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WORKING GROUP ON ACUTE PURCHASING

Prostacyclin and Iloprost in the Treatment of Primary Pulmonary Hypertension

March 1997

GUIDANCE NOTE FOR PURCHASERS 97/02

Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authority and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise, and includes non-clinically qualified scientists and lay members. It is chaired by Professor Sir David Hull.

The committee recommends, on the basis of appropriate evidence, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 22 April 1997 at which this Guidance Note for Purchasers (in a draft form) was considered.

PROSTACYCLIN IN THE TREATMENT OF PRIMARY PULMONARY HYPERTENSION

AUTHORS: Higenbottam TW, Ward SE, Brennan A, McCabe CJ, Richards RG, Stevenson MD. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield, 1996 Guidance Note for Purchasers: 97/02.

EXPERT ADVISORS TO TRENT DEC: Professor T Higenbottam, Royal Hallamshire Hospital, Sheffield, Dr RG Richards, North Nottinghamshire Health Authority and Ms SE Ward, ScHARR.

DECISION: The Committee recommended that prostacyclin should be part of the national programme coordinated by the National Specialist Commissioning Advisory Group so that a favourable price could be negotiated. It should be administered from a limited number of centres according to agreed protocols to ensure that data on costs and outcomes were collected to inform future purchasing decisions.

March 1997

PROSTACYCLIN AND ILOPROST IN THE TREATMENT OF PRIMARY PULMONARY HYPERTENSION

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The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Institute:

- provides advice and support to NHS staff on undertaking Health Services Research (HSR);
- provides a consultancy service to NHS bodies on service problems;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);
Professor C E D Chilvers (Nottingham); and
Professor M Clarke (Leicester).

Professor Akehurst currently undertakes the role of Institute Co-ordinator.

A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within the University of Sheffield in conjunction with the School of Health and Related Research (ScHARR).

FOREWORD

Individuals or small groups in each District Health Authority in Trent have historically considered evidence on the likely effectiveness of new procedures or therapies in conjunction with their cost, making judgements on whether these should be supported. Since all or most Health Authorities face the same issues, there tends to be repetition in analysis and this can be wasteful of scarce professional expertise.

There are national attempts to remedy this situation by providing information on the effectiveness of interventions and these are welcomed. There remains, however, a significant gap between the results of research undertaken and their incorporation into contracts.

Following a request from purchasers, a network has been established in the Trent Region to allow purchasers to share research knowledge about the effectiveness of acute service interventions and to determine collectively their purchasing stance.

ScHARR, which houses the Sheffield Unit of the Trent Institute for Health Services Research, facilitates a Working Group on Acute Purchasing. A list of interventions for consideration is recommended by the purchasing authorities in Trent and approved by the Purchasing Authorities Chief Executives (PACE) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic and is assisted, as necessary, by a support team from ScHARR which provides help including literature searching, health economics and modelling. A seminar is then led by the consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes.

Professor R L Akehurst,
Chairman, Trent Working Group on Acute Purchasing.

ACKNOWLEDGEMENTS

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EXECUTIVE SUMMARY

Primary Pulmonary Hypertension (PPH) is a rare disease characterised by extreme elevations in pulmonary artery pressure and pulmonary vascular resistance, which ultimately results in right ventricular failure and death. Survival in the untreated ranges from one to five years and does not exceed five years post diagnosis. Treatment of patients with mild PPH uses oral calcium antagonists and anticoagulants. Survival with treatment is normally greater than five years. The question of treatment for severe PPH is the reason for this review.

Prostacyclin ((PGI_2), Epoprostenol) is a powerful strong vasodilator and an inhibitor of platelet aggregation. It is licensed as an anticoagulant for use during renal dialysis, but was granted approval for use for severe PPH by the Federal Drug Administration in 1996. It is now advocated as a treatment of severe PPH in the UK.

Since first described in 1984, a number of studies have found evidence of significant morbidity and mortality benefits to patients with severe PPH from prostacyclin treatment. In addition, the improvements in life expectancy increase the chances of a patient receiving a heart and lung transplant. Prostacyclin may also be associated with better outcomes for heart-lung transplantations. Observations on prostacyclin can be generalised to newer analogues such as iloprost.

The cost per patient on prostacyclin typically starts at around £45,000 per year, similar to that for iloprost. Although dose requirements rise over time, dosage levels can generally be controlled within specialist centres, avoiding the rapidly escalating costs which have been reported in the past.

A crude estimate of the cost per Quality Adjust Life Year has been calculated as £127,000. This indicates the broad order of magnitude only. This cost could be reduced if price reductions for the drug in the UK could be achieved through a national negotiating process.

