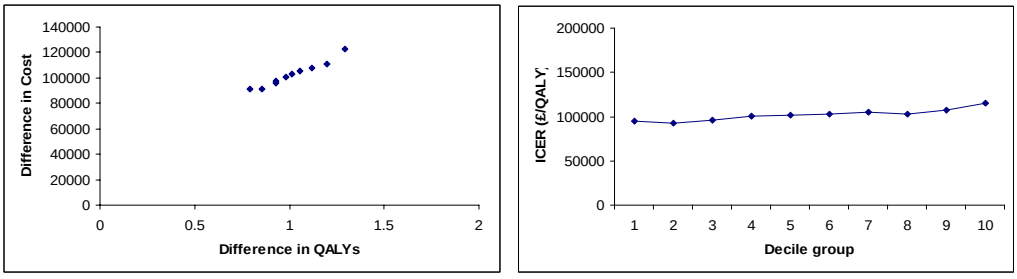

Figure 39 Iloprost variation by probability of deterioration from III to IV after first cycle on supportive care

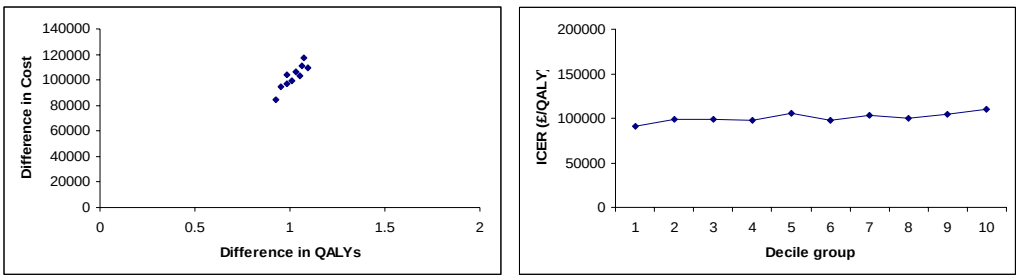

Figure 40 Iloprost variation by mortality in class III on treatment

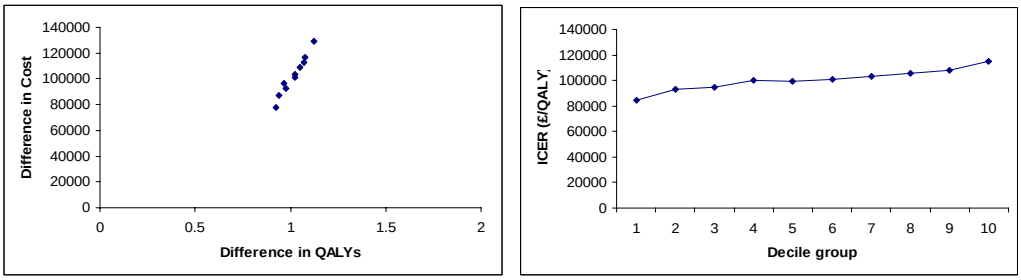

Figure 41 Iloprost variation by mortality in class III on supportive care

Appendix 11.4 Bosentan

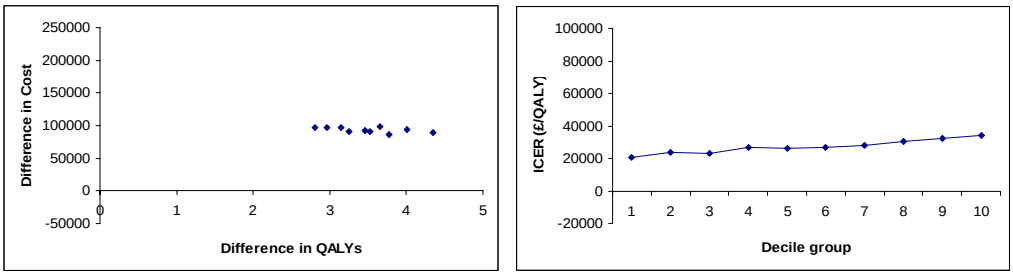

Figure 42 Bosentan variation by odds ratio of improvement from III to II

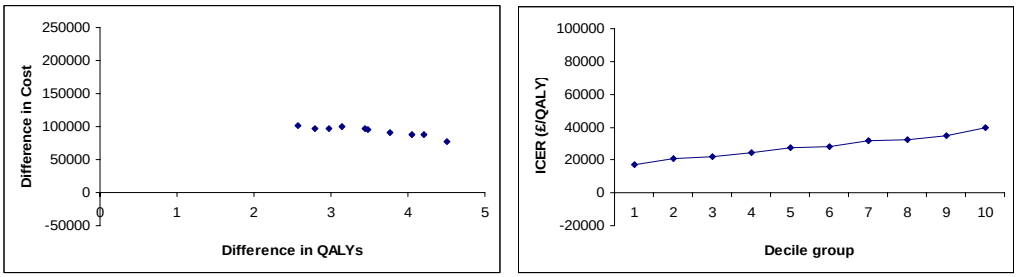

Figure 43 Bosentan variation by odds ratio of deterioration from II to III

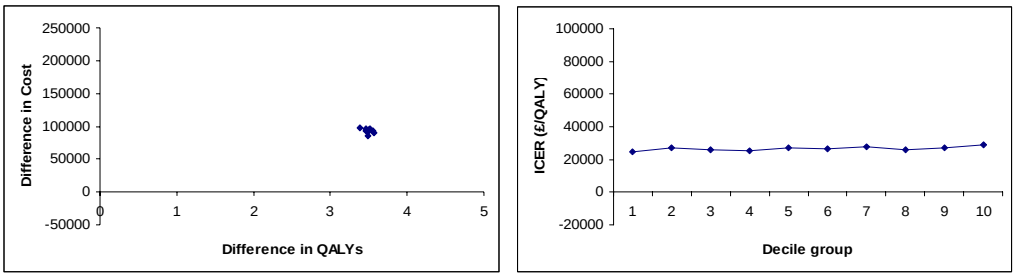

Figure 44 Bosentan variation by odds ratio of deterioration from III to IV in first cycle

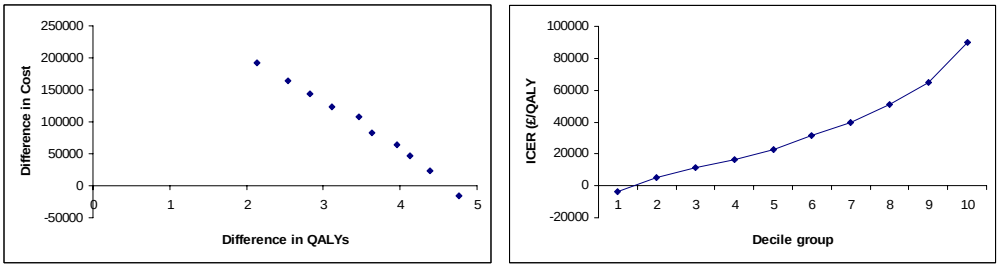

Figure 45 Bosentan variation by odds ratio of deterioration from III to IV after first cycle

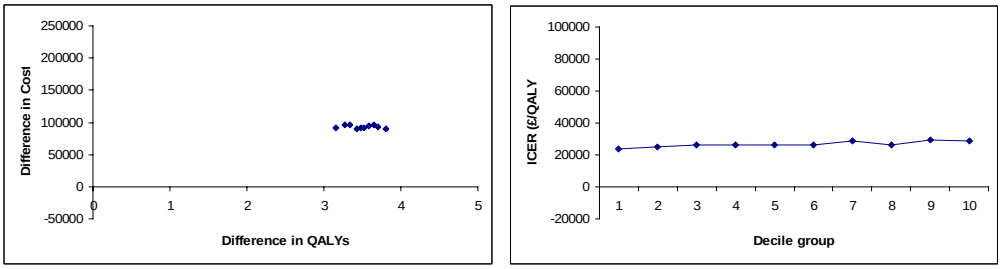

Figure 46 Bosentan variation by probability of improvement from III to II on supportive care

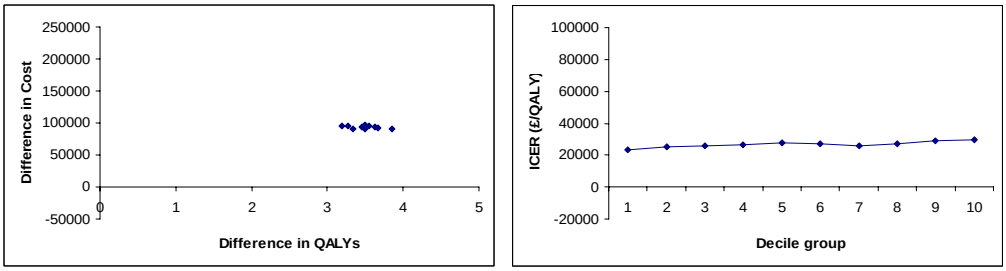

Figure 47 Bosentan variation by probability of deterioration from II to III on supportive care

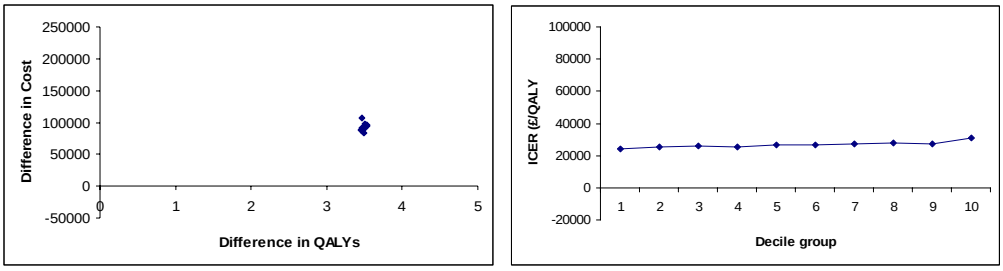

Figure 48 Bosentan variation by probability of deterioration from III to IV in first cycle on supportive care

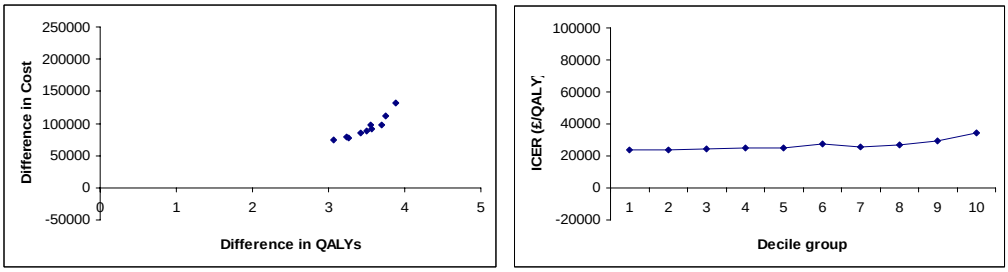

Figure 49 Bosentan variation by probability of deterioration from III to IV after first cycle on supportive care

