

## APPENDIX 2

### *NORCOM POLICY ON PULMONARY HYPERTENSION*

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## **SUMMARY**

The aim of this paper is to present the NORCOM Commissioning Policy on the treatment of Pulmonary Hypertension. Until now funding of treatment has been through PCTs on named patient basis and pharmaceutical company sponsored clinical trials.

Pulmonary hypertension (PH) is a rare disorder of the blood vessels in the lung in which the pressure in the pulmonary artery rises above normal levels and may become life threatening. Conventional treatment with diuretics, vasodilators and anticoagulants has been largely unsuccessful in improving survival.

Conventional estimates of the incidence and prevalence are approximately 2-5 cases per million of population per year and 30-100 cases per million of population respectively.

Four centres have been designated by National Specialised Commissioning Advisory Group to provide pulmonary hypertension services as part of a national Pulmonary Hypertension Services Network for England and Wales. Sheffield Royal Hallamshire Hospital is one of those. National standards have been developed and pooling of data from the centres has been agreed to improve the collection of information on effectiveness of treatment protocols and to give a more accurate measure of incidence and prevalence.

Currently four high cost drugs are used to treat PH: Epoprostenol (prostacyclin analogue), Iloprost (iv and nebulised), Treprostinil (subcutaneous), and Bosentan (oral) of which two are licensed in the UK for PPH (Epoprostenol, Bosentan) and imminently Iloprost. Treprostinil is licensed for the treatment of PH in the USA although not currently licensed in the UK.

Evidence for clinical effectiveness from randomised controlled trials is available but long term outcome indicators of increased survival rate are limited to Epoprostenol although 2 year data is now available from follow-on studies from the multicentre studies examining the efficacy of nebulised Iloprost, oral Bosentan and sc Treprostinil. This data has been presented at International meetings and publications will follow.

A phase III study is currently being conducted to examine the efficacy of Sildenafil, as a treatment for PH and the results will be available next year.

Evidence on cost effectiveness is virtually absent.

There are some methodological weaknesses in the studies including short-term follow-up periods, small sample size inconsistent quality of life assessments and different patient mixture enrolled in the trials. These limitations reflect in part the nature of the disease, in particular its low prevalence and the high mortality, which has limited the duration of placebo-controlled studies to 12 weeks due to ethical concerns.

The current annual cost of treatment for patients resident in the NORCOM area is £585,000 and the projected costs for the year 2007/08 is £1,170,000.

A risk sharing approach will cost each PCT, depending on size of its population between £67,500 to £157,000. The required annual funding additional to current individual PCT spending varies between £0,00 and £39,375.

Due to the evolving nature of our understanding of pulmonary vascular disease it is anticipated that guidelines for treatment are likely to change. Similarly the uncertain incidence and prevalence and changing drug prices will require this policy to be kept under review.

## CONFLICTS OF INTEREST

Dr David Kiely has participated in clinical trials examining the efficacy of Treprostinil, nebulised Iloprost and Sildenafil as treatments for pulmonary hypertension. He currently sits on an advisory board for Actelion Pharmaceuticals, the manufacturers of Bosentan, and sits on the TRAX PMS Advisory Board and has received payment from pharmaceutical companies for organising educational seminars.

## ACKNOWLEDGEMENTS

Claire Walker has provided information from the infoflex database relating to core activity data.