A number of purchasing options are considered in this paper. The conclusion of the Trent Working Group on Acute Purchasing is that stopping the provision of prostacyclin and iloprost would be difficult to justify on ethical grounds, especially with regard to patients presently on therapy. It is recommended, therefore, that prostacyclin and other analogues be made available through specialist centres, according to agreed protocols which ensure that data on costs and outcomes are collected to inform future purchasing decisions. This

would be best organised at a national level and the National Specialist Commissioning Advisory Group (NSCAG) should be requested to consider designating this as a national specialist service.

1. INTRODUCTION

1.1 Primary Pulmonary Hypertension: Incidence and Pathology

'Primary Pulmonary Hypertension (PPH) is a rare disease, characterised by extreme elevations in pulmonary artery pressure and pulmonary vascular resistance which ultimately results in right ventricular failure and death'.[1] It generally afflicts adults, although it is also found amongst the young and the elderly. The median age of patients at presentation is 42 years and it is more common in women.[2]

From lung biopsy, the principal prognostic feature on histological appraisal is intimal thickening of the pulmonary arteries. Also commonly found are small thrombotic obstructions. These features lead to a loss of the pre-capillary resistance vessels through obstruction. At the time of presentation around 80% of these vessels have been 'lost'.[3]

PPH is a rare condition. Higenbottam[4] reported that around 40 patients are diagnosed as having PPH each year in England and Wales. Indications, from a recently published survey[5], suggest that the incidence in Belgium is around 1.7 patients per million per annum (for a population between the ages of 18 and 70 years). This implies an incidence of around 60 patients per annum for England and Wales. An estimate of 400 patients 'at any one time' (i.e. prevalence) advanced by Dr Dent[6] would appear to be on the high side.

Therefore, a typical district of 500,000 population would expect fewer than one new case per year. Only 40% of these patients would be expected to be sufficiently unwell to be considered for expensive medical treatments such as prostacyclin.[2]

1.2 Prognosis and Mortality

Survival in the untreated is poor, with mean survival length between two to three years after the onset of symptoms. Progressive right ventricular failure means that untreated patients do not survive to five years post diagnosis. [7]

1.3 Treatment of Primary Pulmonary Hypertension

In its milder form, affecting around 20% of patients, PPH is managed with oral calcium antagonists and anticoagulants. These patients are characterised by a cardiac index greater than 2 litres per minute per m^2 and mixed venous oxygen saturation greater than 60%.[1,8] There should also be evidence on right heart catherisation of a capacity for vasodilation. Most of these patients will survive on treatment for five years or longer. The treatment of more severe PPH remains in question.

Prostacyclin ((PGI_2), Epoprostenol) is a strong vasodilator and an inhibitor of platelet aggregation. It is licensed as an anticoagulant for use during renal dialysis, but has been granted approval for use for PPH by the Federal Drug Administration in 1996. It is advocated for the treatment of PPH for patients with cardiac index below 2 litres per minute per m^2 and mixed venous oxygen saturation less than 60%. A similar product, an analogue of PGI_2, called iloprost, is also currently used.

A proportion of patients can be identified, from physiological measurements, as having sufficiently poor prognosis to merit consideration for heart-lung or lung transplantation. These are the most severely ill with an elevated right atrial pressure of greater than 15 mm Hg and cardiac index below 2 litres per minute per m^2.[8]

There have been cases of prostacyclin being used for other client groups, in particular, thrombo-embolic pulmonary hypertension and primary pulmonary hypertension with systemic sclerosis. This paper is restricted to consideration of the treatment of patients with PPH.

The major providers of prostacyclin or iloprost treatment for PPH are centres at Sheffield, Glasgow, the Royal Postgraduate Medical School (London) and Papworth Hospital (Cambridge).

2. PROSTACYCLIN IN THE TREATMENT OF PRIMARY PULMONARY HYPERTENSION : SUMMARY OF EVIDENCE OF EFFECTIVENESS

2.1 Review of Evidence of Effectiveness

After an initial report that it was possible continuously to infuse intravenously PGI_2 to treat PPH[9] a series of patients were studied prospectively. This study offered evidence for prolonged physiological benefit from using continuous infusion of prostacyclin in the treatment of PPH as reported by Jones et al.[10] This uncontrolled study found improvements in physiological measures of health, in particular, bed-bound patients returned home and in some cases to work, but no evidence that the treatment influenced the progression of the disease.