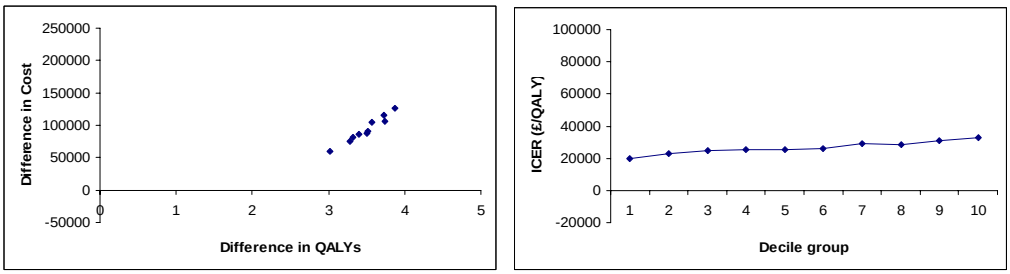

Figure 50 Bosentan variation by mortality in class III on treatment

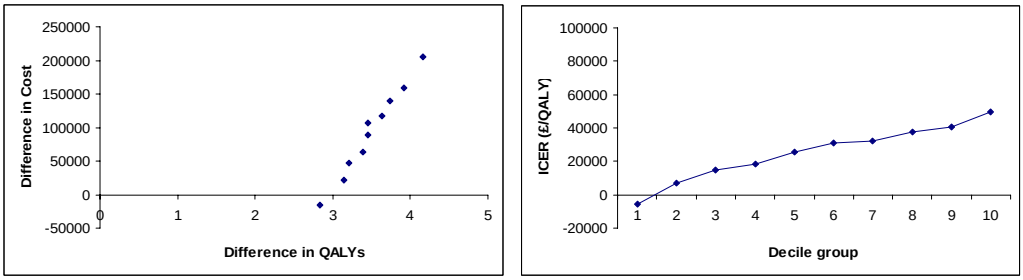

Figure 51 Bosentan variation by mortality in class III on supportive care

Appendix 11.5 Sitaxentan

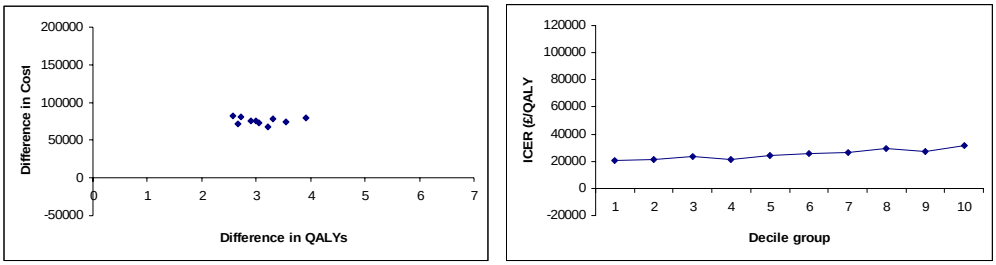

Figure 52 Sitaxentan variation by odds ratio of improvement from III to II

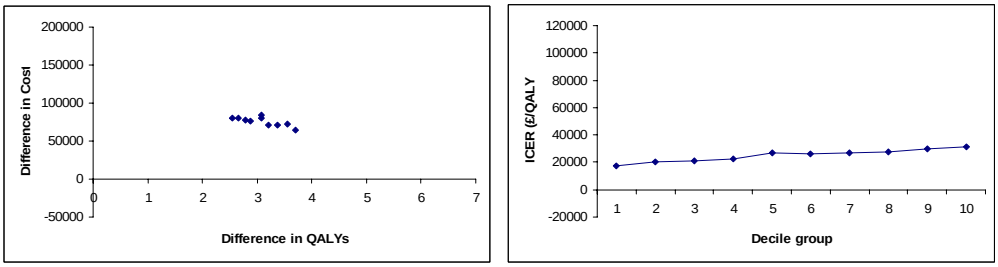

Figure 53 Sitaxentan variation by odds ratio of deterioration from II to III

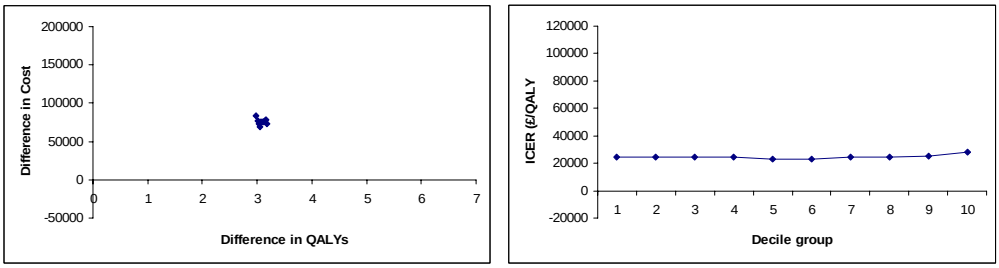

Figure 54 Sitaxentan variation by odds ratio of deterioration from III to IV in first cycle

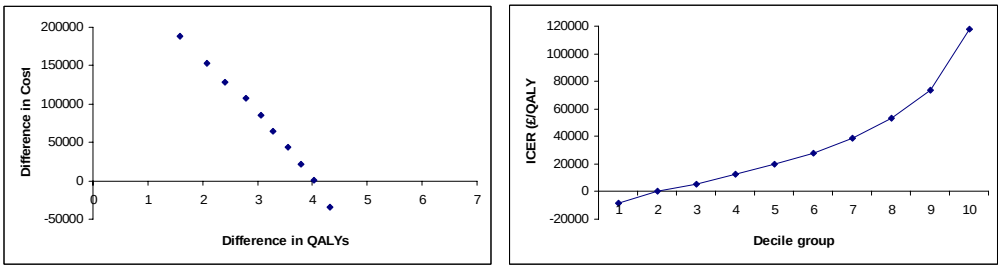

Figure 55 Sitaxentan variation by odds ratio of deterioration from III to IV after first cycle

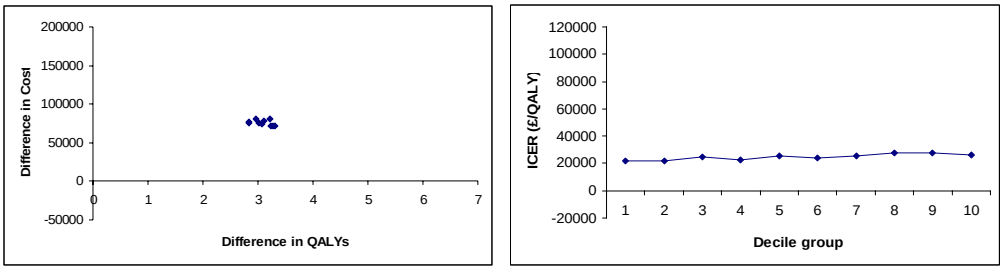

Figure 56 Sitaxentan variation by probability of improvement from III to II on supportive care

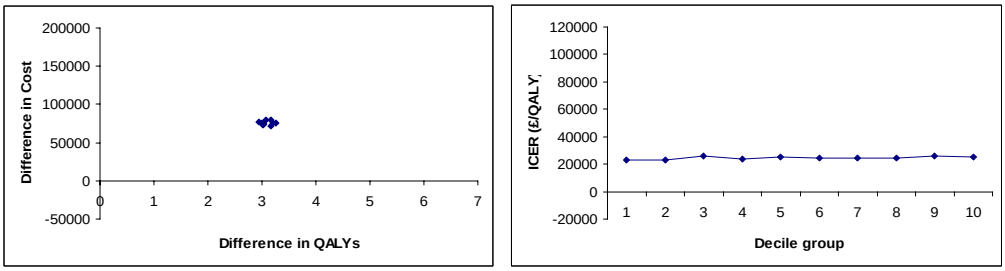

Figure 57 Sitaxentan variation by probability of deterioration from II to III on supportive care

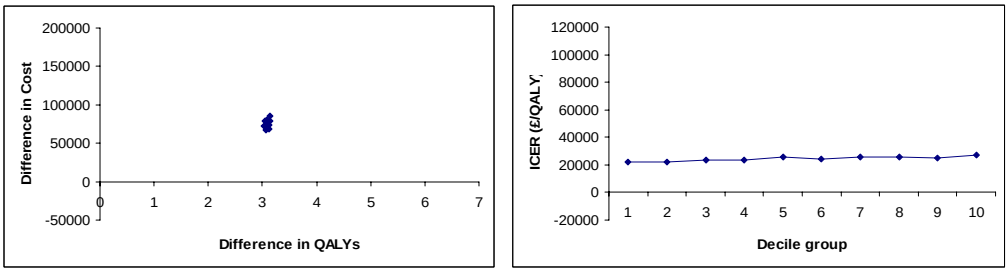

Figure 58 Sitaxentan variation by probability of deterioration from III to IV in first cycle on supportive care

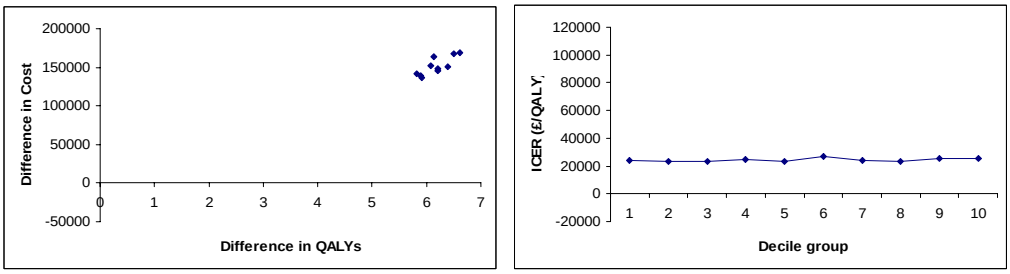

Figure 59 Sitaxentan variation by probability of deterioration from III to IV after first cycle on supportive care

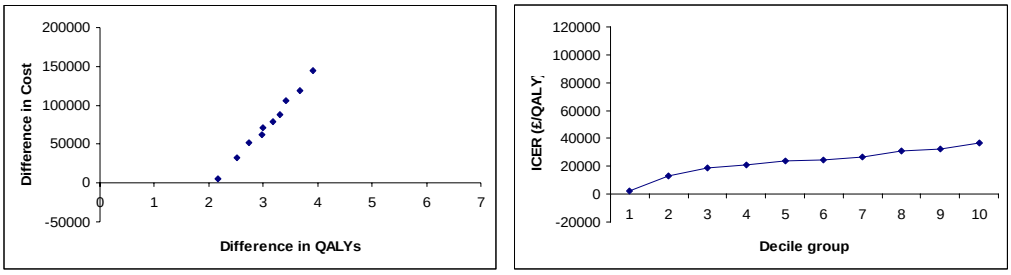

Figure 60 Sitaxentan variation by mortality in class III on treatment

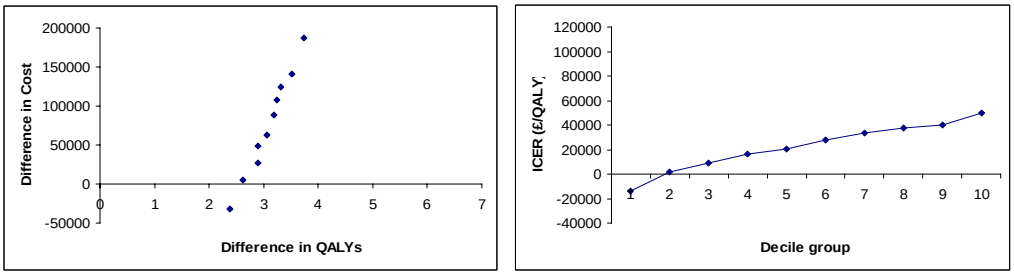

Figure 61 Sitaxentan variation by mortality in class III on supportive care

Appendix 11.6 Sildenafil

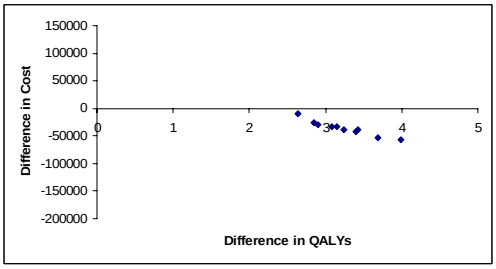

Figure 62 Sildenafil variation by odds ratio of improvement from III to II

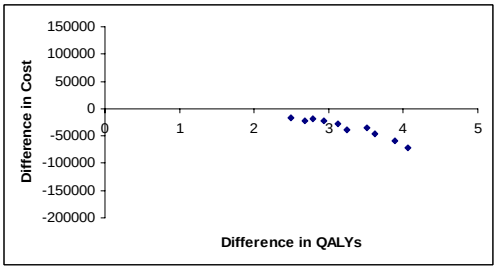

Figure 63 Sildenafil variation by odds ratio of deterioration from II to III

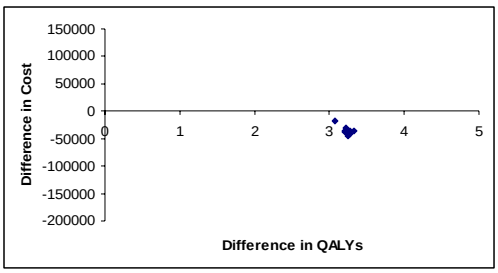

Figure 64 Sildenafil variation by odds ratio of deterioration from III to IV in first cycle

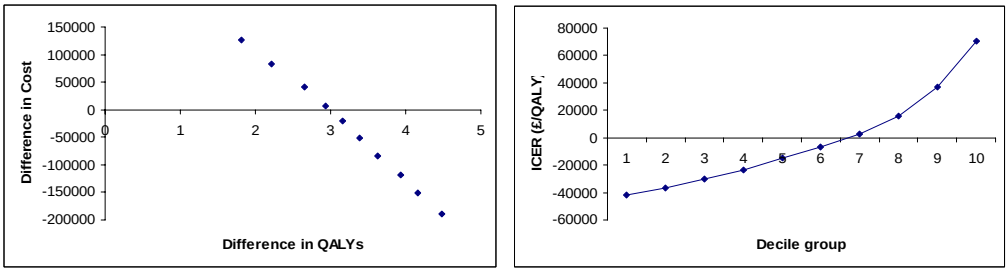

Figure 65 Sildenafil variation by odds ratio of deterioration from III to IV after first cycle