## ABBREVIATIONS

<b>ADL</b>	Activities of daily living
<b>CI</b>	Cardiac index
<b>CT</b>	Computerised tomography
<b>CTEPH</b>	<b><i>Thromboembolic pulmonary hypertension</i></b>
<b>DEC</b>	<b><i>Development &amp; Evaluation Committee</i></b>
<b>IV</b>	<b><i>Human Immunodeficiency Virus</i></b>
<b>ILD</b>	<b><i>Interstitial Lung Disease</i></b>
<b>IPH</b>	Idiopathic Pulmonary Hypertension
<b>MRI</b>	Magnetic Resonance Imaging
<b>NORCOM</b>	North Derbyshire, South Yorkshire & Bassetlaw Commissioning Consortium
<b>NPHS</b>	National Pulmonary Hypertension Services
<b>NSCAG</b>	National Specialised Commissioning Advisory Group
<b>NYHA</b>	New York Heart Association
<b>PH</b>	Pulmonary Hypertension
<b>PAH</b>	Pulmonary Arterial Hypertension
<b>PAP</b>	Pulmonary artery pressure
<b>PPH</b>	Primary Pulmonary Hypertension
<b>PVR</b>	Pulmonary Vascular Resistance
<b>QALY</b>	Quality-adjusted life year
<b>RCT</b>	<b><i>Randomised controlled trial</i></b>
<b>SLE</b>	Systemic Lupus Erythematosus
<b>WHO</b>	World Health Organisation

## **DEFINITIONS**

**atrial septostomy:** surgical incision in the heart between the right and left atria to reduce the pressure in the right side of the heart

**Cardiac index (CI)** is defined as the patient's cardiac output (in litres per minute) divided by the patient body surface area (square metres). This standardises cardiac output for body size. A normal CI is approximately 2.5-3.6.

**Cardiopulmonary haemodynamics:** often used as secondary outcome measure to test efficacy of treatment and includes pulmonary vascular resistance, cardiac index, mean pulmonary artery pressure, pulmonary capillary wedge pressure, and mean right atrial pressure. They can be used as an indicator of disease severity. However, the progressive nature of this disease should preclude a single measurement of haemodynamics at rest defining patients who can and cannot receive pulmonary vascular directed therapy.

**Pulmonary hypertension:** mean pulmonary artery pressure of >25 mmHg at rest or >30 mmHg with exercise. The accepted classification of the different types of the disease is provided by WHO (2003).

The **NYHA/WHO functional classification of PH** is as follows:

**Class I** = patient has no physical limitations and ordinary physical activity does not cause undue discomfort.

**Class II** = patient has mild symptoms while doing light exercise or activities of daily living (ADLs\*), but is comfortable at rest.

**Class III** = patient has marked limitation in physical activity and difficulty doing simple ADLs but is comfortable at rest.

**Class IV** = patient is frequently bed or chair-ridden for most of the day and is too weak and short of breath to do simple activities. They manifest signs of right heart failure.

*\* The **activities of daily living** are: eating, dressing, using the toilet, getting in and out of a bed and chair, getting around inside, bathing.*

**pulmonary endarterectomy:** surgical procedure in PH patients with thrombo-emboli to reduce the high pulmonary blood pressure caused by emboli forming in the pulmonary blood vessels over a prolonged period of time.

## **1 AIM OF PAPER**

- 1.1 This paper presents the NORCOM Commissioning Policy on the treatment of Pulmonary Hypertension at the Sheffield Pulmonary Vascular Disease Unit.
- 1.2 It primarily focuses on pulmonary vascular directed therapies including Bosentan, Epoprostenol, Iloprost, Treprostinil and Sildenafil.
- 1.3 This paper is mainly based on The British Cardiac Society Guidelines and Medical practice Committee<sup>i</sup> recommendations (which are due for review), the Cochrane review on prostacyclin for PH<sup>ii</sup>, A Briefing Document For Commissioners on Pulmonary Hypertension<sup>iii</sup>, Service Specification for the National Pulmonary Hypertension Service (NPHS)<sup>iv</sup>, an update by the Regional Drug and Therapeutics Centre<sup>v</sup> and an updated literature search published until the end of September 2003.
- 1.4 This commissioning policy is to be read in conjunction with Service Specification for the National Pulmonary Hypertension Service (NPHS) of which only extracts are used in this document (see appendix A).