Only a limited number of studies have been identified which compare prostacyclin with conventional treatment and report the impact of this drug on clinical outcomes. Higenbottam et al. [8] compared 44 patients at a UK hospital with historical controls from the Mayo Clinic in the United States. In this prospective study 25 patients received continuous epoprostenol (prostacyclin) over a four year period and 19 did not. Ten patients underwent a heart-lung transplantation (HLT), of whom seven had received epoprostenol and three had not. One hundred and twenty historical controls were recruited from the records of the Mayo Clinic before prostacyclin became available. When compared with the patients from the Mayo Clinic, epoprostenol prolonged median survival; i.e. to death or transplant from eight months to 17 months.

In addition, Higenbottam suggests the possibility of further comparisons with historical data from registries[1] and states that similar comparisons have been used to test the efficacy of transplant surgery. The possibility of adjusting for the improvements in conventional therapy over time remains a key issue in terms of the relevance of such comparisons.

Rubin et al. [11] reported a randomised trial of continuous intravenous infusion of prostacyclin in patients with pulmonary hypertension. Twenty four patients were entered into the study, of whom 19 completed the study. Four patients died and one left. A significant reduction in pulmonary resistance was found in the prostacyclin treated patients when compared to the conventional therapy group ($p<0.03$). Six of ten patients treated with prostacyclin, who completed the eight-week study period, had reductions in mean pulmonary artery pressure

of greater than 10 mm Hg, whereas only one of nine in the conventional treatment group had a similar response. However, the difference was not statistically significant at the 95% level (p=0.057). Follow-up at eighteen months of nine patients on prostacyclin found maintained improvements in haemodynamics, but dose requirements increased to values unspecified in the paper over the same period.

Concerns over the comparability of the two arms of the trial exist, as there were more patients in the worst functional class in the conventional arm than the prostacyclin arm. Also, improvements on the exercise test were observed in the conventional arm. Whether there was a significant difference in the improvement between the two groups was not reported.

Barst et al.[12] randomised 81 patients between conventional therapy and conventional therapy plus continuous infusion of prostacyclin. The two groups were compared at one week, six weeks and 12 weeks. In addition to measuring patients' haemodynamics, exercise tolerance was compared using the six minute walk test, and quality of life was compared using the Nottingham Health Profile (NHP). At 12 weeks, eight out of the 40 patients on conventional therapy had died compared to none of the patients on prostacyclin; exercise tolerance was significantly higher for patients on prostacyclin ($p<0.05$), and scores on the NHP had also improved. However, the results only relate to a short period. Follow-up studies[13] were uncontrolled, but indicated striking survival benefit until two years.

Evidence from Cremona[7] showed that in patients with more severe disease, indicated by mixed venous oxygen saturation below 60%, treatment with prostacyclin improved survival at two and three years. These results suggest that prostacyclin offers greatest benefits in treating patients with a poorer prognosis.

Another possible benefit to this sub-group of patients is that the increased chance of survival in the first two years of treatment may allow a patient to survive long enough to undergo an HLT. Higenbottam et al.[8] found that the chances of a successful HLT were doubled by treatment with prostacyclin. Patients most likely to benefit from an HLT are younger patients with no other systemic disease.[14] The synthetic analogue of PGI_2, iloprost, has similar properties when intraveneously infused into PPH patients, both in terms of acute vasodilatory properties[15] and long-term physiological improvement.[16]

2.2 Conclusions on Direction of Evidence and its Quality

PPH is a rare disease and this in itself has limited large scale randomised controlled studies on the efficacy of prostacyclin. Only one such study for PGI_2 has been reported.[12] It should be noted that the efficacies of other treatments in current use for PPH have not yet been tested by randomised controlled trials.

There is, however, good evidence showing improvements in physiological and psychological well-being for patients on prostacyclin. Patients with less severe disease appear to experience no survival benefits from prostacyclin compared with conventional treatment. However, by defining a sub-group comprising the more severely ill patients, improvements in two and three year survival can be demonstrated.

Observations on prostacyclin can be generalised to newer analogues such as iloprost.