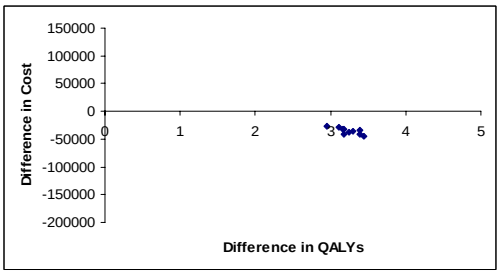

Figure 66 Sildenafil variation by probability of improvement from III to II on supportive care

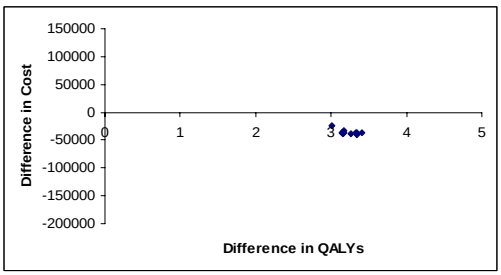

Figure 67 Sildenafil variation by probability of deterioration from II to III on supportive care

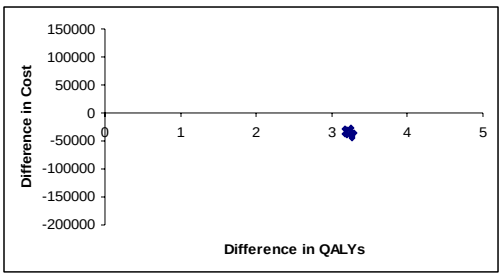

Figure 68 Sildenafil variation by probability of deterioration from III to IV in first cycle on supportive care

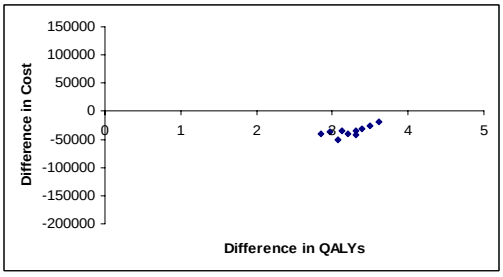

Figure 69 Sildenafil variation by probability of deterioration from III to IV after first cycle on supportive care

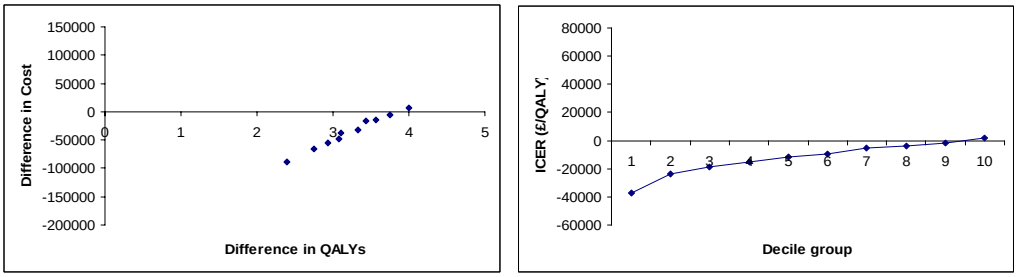

Figure 70 Sildenafil variation by mortality in class III on treatment

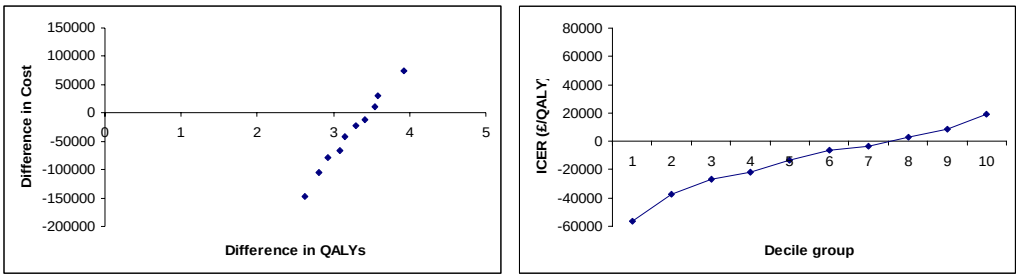

Figure 71 Sildenafil variation by mortality in class III on supportive care

Appendix 12. Non-reference case model runs

The following tables and CEACs 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, FCIII

Alternative time horizon

Time horizon of 20 years

Table 85 Epoprostenol versus supportive care, FCIII: 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

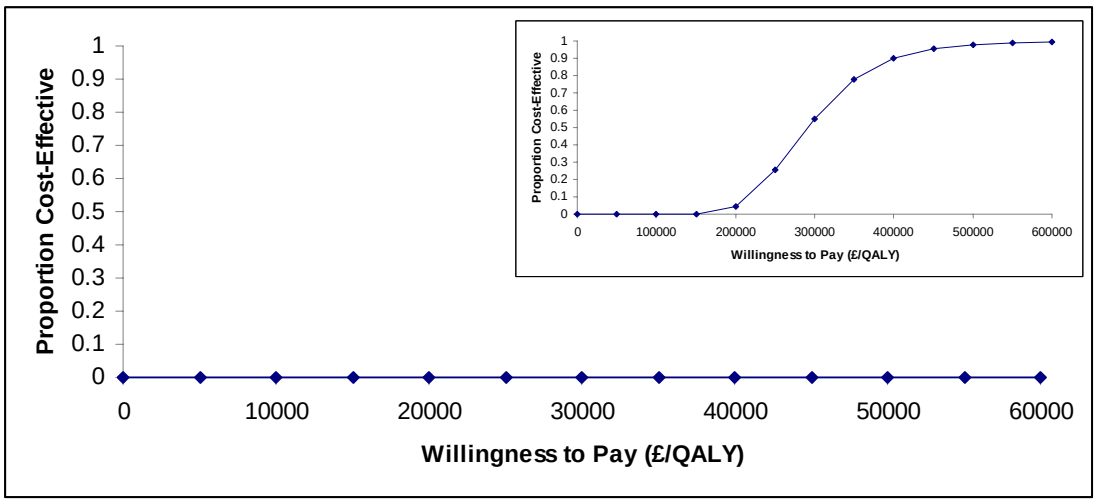

Figure 72 CEAC for epoprostenol versus supportive care, FCIII: Time horizon of 20 years

Time horizon of 10 years

Table 86 Epoprostenol versus supportive care, FCIII: 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

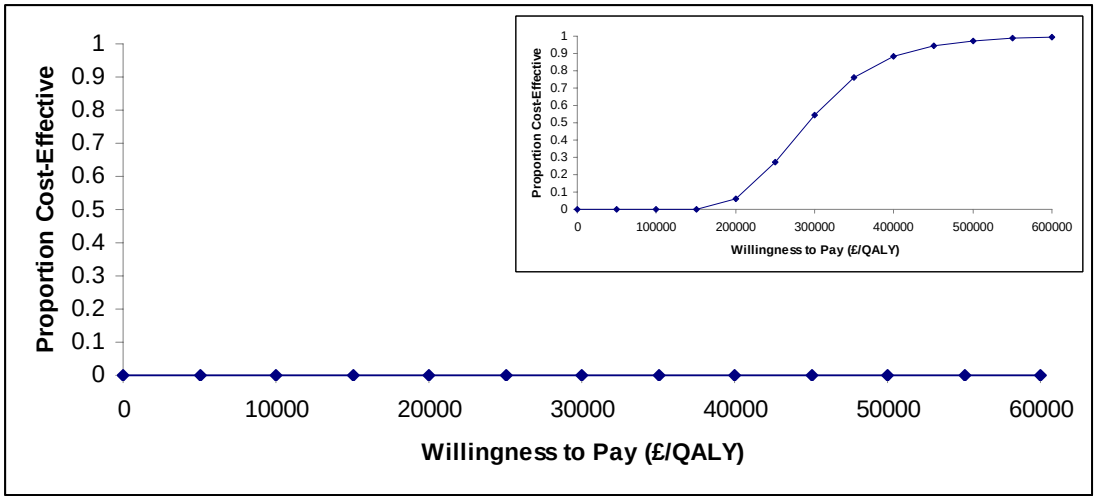

Figure 73 CEAC for epoprostenol versus supportive care, FCIII: Time horizon of 10 years

Alternative prices

Alternative price for epoprostenol

Table 87 Epoprostenol versus supportive care, FCIII: Alternative price for epoprostenol

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	[redacted]		2.056		
Epoprostenol	[redacted]	[redacted]	2.843	0.787	[redacted]

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Figure 74 CEAC for epoprostenol versus supportive care, FCIII: Alternative price for epoprostenol

Alternative health state utility values

Utilities from Meads et al

Table 88 Epoprostenol versus supportive care, FCIII: Alternative health state utility values (Meads)

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	479,000		[redacted]		
Epoprostenol	697,000	218,000	[redacted]	[redacted]	[redacted]

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Figure 75 CEAC for epoprostenol versus supportive care, FCIII: Alternative health state utility values

Utilities from Kirsch et al, 2 year TTO

Table 89 Epoprostenol versus supportive care, FCIII: Alternative health state utility values (Kirsch 2yr TTO)

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

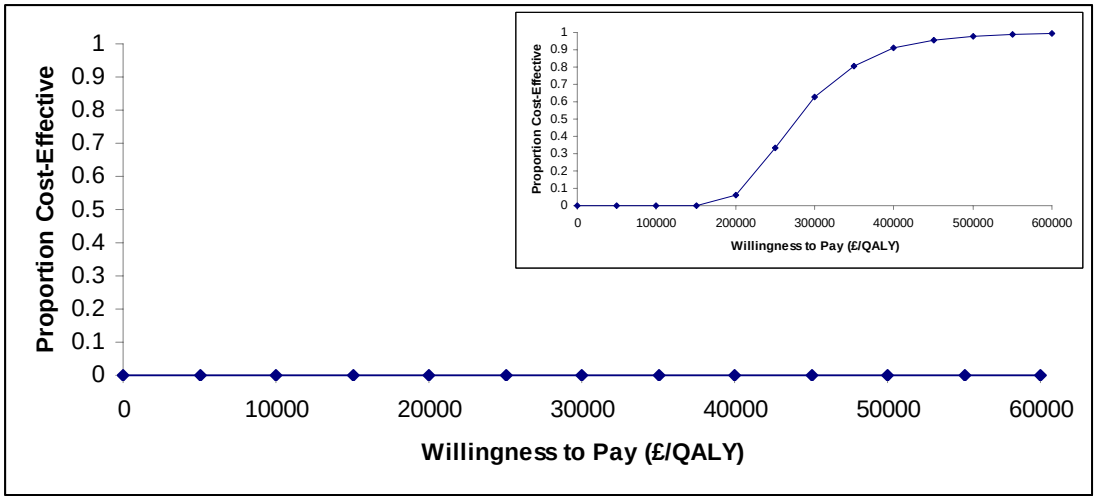

Figure 76 CEAC for epoprostenol versus supportive care, FCIII: Alternative health state utility values (Kirsch 2yr TTO)

Utilities from Kirsch et al, 10 year TTO

Table 90 Epoprostenol versus supportive care, FCIII: Alternative health state utility values (Kirsch 10yr TTO)

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

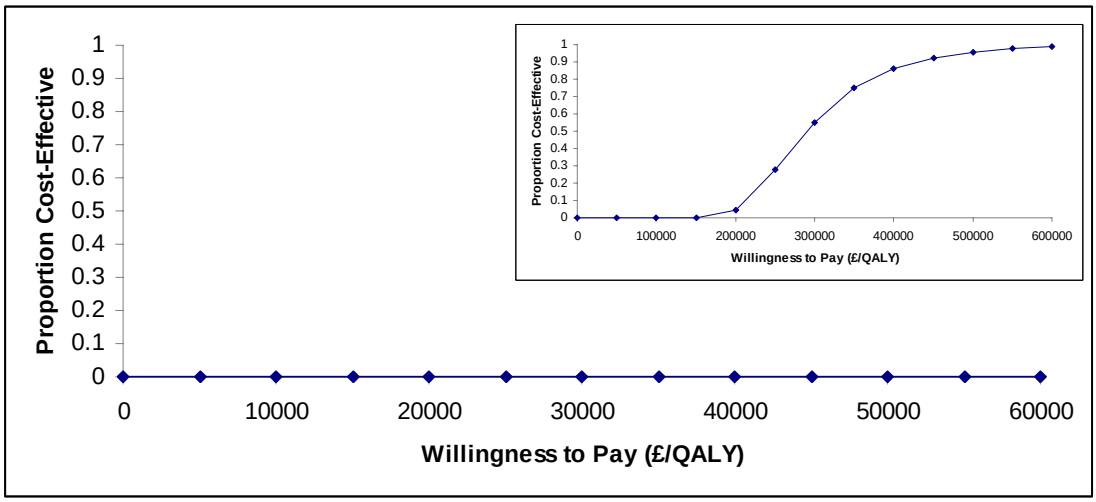

Figure 77 CEAC for epoprostenol versus supportive care, FCIII: Alternative health state utility values (Kirsch 10yr TTO)