## **2 PULMONARY HYPERTENSION**

### **2.1**            *Definition*

- 2.1.1 Pulmonary hypertension (PH) is a rare disorder of the blood vessels in the lung in which the pressure in the pulmonary artery rises above normal levels and may become life threatening.

### **2.2**            *Signs and symptoms*

- 2.2.1 Pulmonary hypertension can be associated with apparently disparate conditions including connective tissue disease, congenital heart disease, chronic pulmonary thromboembolism, HIV infection, use of an appetite suppressant, and liver disease. If the cause is unknown then it is referred to as idiopathic pulmonary hypertension (IPH) previously known as primary pulmonary hypertension (PPH). IPH can occur sporadically or can be familial.
- 2.2.2 The cardinal symptom, breathlessness, is shared with many more common diseases and the signs of pulmonary hypertension are difficult to elicit. The delay between onset of symptoms and diagnosis is often as long as two years.
- 2.2.3 With conventional treatment (not including pulmonary vascular directed therapies), IPH is associated with a progressive course and short survival due often to the development of right heart failure: median survival after diagnosis is 2.8 years, with 1 and 5-year survival rates of 68-77% and 22-38%, respectively.
- 2.2.5 In the past, treatments for pulmonary hypertension were limited, but now several therapies are available as there is a range of drug therapies in use that have been shown to improve the outcome of PH as a result of the treatment.

## 2.3 Incidence and prevalence

- 2.3.1 Lack of systematic and often poor data collection prevents predictions of reliable morbidity, mortality and trend data. The estimated incidence (new cases) is two to five per million of the population for IPH but significantly higher for PH associated with other diseases including connective tissue disease, adult congenital heart disease and chronic thromboembolic disease. Untreated PH has a mortality of 40% per year (similar to untreated advanced heart failure and worse than most cancers).
- 2.3.2 The prevalence (total number of cases) is extremely difficult to establish but is felt to lie in the 30-100 per million of the population range with PH likely to be amenable to treatment with pulmonary vascular directed therapies of which a proportion (possibly 30% - 50%) will require expensive targeted drug therapy.
- 2.3.3 The mean age at diagnosis for IPH is 36 years with a female preponderance (1.7-3.5:1). There is no ethnic predisposition but familial IPH accounts for roughly 10% of cases of IPH.
- 2.3.4 The mean age of patients assessed at the Sheffield Pulmonary Vascular Disease Unit with all forms of PH (including IPH and PH associated with other disease processes) is 55 years<sup>vi</sup>. This reflects the demographic differences of patients with non-IPH who tend to develop PH later in life.
- 2.3.5 The Sheffield Pulmonary Vascular Disease Unit currently has 413 patients on its register of which 148 are from the NORCOM area and the table below shows the breakdown for each local PCT:

Table 1: number of PH patients on Sheffield PH register as at September 2004

Health Community	Primary Care Trust	Number on register	Number on high cost treatments	% on treatment
Barnsley	Barnsley	10	4	40.0
Doncaster	Doncaster Central	6	2	33.3
	Doncaster East	10	3	30.0
	Doncaster West	4	1	25.0
Rotherham	Rotherham	9	2	22.2
Sheffield	North Sheffield	14	4	28.6
	Sheffield South West	14	2	14.3
	Sheffield West	20	3	15.0
	South East Sheffield	32	7	21.9
North Derbyshire	Chesterfield	11	2	18.2
	High Peak & Dales	6	1	16.7
	North Eastern Derbyshire	9	0	0.0
North Nottinghamshire	Bassetlaw	3	1	33.3
<b>NORCOM TOTAL</b>		<b>148</b>	<b>32</b>	<b>21.6</b>
Other former Trent Region PCTs		30	9	30.0
Other commissioners		235	130	55.3
<b>SHEFFIELD UNIT TOTAL</b>		<b>413</b>	<b>171</b>	<b>41.4</b>