3. COSTS AND BENEFIT IMPLICATIONS OF ADOPTING INTERVENTION

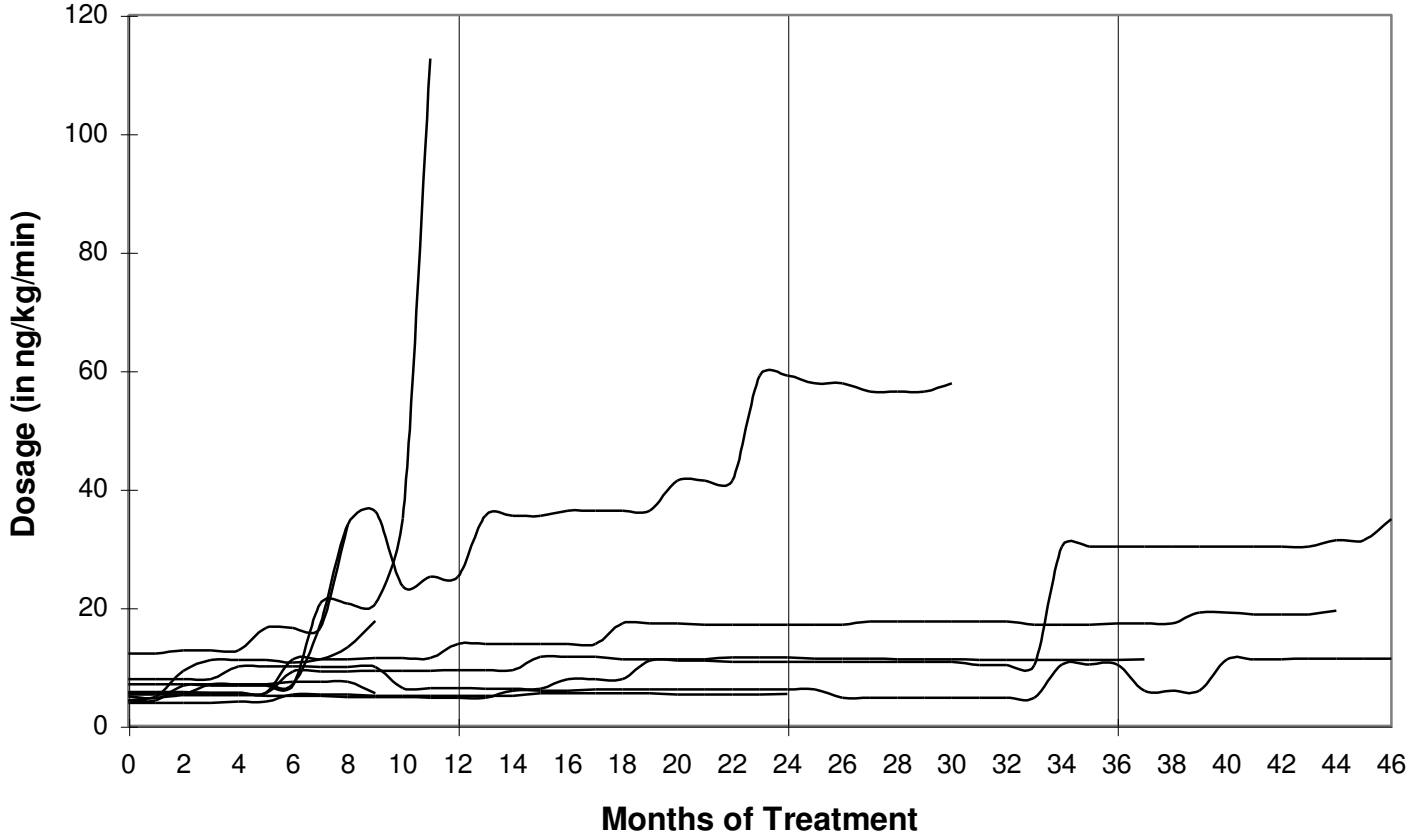
3.1 Costs

The major cost of treatment using prostacyclin is the cost of the drug. Reported price ranges have been as high as £75,800 to £500,000 per patient per year.[6] However, long-term users of prostacyclin for PPH can negotiate price reductions of up to 50%.[4] The cost per patient is typically around £45,000 per year. Experience in Trent has shown that the cost charged to one purchaser has been considerably lower, around £15,000 per patient per year. Similarly, for the analogue iloprost initial annual costs are ranging from £37 - £41,000.

The current UK price is believed to be approximately four times higher than the price in the USA. This, at least partially, reflects the difference in market size and, therefore, the relative significance of the market to Glaxo Wellcome Incorporated. Although total costs of care of a patient in the USA are similar to the UK, equipment costs and care at home are considerably higher. However, there may be some potential for achieving price reductions for the drug in the UK. Due to the relatively low number of patients on prostacyclin in any one treatment centre, negotiations should be handled nationally in order to provide sufficient negotiating power. Also, there are now two companies Glaxo Wellcome (Prostacyclin) and Schering (Iloprost). Again a national approach would offer a more effective negotiating process.

Dose requirements for prostacyclin can rise over time. Drug costs have been reported to escalate rapidly, rising up to £500,000 per year.[6] However, recent experience, in at least one major centre, suggests that dosage can be maintained at gradually increasing levels for the majority of the treatment period, only starting to rise steeply in the period immediately prior to death. Dosage levels taken from a sample of ten casenotes from patients treated at Papworth Hospital are shown in Figure 1. In only one patient is the dosage level seen to escalate rapidly; this was just before the patient died. Such an observation may be indicative of a need for alternative therapies to be considered. In six out of the ten cases, dosage levels remain below 20 nanograms per kilogram per minute (ng/kg/min). This demonstrates that, within the specialist centres, dosage levels can generally be controlled, thereby avoiding the rapidly escalating costs previously reported.