Utilities from Olschewski et al

Table 91 Epoprostenol versus supportive care, FCIII: Alternative health state utility values (Olschewski)

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

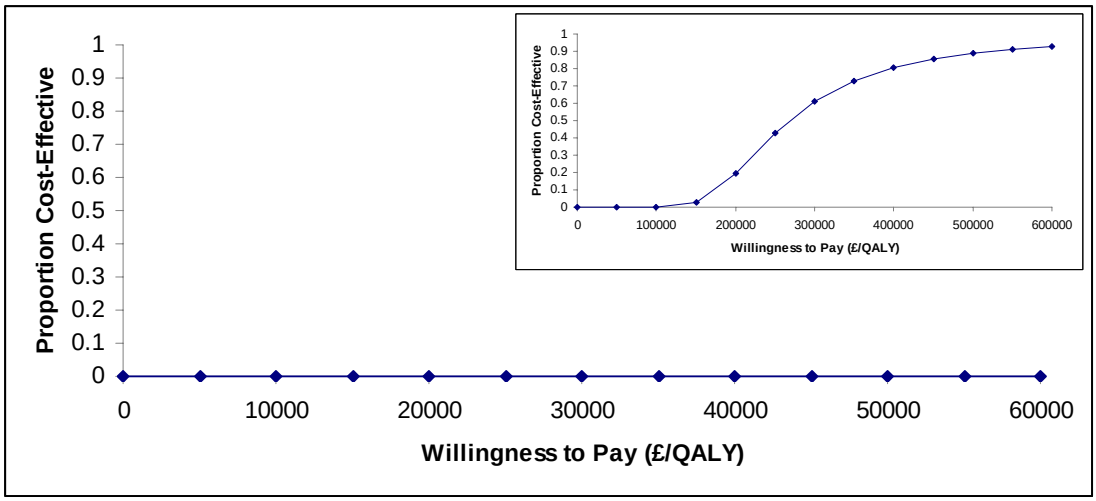

Figure 78 CEAC for epoprostenol versus supportive care, FCIII: Alternative health state utility values (Olschewski)

Appendix 12.2 Epoprostenol with supportive care versus supportive care alone, FCIV

Alternative time horizon

Time horizon of 20 years

Table 92 Epoprostenol versus supportive care, FCIV: 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

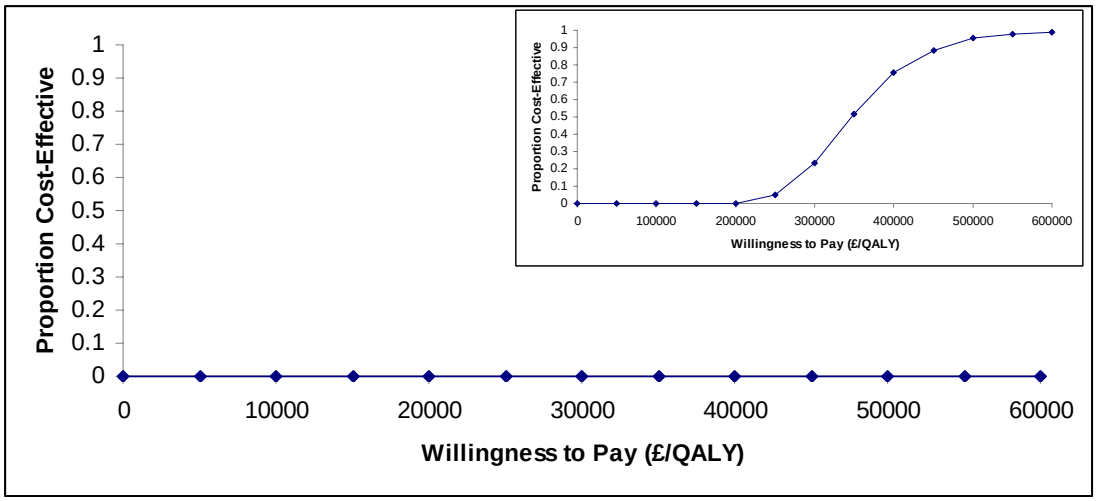

Figure 79 CEAC for epoprostenol versus supportive care, FCIV: Time horizon of 20 years

Time horizon of 10 years

Table 93 Epoprostenol versus supportive care, FCIV: 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

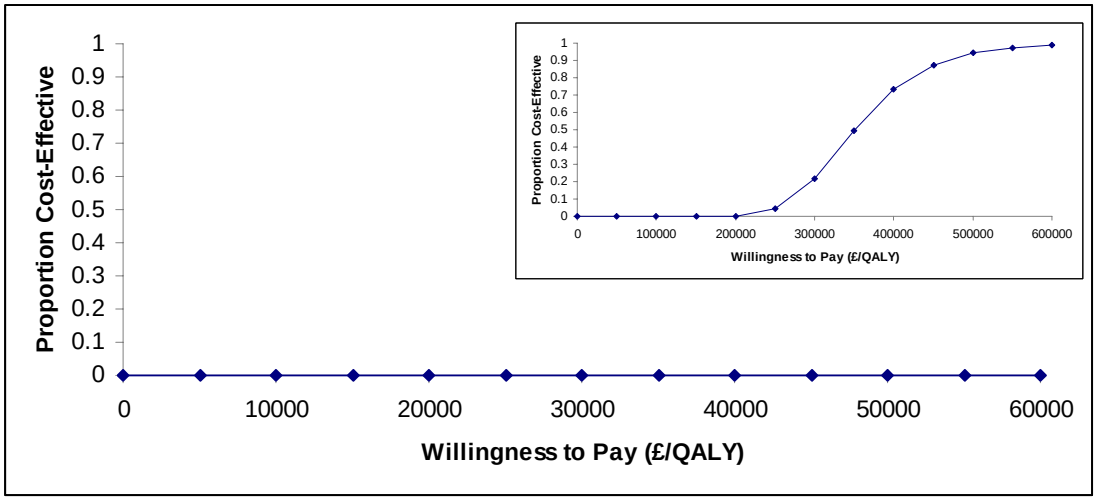

Figure 80 CEAC for epoprostenol versus supportive care, FCIV: Time horizon of 10 years

Alternative prices

Alternative price for epoprostenol

Table 94 Epoprostenol versus supportive care, FCIV: Alternative price for epoprostenol

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	[redacted]		0.829		
Epoprostenol	[redacted]	[redacted]	2.003	1.174	[redacted]

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Figure 81 CEAC for epoprostenol versus supportive care, FCIV: Alternative price for epoprostenol

Alternative health state utility values

Utilities from Meads et al

Table 95 Epoprostenol versus supportive care, FCIV: Alternative health state utility values (Meads)

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	128,000		[redacted]		
Epoprostenol	531,000	403,000	[redacted]	[redacted]	[redacted]

COMERCIAL IN CONFIDENCE – FIGURE REMOVED

Figure 82 CEAC for epoprostenol versus supportive care, FCIV: Alternative health state utility values (Meads)

Utilities from Kirsch et al, 2 year TTO

Table 96 Epoprostenol versus supportive care, FCIV: Alternative health state utility values (Kirsch 2yr TTO)

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

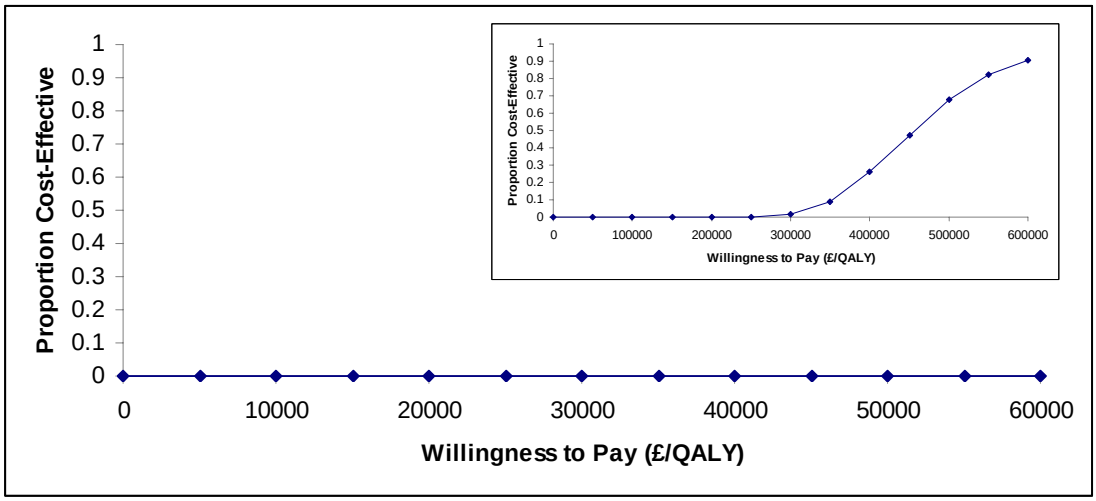

Figure 83 CEAC for epoprostenol versus supportive care, FCIV: Alternative health state utility values (Kirsch 2yr TTO

Utilities from Kirsch et al, 10 year TTO

Table 97 Epoprostenol versus supportive care, FCIV: Alternative health state utility values (Kirsch 10yr TTO)

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

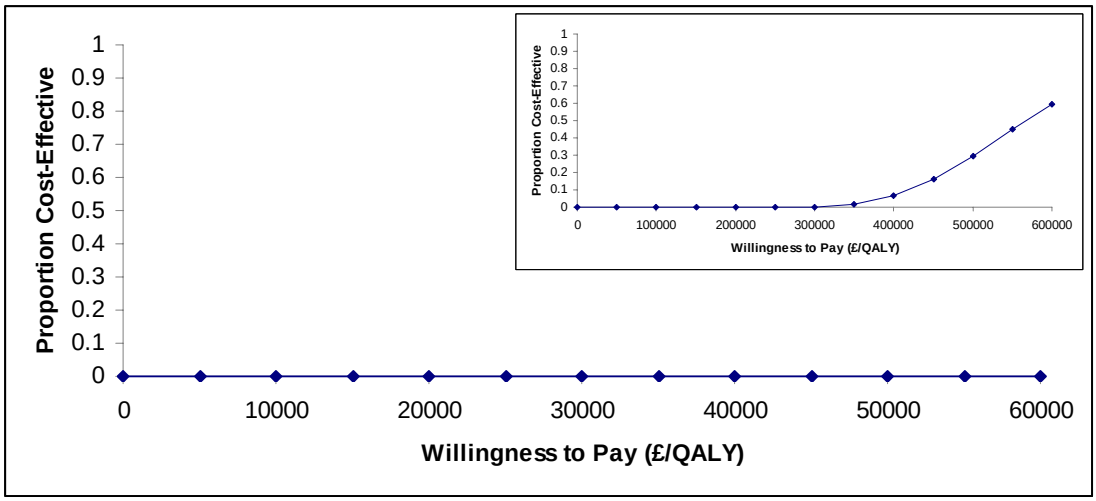

Figure 84 CEAC for epoprostenol versus supportive care, FCIV: Alternative health state utility values (Kirsch 10yr TTO)

Utilities from Olschewski et al

Table 98 Epoprostenol versus supportive care, FCIV: Alternative health state utility values (Olschewski)

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

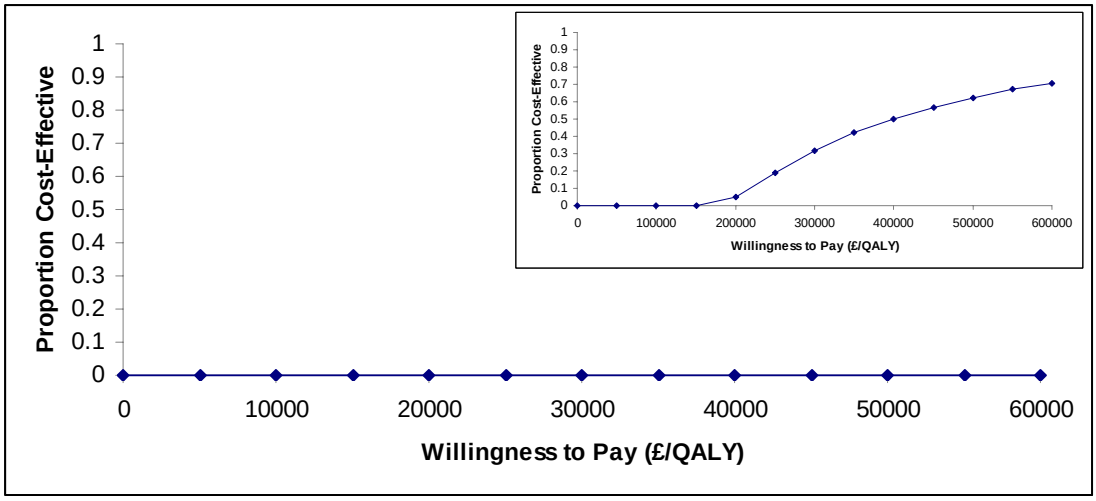

Figure 85 CEAC for epoprostenol versus supportive care, FCIV: Alternative health state utility values (Olschewski)