## 2.4 Diagnosis

- 2.4.1 IPH is a diagnosis of exclusion. Admission for several days is necessary to carry out a series of investigations regarding cause, baseline pulmonary haemodynamics and responsiveness to potential therapy.
- 2.4.2 The diagnostic evaluation of PH includes the following: 12-lead electrocardiogram, chest radiograph, echocardiogram, cardiopulmonary exercise testing (6 minutes walk or shuttle test), ventilation perfusion lung scan, high resolution CT scan, CT pulmonary angiogram and pulmonary function tests and in selected cases MRI and pulmonary angiography. Liver function and thyroid function studies, collagen vascular screen, and HIV antibody are useful in determining whether PAH is associated with systemic disorders.
- 2.4.3 A useful test is right heart catheterisation (although in very sick unstable patients this may be dangerous and treatment may be commenced in the absence of catheter data if other indicators are consistent with severe disease). It is performed primarily to confirm the diagnosis of PH and as indicator of disease severity. Cardiopulmonary haemodynamic measurement and vasoreactivity testing is performed to help guide therapy in selected patients, and decide on the appropriateness of calcium antagonist therapy.

## 2.5 Designated Centres

- 2.5.1 Four centres have been designated by NSCAG to provide pulmonary hypertension services as part of a national Pulmonary Hypertension Services Network for England and Wales. The network offers extensive investigation, treatment to patients with idiopathic pulmonary hypertension, pulmonary hypertension complicating other diseases such as systemic sclerosis, HIV and chronic thromboembolic disease amongst others and assessment of response to treatment. The centres and staff also provide support for patients and their families.
- 2.5.2 A service specification including standards for the delivery of care has been agreed and each centre is measured against these standards by NSCAG.
- The designated centres are:
- **London** - Great Ormond Street, Hammersmith, Royal Brompton and Royal Free Hospitals
  - **Cambridge** – Papworth Hospital
  - **Sheffield** - Royal Hallamshire Hospital
  - **Newcastle** - Freeman Hospital
- 2.5.3 Each centre has an agreed action plan to enable them to move towards meeting all the standards.
- 2.5.4 The only hospital currently designated to treat children is Great Ormond Street Hospital.

- 2.5.5 Many patients with severe pulmonary hypertension present relatively late in the course of their disease and without treatment death is likely to occur in a relatively short space of time. As a consequence it is important that there are no major delays in initiating therapy.

### **3 THERAPY**

#### **3.1 Goals**

- 3.1.1 The goals of medical therapy for PH are to improve not only the survival of the patient but also their quality of life. The assessment of quality of life must take into consideration the overall risks and benefits of the therapies available. For example many of the currently used drugs have significant adverse effects such as nausea, diarrhoea and arthralgias as well as complications from the delivery systems such as sepsis associated with long-term intravenous drug use and site pain associated with sub-cutaneous administration of treprostinil. However, the severity of the underlying disease is such that the vast majority of patients perceive some of these problems as only a minor inconvenience compared to the burden of their disease.
- 3.1.2 Treatment for PH is a fast developing area and treatment often needs to be tailored to the needs of the individual patients and given the range of conditions associated with PH the treatment options are variable and lie in several major drug groups.
- 3.1.3 PH treatment is usually given for life and is comparatively costly with targeted therapies costing between £22,500 and £37,000 per patient per annum for single therapies.

### **4 DRUG TREATMENTS**

#### **4 Conventional Treatments**

- 4.1.1 Conventional treatments for pulmonary hypertension includes oral vasodilators (particularly high-dose calcium channel blockers), although they can result in an acute deterioration in patients with severe disease and the evidence base for this form of therapy is poor (i.e. there are no controlled trials); anticoagulants; diuretics; digitalis; and supplemental oxygen. However, the disease may progress despite these.

#### **4.2 Calcium Antagonists**

- 4.2.1 These drugs should only be used in patients with good baseline haemodynamics and a positive vasodilator response. The evidence base for this therapy is poor as there have only been uncontrolled trials.