Figure 1: Dosage Levels for Patients with Primary Pulmonary Hypertension on Long-Term Infusion of PGI2
Random Sample of 10 Patients from Papworth Hospital



A potential alternative to prostacyclin exists in the form of iloprost. Iloprost has a similar molecular structure and is similar in function to prostacyclin.[15,16] Early evidence, based on a small number of patients, suggests that iloprost, like prostacyclin, produces significant improvements in exercise tolerance. Although the impact on long-term survival has not yet been demonstrated, iloprost may well offer similar benefits to prostacyclin in the long-term treatment of severe PPH. If the costs of iloprost prove to be lower than those for prostacyclin it could provide a more cost-effective treatment alternative in the future.

Other treatment costs, including equipment, training and follow-up are less significant. Initial investigation costs are approximately £2,000, with follow-up costs of around £250 at three monthly intervals (figures for Sheffield). These costs are incurred whether or not the patients receive prostacyclin or conventional therapy. Equipment costs for prostacyclin patients include the costs of two pumps (approx. £500 each), long-lasting intravenous cannulae, plus consumables. Additional costs may include antibiotics and re-siting of the subcutaneously tunnelled line.

3.2 Benefits

The majority of studies on the use of prostacyclin in PPH have not reported long-term follow-up data. Jones et al.[10] reported no significant impact on the progression of the condition from using prostacyclin. Higenbottam et al.[8] found that survival beyond two years was not significantly different between patients on prostacyclin and those on conventional therapy. However, for patients with more severe disease (i.e. mixed venous oxygen saturation (SvO_2) < 60% and evidence of right ventricular failure) treatment with prostacyclin improves two and three year survival.[8] Mean survival until death or transplant was 752 days and 303 days for patients on prostacyclin and patients on conventional therapy respectively. In follow-up studies from the North American Study[12] survival of 80% at two years in PGI_2 treated patients was reported.[13]

Higenbottam et al.[8] also found that the chances of a successful HLT were increased by treatment with prostacyclin. These are subject to significant uncertainty. Evidence from the International Registry of Heart Lung Transplantation indicates that mean survival for patients following HLT is around 4.5 years (Personal communication from JD Hosenpud). This figure is for patients with all conditions; survival for PPH patients may be poorer than for HLT patients generally, as has been shown to be the case for lung transplants.[17] Overall two year survivial from lung and heart-lung transplantation for PPH patients is less than 70%.[17]

Prostacyclin has been effective enough in improving quality of life for some individuals to cause them to remove themselves from the transplant scheme register, at least on a temporary basis. Once exercise tolerance has dropped to pre-treatment levels, despite increasing doses of prostacyclin, patients are likely to return to the register.

Heart-lung and lung transplantation both offer a means to correct the physiological abnormality in PPH. However, the role of lung transplantation has not been fully evaluated. Early evidence confirms that haemodynamic benefit occurs[18] although the longevity of these benefits depends on graft survival. There is evidence of increased risk of early pulmonary hypertensive crises and reperfusion oedema in single-lung transplantation.[19] Double lung transplantation, on the other hand, has a high incidence of airway complications.[19] Long-term (>3 months) obliterative bronchiolitis develops in the engrafted lung causing disability and death. Within five years over 30% of patients have died and 30% are disabled.

Very little work has been done to date on the cost-effectiveness of transplantation. A recent American pilot study by Ramsey et al.[20] suggests that lung transplantation is expensive when considered as a therapeutic treatment for pulmonary disorders. This was principally as a result of the high cost of post recovery care. Transplants are unlikely to be cost-effective unless offering significant gains in life expectancy. Further work is required in the UK to consider in more detail the cost-effectiveness of transplants as a treatment for PPH.

There is little information from published literature on quality of life gains from treating patients with prostacyclin rather than conventional therapy. Outcome from trials is generally measured in terms of exercise capacity and haemodynamic improvements. However, Barst et al.[12] assessed the impact on quality of life using the Nottingham Health Profile. For patients on prostacyclin significant improvements were seen on two out of the six dimensions - emotional reaction and sleep.

3.3 Evidence on Cost-effectiveness

Modelling work has been undertaken to provide a **crude** indication of cost per Quality Adjusted Life Year (QALY) from the limited information available. The figures generated are intended to illustrate broad orders of magnitude only.