Appendix 12.3 Iloprost with supportive care versus supportive care alone, FCIII

Alternative time horizon

Time horizon of 20 years

Table 99 Iloprost versus supportive care, FCIII: 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

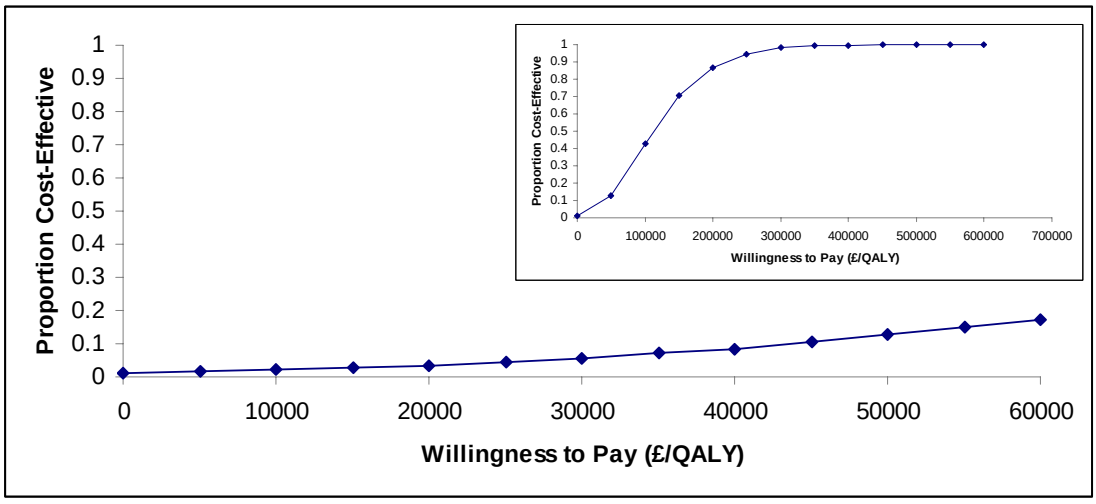

Figure 86 CEAC for iloprost versus supportive care, FCIII: Time horizon of 20 years

Time horizon of 10 years

Table 100 Iloprost versus supportive care, FCIII: 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

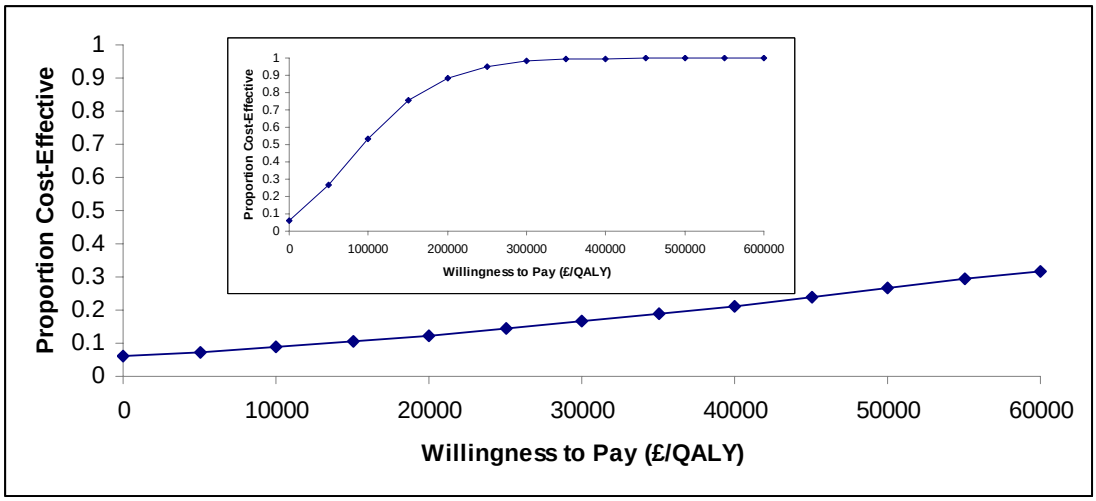

Figure 87 CEAC for iloprost versus supportive care, FCIII: Time horizon of 10 years

Alternative prices

Alternative price for epoprostenol

Table 101 Iloprost versus supportive care, FCIII: Alternative price for epoprostenol

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	[redacted]		1.958		
Iloprost	[redacted]	[redacted]	2.975	1.017	[redacted]

COMERCIAL IN CONFIDENCE – FIGURE REMOVED

Figure 88 CEAC for iloprost versus supportive care, FCIII: Alternative price for epoprostenol

Alternative iloprost price, reference case epoprostenol price

Table 102 Iloprost versus supportive care, FCIII: 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

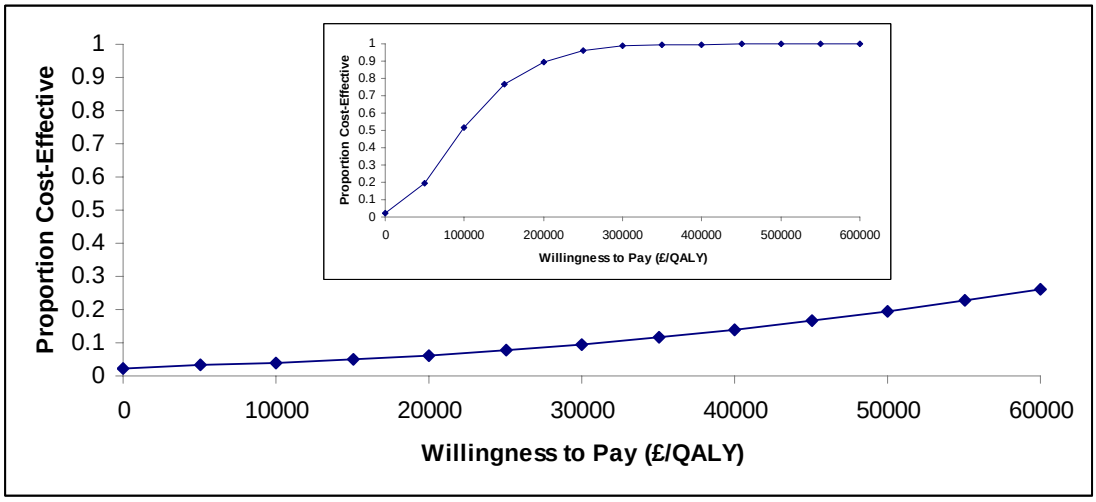

Figure 89 CEAC for iloprost versus supportive care, FCIII*:* Alternative iloprost price, reference case epoprostenol price

Alternative iloprost and epoprostenol price

Table 103 Iloprost versus supportive care, FCIII: Alternative iloprost and epoprostenol price

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	[redacted]		1.958		
Iloprost	[redacted]	[redacted]	2.975	1.017	[redacted]

COMERCIAL IN CONFIDENCE – FIGURE REMOVED

Figure 90 CEAC for iloprost versus supportive care, FCIII: Alternative iloprost and epoprostenol price

Alternative health state utility values

Utilities from Meads et al

Table 104 Iloprost versus supportive care, FCIII: Alternative health state utility values (Meads)

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	434,000		[redacted]		
Iloprost	537,000	103,000	[redacted]	[redacted]	[redacted]

COMERCIAL IN CONFIDENCE – FIGURE REMOVED

Figure 91 CEAC for iloprost versus supportive care, FCIII: Alternative health state utility values (Meads)

Utilities from Kirsch et al, 2 year TTO

Table 105 Iloprost versus supportive care, FCIII: Alternative health state utility values (Kirsch 2yr TTO)

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

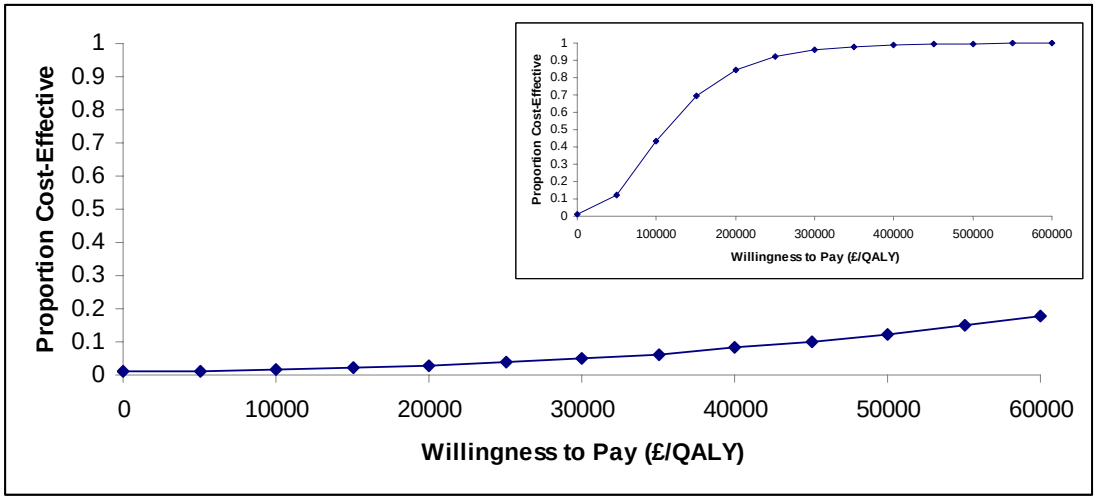

Figure 92 CEAC for iloprost versus supportive care, FCIII: Alternative health state utility values (Kirsch 2yr TTO)

Utilities from Kirsch et al, 10 year TTO

Table 106 Iloprost versus supportive care, FCIII: Alternative health state utility values (Kirsch 10yr TTO)

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

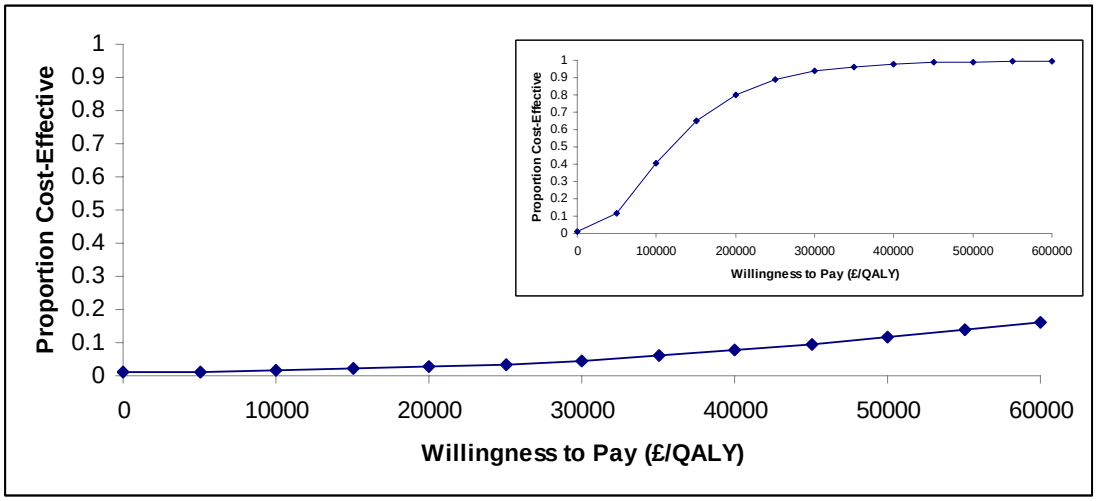

Figure 93 CEAC for iloprost versus supportive care, FCIII: Alternative health state utility values (Kirsch 10yr TTO)

Utilities from Olschewski et al

Table 107 Iloprost versus supportive care, FCIII: Alternative health state utility values (Olschewski)