#### **4.3 Prostaglandin Therapy**

- 4.3.1 The recommendations produced by the British Cardiac Society Guidelines and Medical Practice Committee outline agents used to treat PH. It is important to recognise that these recommendations were produced prior to completion of studies examining the efficacy of Iloprost, Treprostinil and Bosentan as therapies for PH. The rationale for using prostaglandin therapy is that it reverses vascular remodelling, causing progressive improvement long-term. It is also a vasodilator, which accounts for acute clinical improvement.

- 4.3.2 The degree of reversibility of vasoconstriction of pulmonary vessels and therefore the most suitable therapy may be estimated using vasodilatation test.
- 4.3.3 Common adverse effects of prostaglandins treatment include local central intravenous line infection (in patients treated with iv drug) and sepsis, diarrhoea, jaw pain, photosensitivity, abdominal and muscle pain, and flushing.
- 4.3.4 Dangerous rebound pulmonary hypertension can occur and tolerance to the drugs may require dose increase over time.
- 4.3.5 Epoprostenol (Prostacyclin)
- 4.3.5.1 Prostacyclin was discovered in 1976. It is derived from the endothelium and has vasodilating and anti-platelet effects. It was first used in 1980 to treat a young girl suffering from idiopathic pulmonary hypertension<sup>vii</sup> and in 1990 the results of the first randomised trial were published<sup>viii</sup> and subsequently the results of a long-term follow up study.<sup>ix</sup> These studies, together with various other observations and reports, were instrumental for the approval of continuous intravenous epoprostenol (Flolan ®) in the United States of America. In the following years this therapy was also approved in several European countries. There are multiple studies reporting beneficial long-term effects of intravenous prostacyclin that clearly are superior to the acute and short-term effects.<sup>x</sup> A recent long-term study from Chicago included 162 patients over a median period of 31 months. Observed survival with epoprostenol therapy at 1, 2 and 3 years was 87.8%, 76.3% and 62.8% respectively and was significantly greater than expected survival of 58.9%, 46.3% and 35.4%.<sup>xi</sup>
- 4.3.5.2 Prostacyclin has also been used in conditions with pulmonary hypertension other than IPH. Several of the early studies included chronic thromboembolic pulmonary hypertension. This therapy has also been successfully applied in children with IPH, HIV-associated PH, portopulmonary hypertension and Eisenmenger's syndrome. The only controlled study in patients other than IPH enrolled patients with pulmonary hypertension associated with systemic sclerosis. It demonstrated a significant improvement in physical capacity and haemodynamics.<sup>xii</sup>
- 4.3.5.3 Because of a half-life of only 2-3 minutes, epoprostenol can only be applied in the form of a continuous infusion by means of an implanted intravenous catheter. In addition, because of the instability of the compound, it should be administered via a pump enclosed in a "cool pack".
- 4.3.6 Iloprost
- 4.3.6.1 This is a stable prostacyclin analogue, which has a longer half-life (time taken for quantity of substance to decrease by half) than epoprostenol. When it is given intravenously it has a number of theoretical advantages over conventional epoprostenol therapy. In particular the drug is stable which necessitates only daily change of the syringe driver. If Epoprostenol is used without a cooling system the drug should be changed twice daily as the half-life of the drug reduces its efficacy. The longer half-life also allows nebulised Iloprost administered by inhalation and so obviates the problems of long-term intravenous infusion. The main limiting factor with Iloprost is that for a sustained effect it must be inhaled every two to three hours while the patient is awake. It is anticipated that studies may evaluate the potential use of nebulised treprostinil, which has a longer half-life than Iloprost allowing it to be given 2 to 3 times per day.