Forecasts for the incidence of PPH in the UK vary between 40 and 60 per annum, of which only 40% (around 20 patients) would be sufficiently unwell to be considered for treatment with prostacyclin. Therefore two cohorts of 20 patients with severe PPH are modelled over a ten year period. One cohort is assumed to be treated with prostacyclin, the other with conventional therapy. The marginal costs and benefits of treating patients on prostacyclin rather than conventional therapy are estimated and expressed in terms of £ per QALY.

3.3.1 Assumptions

The following assumptions have been made:

(1) All patients have severe PPH, with mixed venous oxygen saturation below 60% (sampled from pulmonary artery).
(2) Prostacyclin costs start at around £47,000 per annum, rising by an average of 28% per annum.
(3) The cost of prostacyclin is the only significant difference in costs between prostacyclin treatment and conventional therapy.
(4) The probability of an HLT is approximately double for patients on prostacyclin compared with patients on conventional therapy.
(5) Mean life expectancy following heart-lung transplantation is 4.5 years.

The survival figures used in the modelling are based on survival data from Cremona[7] for patients with severe PPH, indicated by mixed venous oxygen saturation below 60%. These values, shown in Figure 2, indicate that treatment with prostacyclin may improve survival at two and three years.

The dosage levels are based on the average dosage levels of patients from the sampled casenotes from Papworth Hospital. Over the four year period the annual dosage started at 10.3 ng/kg/min and increased by an average of 28% per annum. From year five onwards it has been assumed that the average annual increase of 28% was maintained.
Costing information was calculated for the annual average dosage levels based on a formula provided by Ms N McGarry at the pharmacy at the Royal Hallamshire Hospital, Sheffield. Costs are based on a price per vial of £61.02. Figure 3 shows the cost

assumptions for the ten year period, both for the cost per patient and the total cost for treatment of all surviving patients on an annual basis.

The NHP scores for individual patients from the Barst trial[12] have been made available by Glaxo Wellcome Incorporated. Using the three methodologies developed by O'Brien et al.[21] the NHP scores for patients on conventional therapy and patients on prostacyclin have been aggregated into a single index score. Details of the methodologies are outlined in Appendix A. The process of generating a single index of quality of life from multi-dimensional measures is not without its problems and obviously care must be taken with its interpretation. However, in the absence of better measures, it provides a starting point for modelling work.

Out of the 81 patients in the Barst trial, 12 were excluded from the analysis due to incomplete records. The quality of life measures indicated by the three methodologies were very close and are shown in Table 1 below.

Table 1: Quality of Life Indices Derived from Nottingham Health Profile Scores

GROUP ON PROSTACYCLIN					**GROUP ON CONVENTIONAL THERAPY**			
Methodology					**Methodology**			
Q of Life	A	B	C	**Mean**	A	B	C	**Mean**
At Day 1	0.67	0.67	0.65	**0.67**	0.72	0.71	0.69	**0.70**
At Day 87	0.82	0.82	0.81	**0.82**	0.72	0.70	0.68	**0.70**

Mean values for the three methodologies were calculated. The mean values of 0.82 and 0.70 were used to represent the quality of life for patients treated with prostacyclin and conventional therapy respectively.

Quality of life for patients following HLT is assumed to be 0.85. Available evidence is limited. The quality of life for patients following heart transplants in the O'Brien paper[21] is estimated to be 0.9. However, a more recent estimate for the quality of life following lung transplantation, taken from a paper by Ramsey et al.[20] is 0.8.

These quality of life values have been combined with life expectancy gains to produce an estimate of QALYs gained for patients on prostacyclin.

Using these assumptions the average cost per QALY of treating PPH patients with prostacyclin over the ten year period is £120,121. Discounting both the costs and benefits over the ten year period, at the 6% level, increases this figure slightly to £127,244 per QALY.

Based on an annual incidence of 20 patients with severe PPH per year, the annual drug cost to the NHS for prostacyclin would be approximately £2.9 million.

The short life expectancy and the high cost of prostacyclin result in a cost per QALY above the level normally considered acceptable within the NHS. Typically, interventions with a cost of more than £25,000 per life year are unlikely to be considered.

3.3.2 Sensitivity Analysis

(a) Cost of Drug Treatment

The cost assumptions are subject to major uncertainties. The results of the modelling work are sensitive to these cost assumptions. If the dosage levels of prostacyclin are assumed to escalate more rapidly, say doubling every 12 months, with prices rising to a maximum of £500,000 per annum, the undiscounted cost per QALY increases to over £270,000.

The central scenario assumes that the price of prostacyclin will remain at current levels. It is possible that the price reductions can be negotiated with Glaxo Wellcome Incorporated. However, this reduction would need to be in the order of 85% for the illustrative QALY figures to approach £25,000.