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

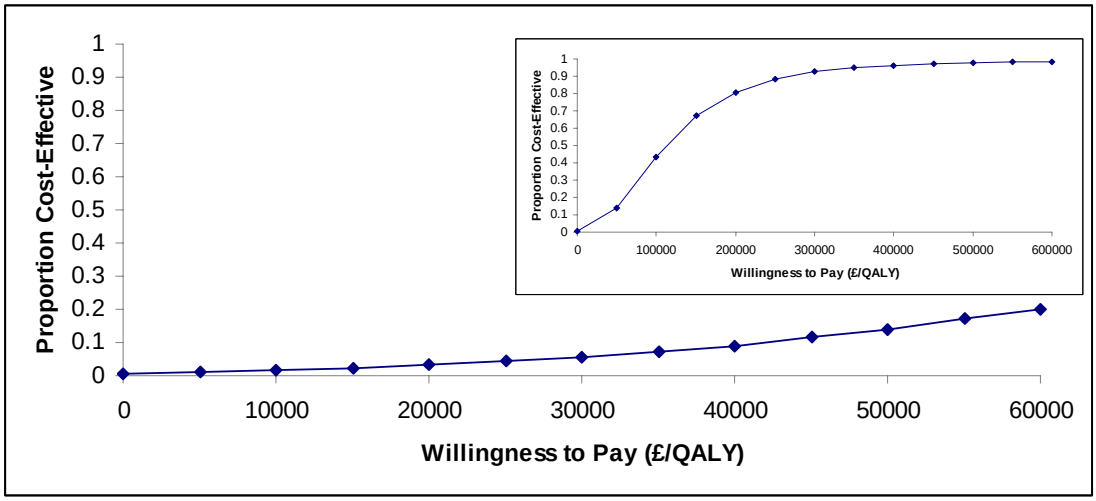

Figure 94 CEAC for iloprost versus supportive care, FCIII: Alternative health state utility values (Olschewski)

Appendix 12.4 Bosentan with supportive care versus supportive care alone, FCIII

Alternative time horizon

Time horizon of 20 years

Table 108 Bosentan versus supportive care, FCIII: 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

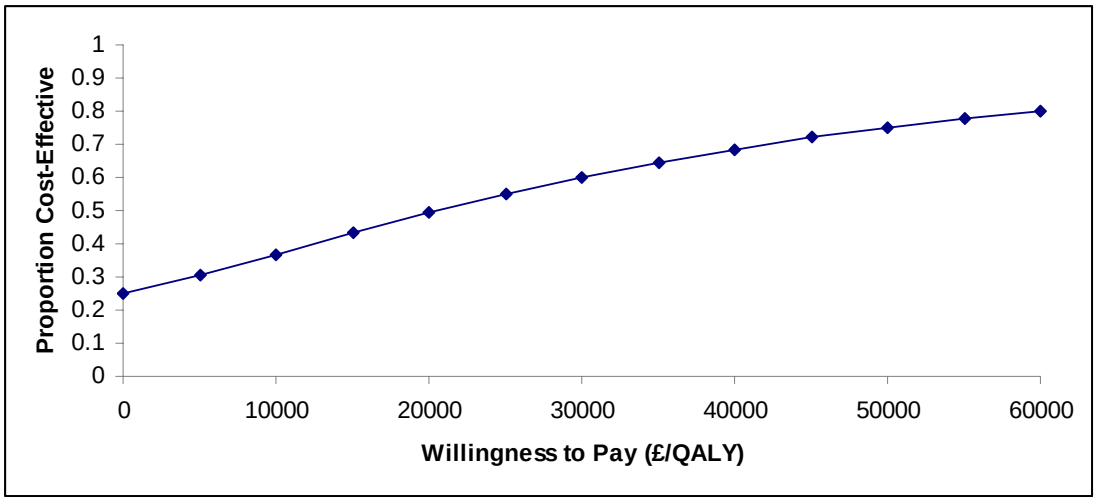

Figure 95 CEAC for bosentan versus supportive care, FCIII: Time horizon of 20 years

Time horizon of 10 years

Table 109 Bosentan versus supportive care, FCIII: 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**

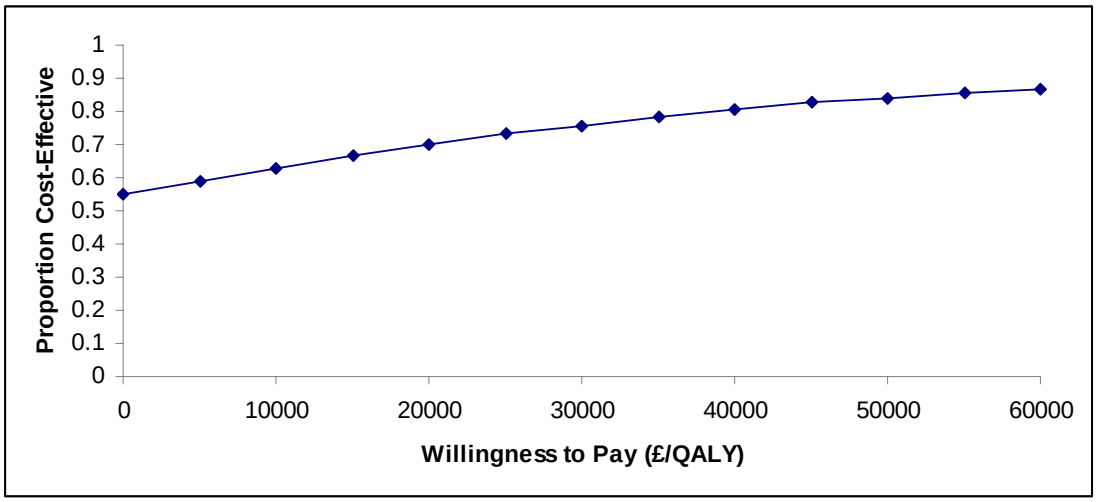

Figure 96 CEAC for bosentan versus supportive care, FCIII: Time horizon of 10 years

Alternative prices

Alternative price for epoprostenol

Table 110 Bosentan versus supportive care, FCIII: Alternative price for epoprostenol

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	[redacted]		2.201		
Bosentan	[redacted]	[redacted]	5.696	3.494	[redacted]

COMERCIAL IN CONFIDENCE – FIGURE REMOVED

Figure 97 CEAC for bosentan versus supportive care, FCIII: Alternative price for epoprostenol

Alternative health state utility values

Utilities from Meads et al

Table 111 Bosentan versus supportive care, FCIII: Alternative health state utility values (Meads)

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		[redacted]		
Bosentan	436,000	93,000	[redacted]	[redacted]	[redacted]

COMERCIAL IN CONFIDENCE – FIGURE REMOVED

Figure 98 CEAC for bosentan versus supportive care, FCIII: Alternative health state utility values (Meads)

Utilities from Kirsch et al, 2 year TTO

Table 112 Bosentan versus supportive care, FCIII: Alternative health state utility values (Kirsch 2yr TTO)

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

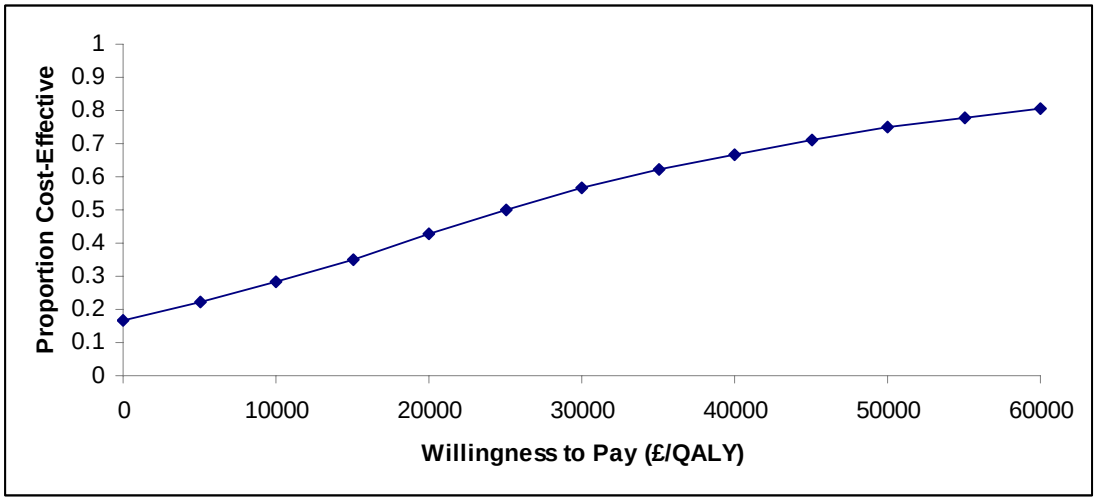

Figure 99 CEAC for bosentan versus supportive care, FCIII: Alternative health state utility values (Kirsch 2yr TTO)

Utilities from Kirsch et al, 10 year TTO

Table 113 Bosentan versus supportive care, FCIII: Alternative health state utility values (Kirsch 10yr TTO)

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

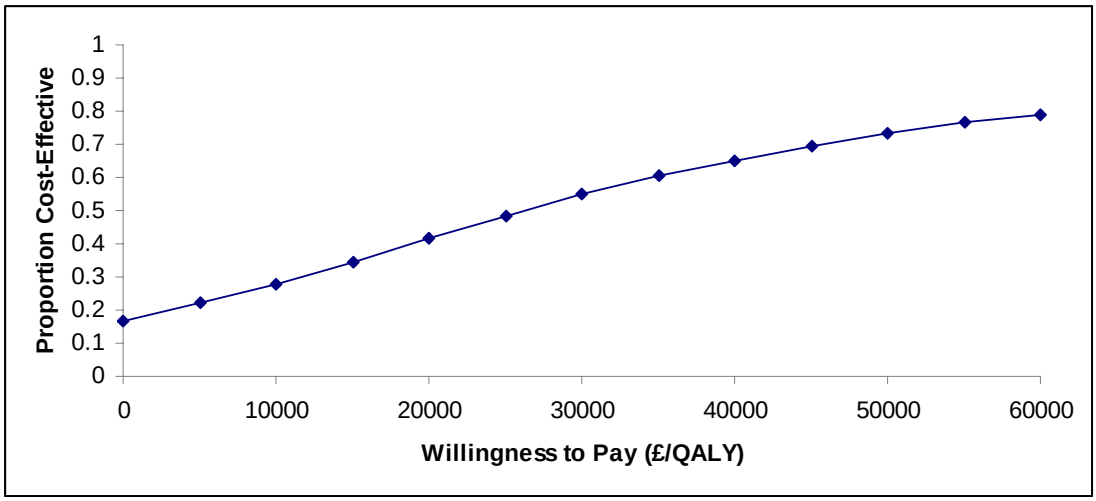

Figure 100 CEAC for bosentan versus supportive care, FCIII: Alternative health state utility values (Kirsch 10yr TTO)

Utilities from Olschewski et al

Table 114 Bosentan versus supportive care, FCIII: Alternative health state utility values (Olschewski)

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

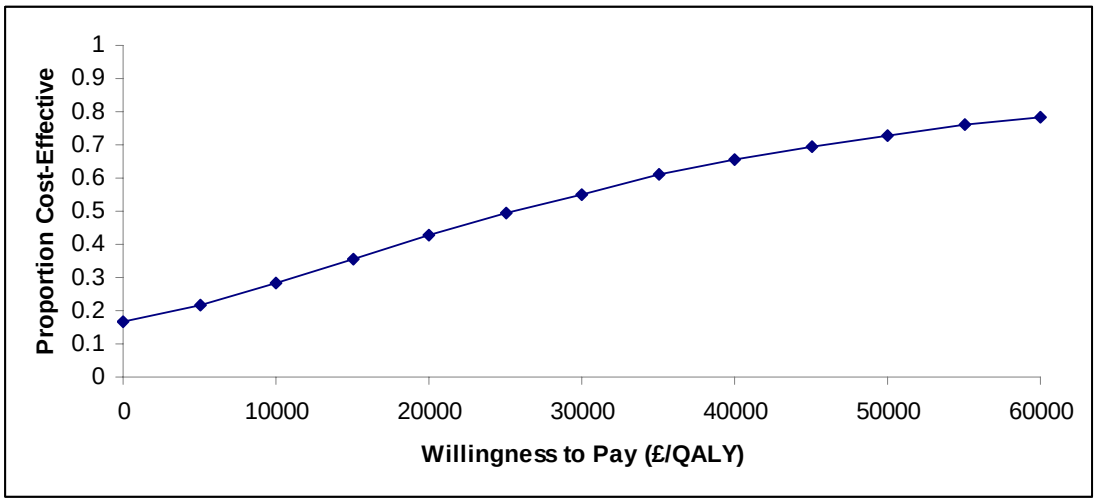

Figure 101 CEAC for bosentan versus supportive care, FCIII: Alternative health state utility values (Olschewski)