- 4.3.6.2 Nebulised Iloprost was approved for IPH in the European Union in September 2003. Its launch in the United Kingdom is expected in the near future.
- 4.3.6.3 Although currently unlicensed, Iloprost is the most commonly used prostaglandin in the UK for the treatment of PH because of its ease of administration.
- 4.3.7 Treprostinil (UT-15, Remodulin)
- 4.3.7.1 This is a sub-cutaneously administered prostacyclin analogue that provides an additional mode of therapy. Currently, it offers a potentially more convenient mode of delivery than intravenous Epoprostenol / Iloprost as it can be given safely to an ambulatory patient with a novel subcutaneous delivery pump system.
- 4.3.7.2 Subcutaneous Treprostinil has been FDA approved for the treatment of New York Heart Association Functional Class II - IV pulmonary arterial hypertension.
- 4.3.8 Beraprost
- 4.3.8.1 Beraprost is a stable, orally active prostacyclin analogue with vasodilatory, antiplatelet and cytoprotective effects. Beraprost has a short half-life and therefore needs frequent administration. Studies are ongoing but this drug is infrequently used in the NHS at the present time.
- 4.4 Endothelin Antagonist**
- 4.4.1 Endothelin-1 receptor antagonist (Bosentan):oral drug  
An alternative to treatment with prostacyclins is Bosentan. It blocks the action of endothelin, a substance made in the body that narrows blood vessels and elevates blood pressure. Bosentan was licensed in the UK in May 2002 and launched in June 2002.
- 4.5 Surgical Treatments**
- 4.5.1 Transplantation (heart-lung or double lung)
- 4.5.1.1 This remains a last option for very severe disease but very few (<10) are done in the UK. Survival is lower after lung /heart lung transplantation (50%) than on prostaglandin therapy (65%). Therefore transplantation is not a realistic option for most patients.<sup>5</sup>
- 4.5.2 Pulmonary endarterectomy
- 4.5.2.1 This operation is currently only performed in Papworth Hospital, Cambridgeshire on patients with chronic thromboembolic PH although in the future it is anticipated that it will be performed at a further centre in England.
- 4.5.3 Atrial septostomy
- 4.5.3.1 Clear criteria for this procedure are not agreed and should be carried out in a designated centre only. The advantage of reducing the pulmonary pressure is often greater than the disadvantage of reducing the systemic oxygen levels. No controlled trial data is currently available.
- 4.6 Other Therapies**

4.6.1 Inhaled nitric oxide therapy  
4.6.1.1 This gaseous drug is mainly used in the diagnostic phase to predict a response to prostaglandin. There is little published data looking at the long term administration of this drug.

4.6.2 Sildenafil (Viagra): oral  
This is a selective inhibitor of phosphodiesterase-5 (PDE5) and causes vasodilatation. Clinical case reports and small series suggest acceptable tolerance and symptomatic improvement following oral treatment with Sildenafil alone or in combination with Iloprost or Epoprostenol in patients with PH. The result of a phase 3 trial will be available in 2004.

## **5 EVIDENCE BASE**

5.1 A literature search was done on the Medline and Embase databases up to the end of September 2003 using the drug names (Epoprostenol, Iloprost, Treprostinil, Beraprost, Sildenafil), PH and/or costs as search terms in the major descriptors area of publications. No language exclusions were made. Also HTA and Cochrane databases were assessed.

### **5.2 Clinical effectiveness**

5.2.1 Many studies have limitations regarding the small sample size, non-randomisation of treatment and limited duration of follow-up.

### **5.3 Prostaglandin therapy (Epoprostenol, Iloprost, Treprostinil, Beraprost)**

5.3.1 There is a large body of evidence demonstrating clinical effectiveness of Epoprostenol (prostacyclin) use on both quality and quantity of life in.<sup>1,2</sup>