Early evidence suggests that iloprost may offer an alternative to prostacyclin. Typically starting dosages are around 2 ng/kg/min, at an annual cost of approximately £37,000-£41,000. Evidence on the likely escalation in dosage is required to determine the cost-effectiveness of iloprost relative to prostacyclin. Even taking the extreme assumption that dosage levels do not escalate over time, using the current modelling assumptions, the cost of the starting dose of iloprost would need to be reduced by more than £15,000 per annum for the illustrative QALY figures to approach £25,000.

(b) Survival

The survival data from the Cremona study are only available for five years for the patients on prostacyclin and six years for patients on conventional therapy. It is assumed that the remaining patients die in the year following the last available data. However, if it is assumed that the remaining patients survive for the rest of the ten year period, this increases the undiscounted cost per QALY to just under £179,000.

(c) Quality of Life

The quality of life figures are also very uncertain. To illustrate the potential impact of these uncertainties on the results two sensitivity analyses have been undertaken.

Firstly, the index of quality of life for the group on prostacyclin is maintained at 0.82 and reduced by 0.2 to 0.5 for the group on conventional treatment thus increasing the benefits of being on prostacyclin. This reduces the undiscounted cost per QALY to just over £54,000.

Secondly, the index of quality of life for the group on prostacyclin is reduced by 0.2 to 0.62, whilst the index for the group on conventional treatment remains unchanged at 0.7. This increases the undiscounted cost per QALY to just over £179,000.

(d) Heart-Lung Transplantation

Records from patients treated at Papworth Hospital from 1982 onwards show that for patients with severe PPH treated with prostacyclin (n=26), 7 received an HLT and 13 died prior to transplantation. This compares with the patients on conventional therapy (n=13), none of whom received an HLT. Using these figures to model the relative probability of receiving an HLT for the two groups results in a decrease in the cost per QALY to £87,851.

4. OPTIONS FOR PURCHASERS AND PROVIDERS

Several possible policy options were presented and discussed, as follows, by the Trent Institute Working Group on Acute Purchasing on 8 February, 1996:-

Option 1. The NHS should encourage the recruitment of patients with PPH to randomised controlled trials of prostacyclin and fund them out of NHS funds.

This would provide better evidence on efficacy, but the numbers of patients are too small for RCTs. It is accepted that treatment is effective, but there are uncertainties about the costs involved and the timespan of the gains.

Option 2. The makers of prostacyclin should be required to produce evidence on its cost-effectiveness in treating PPH, before it is funded by the NHS.

Again, this would provide better evidence and in this case would not impose costs on the NHS. However, it is unlikely that the drug company will undertake research, unless the market potential is substantial. In addition, there would be no control over the nature of the research undertaken.

Option 3. Prostacyclin should be prescribed for PPH only through specialist centres and according to agreed protocols which guarantee the collection of data on costs and outcomes to inform future policy decisions.

This approach has the advantage of maximising control over patient selection and total expenditure, whilst at the same time ensuring that outcomes data continue to be collected. This will allow the policy to be regularly reviewed and future decisions to be based on more and better quality data than are presently available.

Option 4. The use of prostacyclin should be proscribed.

This has the advantage of being the no cost option and removes any liability issue. Prostacyclin is not licensed for use in PPH in the UK. The question arises, therefore, as to whether it should it be funded by the NHS given that the manufacturers have no liability. This is of increasing importance since the NHS now covers medical liability in the secondary sector.

This would be a reversal of existing practice, however, and would raise ethical issues for individual current cases. Also, it is unlikely that further evidence would be produced on which to make better informed decisions.

5. DISCUSSION AND CONCLUSION

The Working Group on Acute Purchasing supports the view that prostacyclin should be prescribed for PPH only through specialist centres according to agreed protocols which guarantee the collection of data on costs and outcomes to inform future policy decisions (Option 3 in Section 4).

On the basis of the evidence available, the current cost per QALY is too high to support funding from mainstream NHS funds and any funding should be part of an agreed research programme. In view of the small number of patients involved, there is a need for the development of a national network to co-ordinate research activity. In addition, the grounds for designation as a national specialist service are strong and a case should be made to NSCAG for consideration.

Prostacyclin is only one of a range of new, expensive drugs. A broader issue exists regarding the best means of achieving the move from true research to the development of a new therapy for these drugs. The Group supports the view that such development work should be funded by Research and Development monies.

The price of prostacyclin has a major impact on the calculation of cost per QALY. Prices are only likely to be reduced by pressure from purchasers. A co-ordinated supra-regional approach to pricing is recommended. Early evidence suggests that prostacyclin and iloprost produce equivalent improvements in haemodynamics and significant improvement in exercise tolerance. Iloprost may have a role in the long-term treatment of severe primary pulmonary hypertension.