Appendix 12.5 Sitaxentan with supportive care versus supportive care alone, FCIII

Alternative time horizon

Time horizon of 20 years

Table 115 Sitaxentan versus supportive care, FCIII: 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

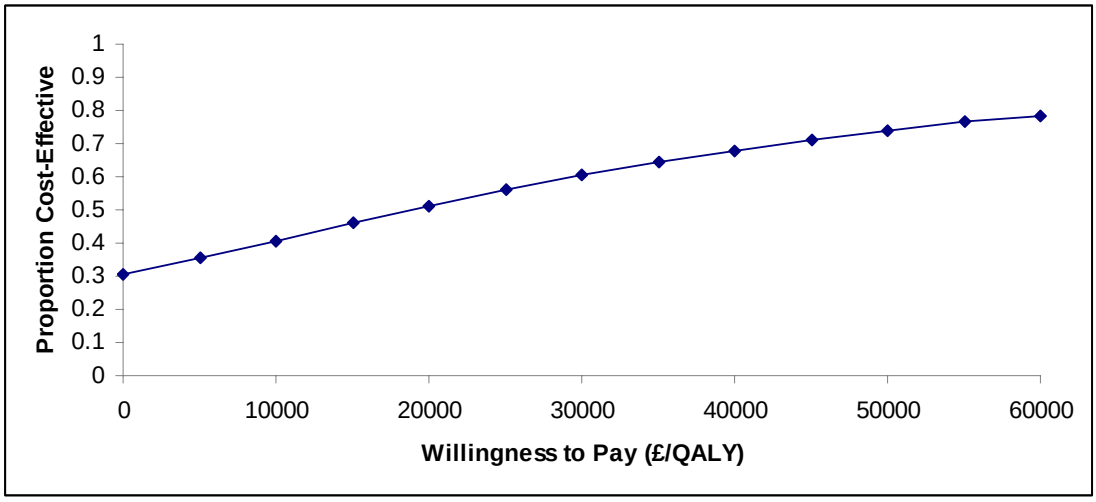

Figure 102 CEAC for sitaxentan versus supportive care, FCIII: Time horizon of 20 years

Time horizon of 10 years

Table 116 Sitaxentan versus supportive care, FCIII: 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

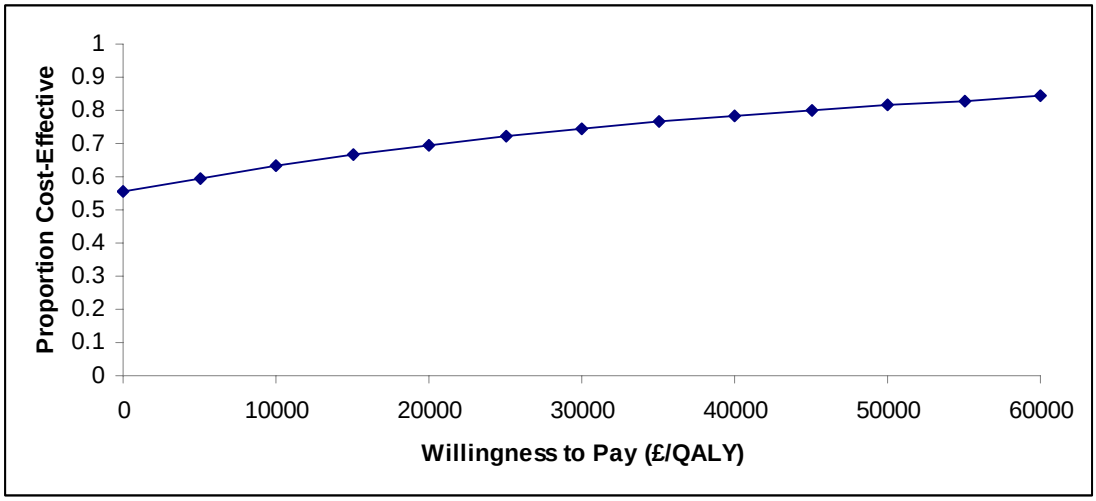

Figure 103 CEAC for sitaxentan versus supportive care, FCIII: Time horizon of 10 years

Alternative prices

Alternative price for epoprostenol

Table 117 Sitaxentan versus supportive care, FCIII: Alternative price for epoprostenol

Strategy	**Cost (£)**	**Cost difference (£)**	**QALYs**	**QALY difference**	**ICER (£/QALY)**
Supportive care	[redacted]		2.201		
Sitaxentan	[redacted]	[redacted]	5.289	3.087	[redacted]

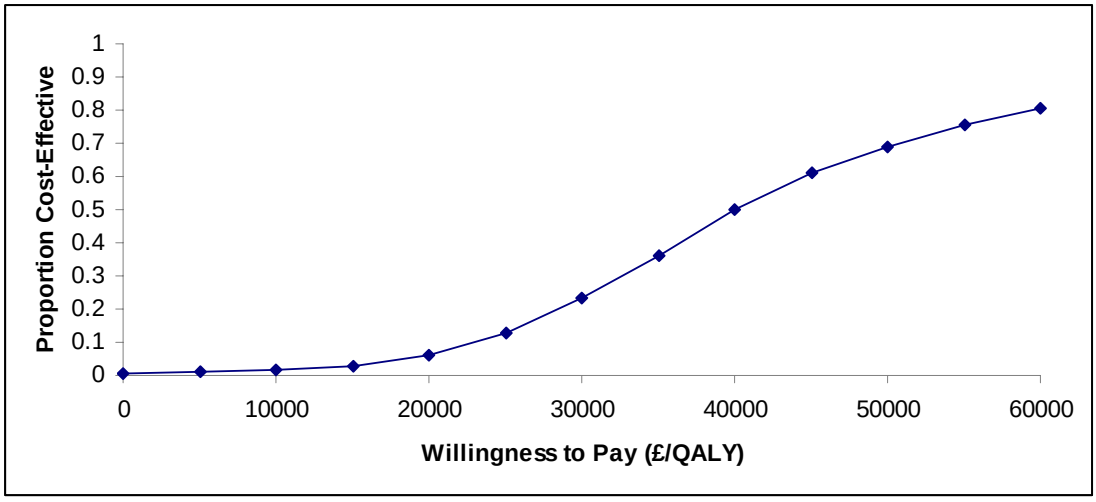

Figure 104 CEAC for sitaxentan versus supportive care, FCIII: Alternative price for epoprostenol

Alternative health state utility values

Utilities from Meads et al

Table 118 Sitaxentan versus supportive care, FCIII: Alternative health state utility values (Meads)

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		[redacted]		
Sitaxentan	419,000	76,000	[redacted]	[redacted]	[redacted]

COMERCIAL IN CONFIDENCE – FIGURE REMOVED

Figure 105 CEAC for sitaxentan versus supportive care, FCIII: Alternative health state utility values (Meads)

Utilities from Kirsch et al, 2 year TTO

Table 119 Sitaxentan versus supportive care, FCIII: Alternative health state utility values (Kirsch 2yr TTO)

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

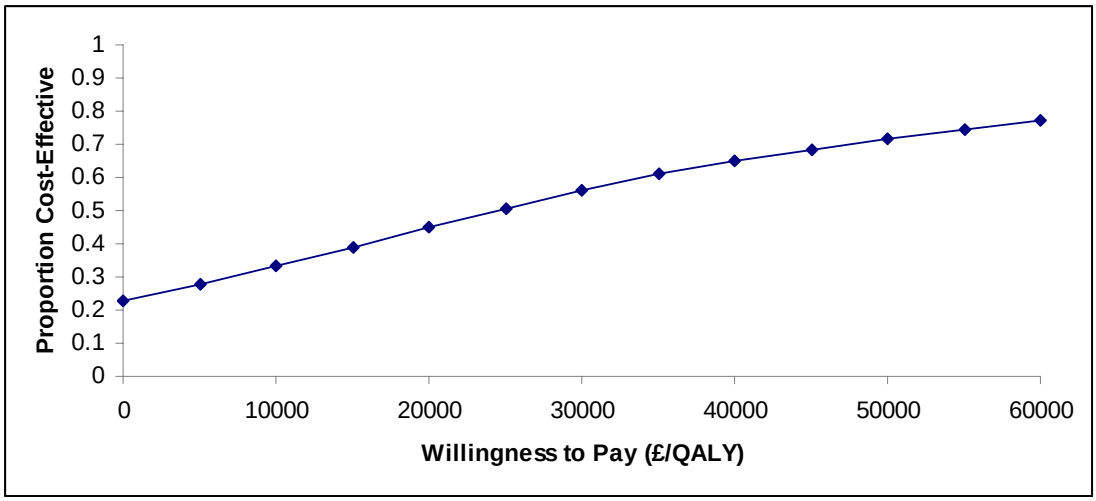

Figure 106 CEAC for sitaxentan versus supportive care, FCIII: Alternative health state utility values (Kirsch 2yr TTO)

Utilities from Kirsch et al, 10 year TTO

Table 120 Sitaxentan versus supportive care, FCIII: Alternative health state utility values (Kirsch 10yr TTO)

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

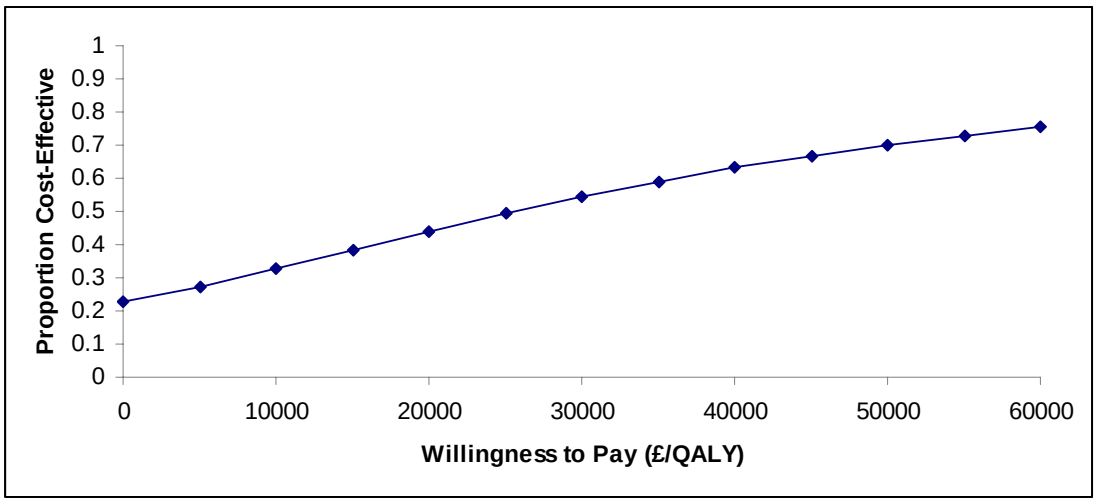

Figure 107 CEAC for sitaxentan versus supportive care, FCIII: Alternative health state utility values (Kirsch 10yr TTO)

Utilities from Olschewski et al

Table 121 Sitaxentan versus supportive care, FCIII: Alternative health state utility values (Olschewski)

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

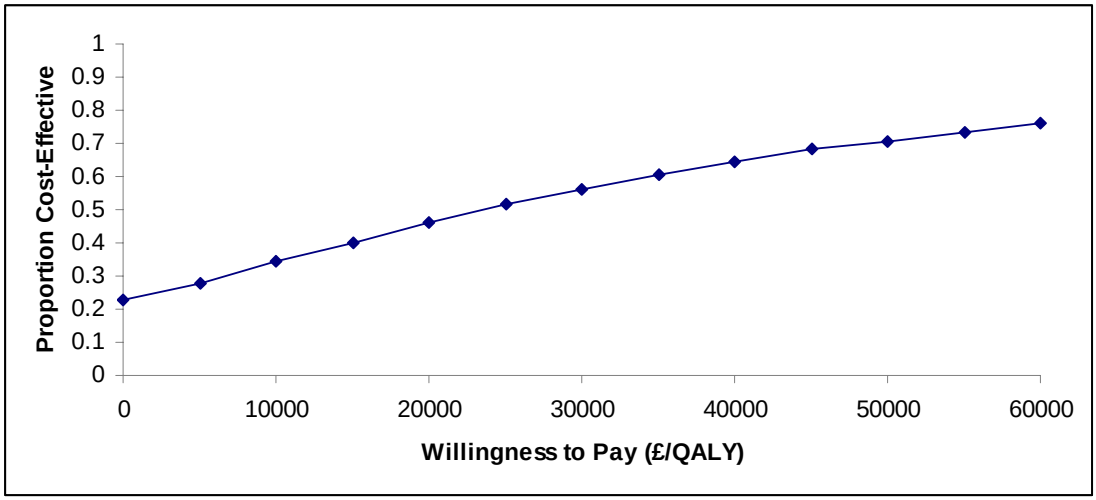

Figure 108 CEAC for sitaxentan versus supportive care, FCIII: Alternative health state utility values (Olschewski)