5.3.2 The largest gains from treatment are among the cases with more severe disease (NYHA III, IV)

#### **5.3.3 Epoprostenol**

5.3.3.1 Most of the published clinical trials studied patients in WHO functional classes 2-4 and lasted between 12 and 16 weeks. The main primary end point was a measurement of exercise capacity as defined by the six-minute walk test (which measures how far someone can walk in six minutes and has been shown to be a good surrogate marker of morbidity). The main secondary end points were improvements in pulmonary haemodynamics (at rest) and breathlessness. Three randomized studies (Badesch 2000, Barst 1996, Rubin 1990) including 216 patients demonstrated that the continuous intravenous infusion of Epoprostenol improved functional capacity by increasing the walking distance by around 90 meters, cardiopulmonary haemodynamics, and survival in patients with severe PAH.<sup>ii,iii</sup>

#### **5.3.4 Iloprost**

5.3.4.1 The first randomised placebo-controlled multi-centre trial of inhaled prostaglandin in primary and secondary pulmonary hypertension (Olschewski 2002) showed that inhaled Iloprost was effective in patients with severe pulmonary hypertension (NYHA III and IV) with improvement in a combined endpoint of NYHA functional class and exercise capacity. Improvements in breathlessness and quality of life were also observed. It was unclear from the results and baseline characteristics

whether those with idiopathic pulmonary hypertension represented the more severe cases, and whether they responded more favourably to treatment. The dosage of inhaled Iloprost administered was much lower than an effective intravenous or subcutaneous dose. It may be that a bigger dose with a more efficient mode of delivery may show greater clinical response.<sup>xiii,ii</sup> The data from this study confirms earlier non-controlled trials suggesting that this form of therapy is efficacious.

5.3.4.2 Administration of prostaglandin via the inhaled route removes the risk of life threatening line infections and body image problems.

### 5.3.5 Treprostinil

5.3.5.1 In clinical studies Treprostinil has shown modest improvements in symptoms. A 12-week, double-blind, placebo-controlled multi-centre trial has recently been concluded.<sup>xiv</sup> The trial involved 470 patients with pulmonary arterial hypertension. Overall, the trial was adequately powered and was well described. It showed that the more severely ill patients had the greatest improvement in exercise capacity (primary endpoint) with greater doses of the drug achieving a greater effect. Symptoms and cardio-pulmonary haemodynamics also improved. It included patients in NYHA functional class II (53/469) who would not normally be treated with intravenous prostaglandin.

There were no differences in response to treatment between primary and secondary pulmonary hypertension and in mortality. The main side-effect observed was infusion site pain, resulting in discontinuation in 19 patients (18 in the active treatment group). The dose of prostacyclin given subcutaneously was equivalent to that given intravenously. There is a significant dose response to this drug and it is generally accepted that the dose of drug used in this study (9ng/kg/min) is likely to have underestimated the efficacy of this drug with target doses of 30 ng/kg/min used in usual clinical practice.

5.3.5.2 Additional studies are ongoing, designed to further elucidate its safety, tolerability, and efficacy.

### 5.3.6 Beraprost

5.3.6.1 Short-term beneficial effects on pulmonary haemodynamics and exercise tolerance have been demonstrated, but reported trials to date have only compared Beraprost to conventional medical treatment not intravenous prostacyclin. Over a 12-week period Galie et al (2002) conducted a double-blind placebo-controlled randomised trial of 130 patients. The patients in this study were not as compromised as those in the other studies (64 were in NYHA functional class II, 66 in NYHA III and none in NYHA IV). Exercise capacity improved only in those with primary pulmonary hypertension treated with Beraprost, although there was no statistically significant improvement in NYHA functional class and cardio-pulmonary haemodynamics. Patients with other forms of primary pulmonary hypertension did not show a statistically significant improvement. This included patients with congenital cardiac shunts, portal hypertension, collagen vascular diseases and HIV infection. It is not clear whether the patients with IPH were more compromised, and therefore showed a greater response. Side effects were similar to those usually associated with prostacyclin (flushing, headaches and diarrhoea).