6. USE OF PROSTACYCLIN IN PRIMARY PULMONARY HYPERTENSION: SUMMARY MATRIX

PATIENT GROUP	PATIENT CRITERIA (GUIDELINES NOT PROTOCOLS)	ESTIMATED FUTURE ACTIVITY	OPPORTUNITY FOR COST SAVING	AUDIT POINTS	EFFECTS THAT COULD BE EXPECTED IN RELATION TO STARTING POINT	COST-EFFECTIVENESS
Adults and children with Primary Pulmonary Hypertension with agreed criteria for treatment	**Criteria for starting treatment:** • Diagnosis of Primary Pulmonary Hypertension • Mixed venous oxygen saturation below 60% (sampled from pulmonary artery) • Cardiac index below 2 litres per minute per m^2 and • Treatment as part of agreed research programme at major centre **Criteria for continuing treatment:** • Stabilisation or reduction of disability is seen **Criteria for discontinuing treatment:** • No response to treatment after 3 months • Development of complications • Increasing disability, even with escalating dosage	40% of affected individuals - less than 1 per year in a district of 500,000 population	Effective management of dosing to avoid escalation	1. Dosage monitoring 2. Adherence to guidelines for use 3. Mortality / survival analysis	1. Improvement in exercise capacity 2. Improved haemodynamics 3. Improved 2-3 year survival	The undiscounted cost = £120,000 per QALY and the discounted cost= £127,000 per QALY The results are sensitive to : 1. Costs of prostacyclin 2. Survival assumption 3. The number of patients receiving HLTs in the treatment groups

APPENDIX A : Methodologies for Aggregating the Profile Dimensions into a Global Score

Part 1 of the Nottingham Health Profile comprises 38 statements relating to six dimensions of quality of life - energy, pain, emotional reactions, sleep, social isolation, and physical mobility. Patients are asked to respond 'yes' or 'no' to each statement.

The statements contained within each dimension and the weights attached to them are shown overleaf.

O'Brien et al. [21] cautiously attempted to aggregate the profile dimensions into a single score using the three methodologies listed below. (The methods are presented algebraically in Appendix C of their paper).

Method A: Calculate the proportion of the 38 statements to which an affirmative answer is given and subtract this from 100.
Answering Yes to 25% of the statements would give a score of 75 out of 100.
Method B: Apply the differential weights for statements within each dimension and give equal weight to each dimension.
Method C: Apply unitary statement weights within dimensions and weight the dimension on the basis of the proportion of the total number of questions that relate to each dimension (see below).

Dimension	Weight
Energy	2.0833
Sleep	1.2821
Pain	0.7937
Social Isolation	1.2821
Emotional Reactions	0.6944
Physical Mobility	0.7937

Nottingham Health Profile, List of Statements and Associated Weights

Energy	
I soon run out of energy	24.00
Everything is an effort	36.80
I'm tired all the time	39.20
	100.0
Pain	
I'm in pain when going up and down stairs or steps	5.83
I'm in pain when I'm standing	8.96
I find it painful to change position	9.99
I'm in pain when I'm sitting	10.49
I'm in pain when I walk	11.22
I have pain at night	12.91
I have unbearable pain	19.74
I'm in constant pain	20.86
	100.0
Emotional reactions	
The days seem to drag	7.08
I'm feeling on edge	7.22
I've forgotten what it's like to enjoy myself	9.31
I lose my temper easily these days	9.76
Things are getting me down	10.47
I wake up feeling depressed	12.01
Worry is keeping me awake at night	13.95
I feel as if I'm losing control	13.99
I feel that life is not worth living	16.21
	100.0
Sleep	
I'm waking up in the early hours of the morning	12.57
It takes me a long time to get to sleep	16.10
I sleep badly at night	21.70
I take tablets to help me sleep	23.37
I lie awake for most of the night	27.26
	100.0
Social isolation	
I'm finding it hard to get on with people	15.97
I'm finding it hard to make contact with people	19.36
I feel there is nobody I am close to	20.13
I feel lonely	22.01
I feel I am a burden to people	22.53
	100.0
Physical mobility	
I find it hard to reach for things	9.30
I find it hard to bend	10.57
I have trouble getting up and down stairs and steps	10.79
I find it hard to stand for long (e.g. at the kitchen sink, waiting for a bus)	11.20
I can only walk about indoors	11.54
I find it hard to dress myself	12.61
I need help to walk about outside (e.g. walking aid or someone to support me)	12.69
I'm unable to walk at all	21.30
	100.0

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