Appendix 12.6 Sildenafil with supportive care versus supportive care alone, FCIII

Alternative time horizon

Time horizon of 20 years

Table 122 Sildenafil versus supportive care, FCIII: 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

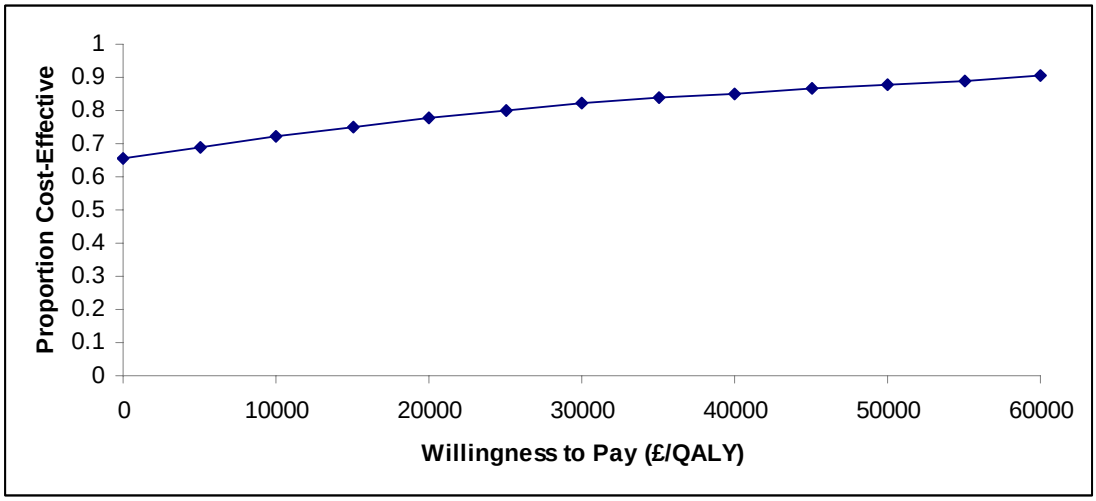

Figure 109 CEAC for sildenafil versus supportive care, FCIII: Time horizon of 20 years

Time horizon of 10 years

Table 123 Sildenafil versus supportive care, FCIII: 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

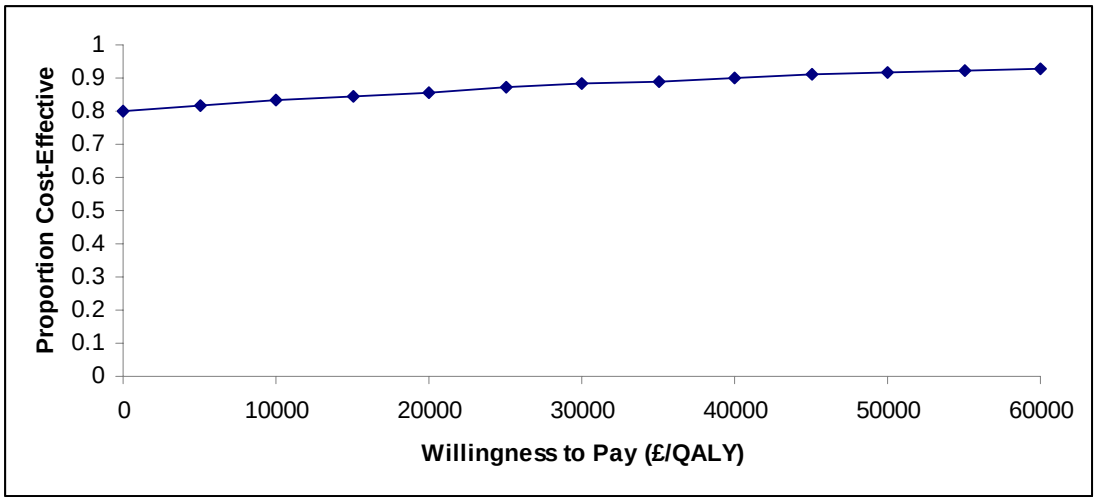

Figure 110 CEAC for sildenafil versus supportive care, FCIII: Time horizon of 10 years

Alternative prices

Alternative price for epoprostenol

Table 124 Sildenafil versus supportive care, FCIII: Alternative price for epoprostenol

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	[redacted]		2.201		
Sildenafil	[redacted]	[redacted]	5.436	3.235	[redacted]

COMERCIAL IN CONFIDENCE – FIGURE REMOVED

Figure 111 CEAC for sildenafil versus supportive care, FCIII: Alternative price for epoprostenol

Alternative health state utility values

Utilities from Meads et al

Table 125 Sildenafil versus supportive care, FCIII: Alternative health state utility values (Meads)

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Supportive care	343,000		[redacted]		
Sildenafil	307,000	-36,000	[redacted]	[redacted]	[redacted]

COMERCIAL IN CONFIDENCE – FIGURE REMOVED

Figure 112 CEAC for sildenafil versus supportive care, FCIII: Alternative health state utility values (Meads)

Utilities from Kirsch et al, 2 year TTO

Table 126 Sildenafil versus supportive care, FCIII: Alternative health state utility values (Kirsch 2yr TTO)

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

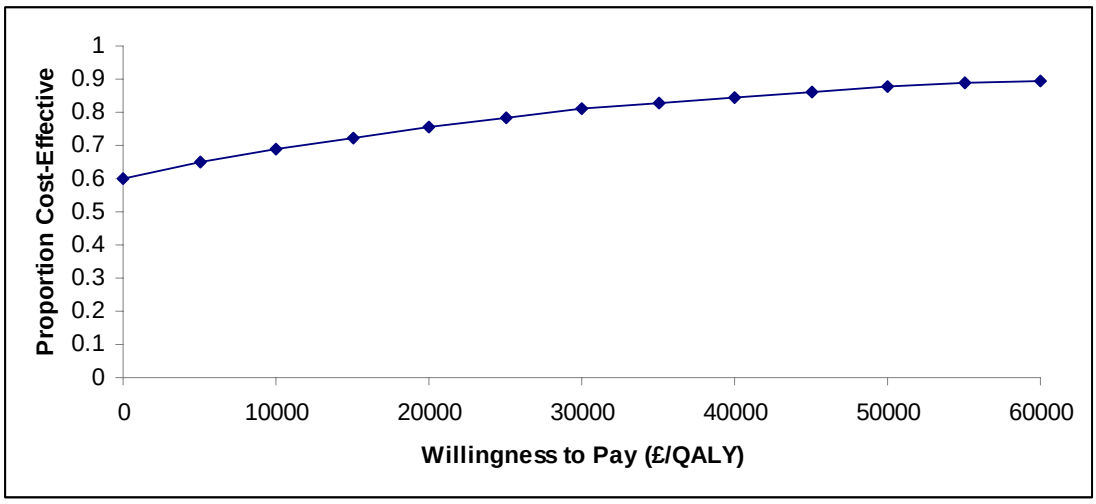

Figure 113 CEAC for sildenafil versus supportive care, FCIII: Alternative health state utility values (Kirsch 2yr TTO)

Utilities from Kirsch et al, 10 year TTO

Table 127 Sildenafil versus supportive care, FCIII: Alternative health state utility values (Kirsch 10yr TTO)

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

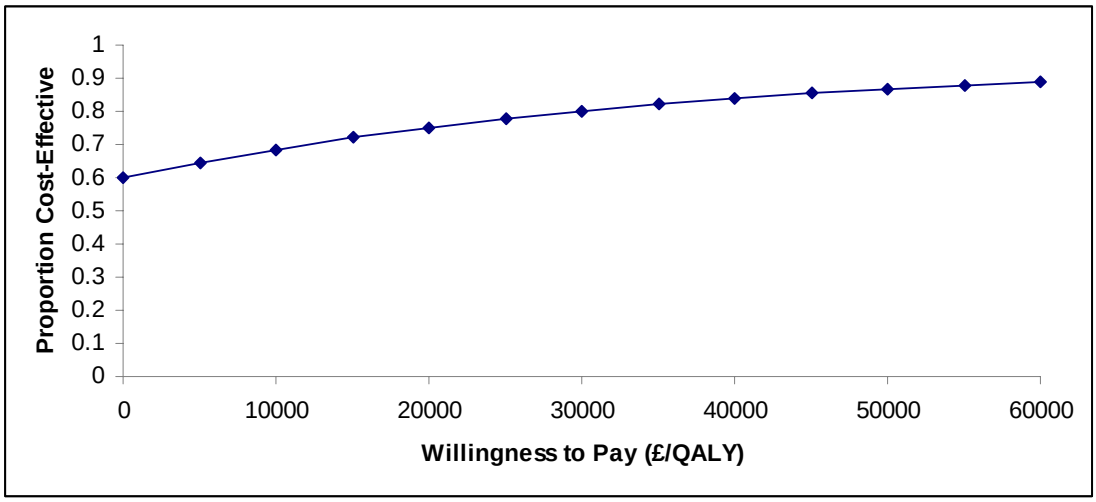

Figure 114 CEAC for sildenafil versus supportive care, FCIII: Alternative health state utility values (Kirsch 10yr TTO)

Utilities from Olschewski et al

Table 128 Sildenafil versus supportive care, FCIII: Alternative health state utility values (Olschewski)

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

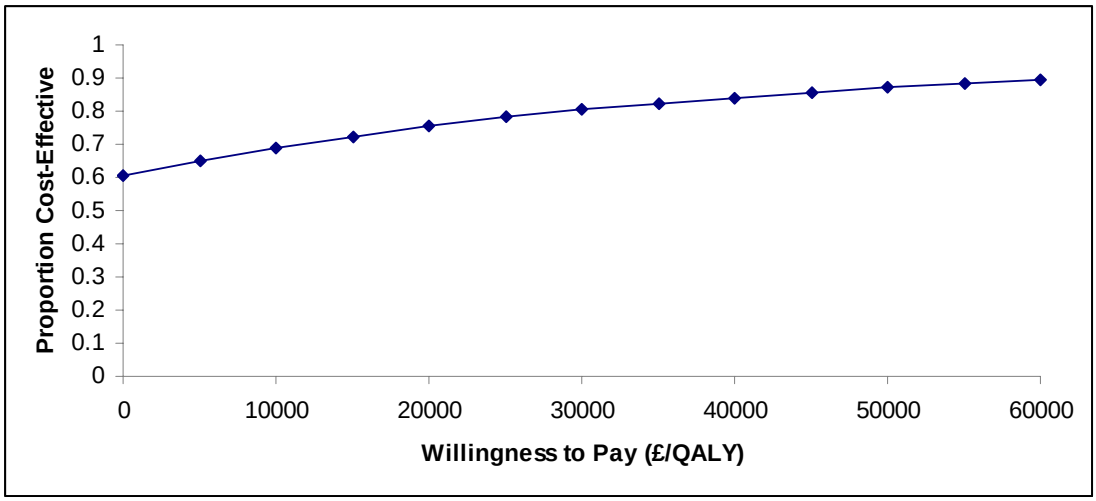

Figure 115 CEAC for sildenafil versus supportive care, FCIII: Alternative health state utility values (Olschewski)

Appendix 13. Budget Impact

The annual budgetary impact of uptake of the 5 technologies was assessed using the drug (licensed dose) and service fee cost for each intervention, as outlined in Table 129, 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 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 uptake were produced. Budgetary impact for epoprostenol is shown in Figure 116, iloprost in Figure 117 and bosentan, sitaxentan and sildenafil in Figure 118.

COMERCIAL IN CONFIDENCE – FIGURE REMOVED

Figure 116 Budgetary Impact per annum - epoprostenol

COMERCIAL IN CONFIDENCE – FIGURE REMOVED

Figure 117 Budgetary Impact per annum – iloprost

COMERCIAL IN CONFIDENCE – FIGURE REMOVED

Figure 118 Budgetary Impact per annum - bosentan, sitaxentan, sildenafil

Table 129 Budgetary Impact - Annual cost of each technology

	epoprostenol year1 list price	epoprostenol year1 reduction	epoprostenol year2+ list price	epoprostenol year 2+ reduction	iloprost list price	iloprost ventafee	bosentan	sitaxentan	sildenafil
Drug	55,869	[redacted]	127,702	[redacted]	36,178	[redacted]	20,102	20,089	4,547
Service fee	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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