- 5.3.6.2 A second double-blind randomised, placebo controlled study of a follow-up of 12 months of 116 patients showed no detectable benefits in symptomatic status, haemodynamics, and quality of life at 12 months.<sup>xvi</sup>
- 5.3.6.3 A cohort study of 43 patients with 5-year follow-up suggests that oral administration of Beraprost may improve haemodynamics and survival in patients with peripheral vessel chronic thromboembolic pulmonary hypertension (CTEPH), for which there is no surgical option.<sup>xvii</sup>
- 5.3.7 Endothelin-1 receptor antagonist (Bosentan)
- 5.3.7.1 In two clinical trials with a 12-20 weeks follow-up period and involving 245 people with from mainly NYHA class III, treatment with Bosentan significantly increased the six-minute walking distance, reduced their breathlessness and improved their haemodynamic parameters and functional NY-class of those taking the drug compared to those taking a placebo. In both studies, Bosentan or the placebo was given in addition to any other medications and included only PPH and PH associated with connective tissue/autoimmune disease (Scleroderma/SLE).<sup>xviii,xix</sup>
- 5.3.7.2 There is some evidence from an open-label, multi-centre, non-comparative study (n=16) that patients with HIV gain similar benefits.<sup>xx</sup>
- 5.3.7.3 The use of Bosentan requires attention to two significant risks: liver toxicity and the drug's potential to damage a foetus.
- 5.3.7.4 At present Bosentan is licensed for NYHA functional class III patients only. In future it may be used for modified NYHA class IV patients as a single agent or in combination with intravenous prostaglandins.
- 5.3.8 Sildenafil (Viagra)
- 5.3.8.1 A number of uncontrolled studies have shown benefits in terms of exercise capacity in patients with IPH. This has resulted in a phase 3 study that will report in 2004. There is some evidence that a combination of inhaled Iloprost with oral Sildenafil may have a synergistic effect, improving mean PAP and PVR (Ghofrani 2002) but larger randomised trials will be necessary before firm conclusions can be drawn.<sup>xxi</sup>
- 5.3.8.2 Sildenafil caused a significant improvement of pulmonary haemodynamics and exercise capacity in patients with severe non-operable chronic thromboembolic pulmonary hypertension (CTEPH) in a small before-after study. These findings must be confirmed by a randomised placebo-controlled multicentre study.<sup>xxii</sup>
- 5.3.9 Combination Treatment
- 5.3.9.1 Clinical trials examining the safety and efficacy of prostanoids plus endothelin antagonists or phosphodiesterase inhibitors are ongoing or planned.
- 5.4 Summary**
- 5.4.1 The prostacyclin analogues Epoprostenol, Treprostinil, Beraprost and Iloprost, and the endothelin receptor antagonist Bosentan have been tested in randomised controlled clinical trials. All compounds have improved by different degrees the mean exercise capacity as assessed by 6 minutes walking distance. Conversely, these trials differ for the severity and aetiology of included PAH patients as well as

for the effects on combined clinical events, quality of life, and haemodynamics.

- 5.4.2 Epoprostenol has been used for many years as a treatment for PAH and has been shown to improve survival compared to estimates of survival based on the D'Alonzo criteria. Follow on data from trial patients treated with Bosentan, Iloprost and Treprostinil will shortly be available. This provisional data has been presented at international meetings and suggests a survival benefit of at least a similar degree to that seen with IV epoprostenol.<sup>xxiii</sup>
- 5.4.3 Each new compound presents different side effects that may be unpredictable in the individual patient. It may also be that individual patients may respond better to different forms of therapy although currently there is no evidence to suggest any types of therapy are more efficacious for different patient groups.
- 5.4.4 At present, additional new compounds such as Sitaxentan, Ambisentan, L-arginine, and Sildenafil are studied in clinical trials. The new therapeutic options are currently in different phases of approval by regulatory agencies, and when they will become available we will have the opportunity to select the most appropriate treatment for the single patient, according to an individualized benefit-to-risk ratio.

## **5.5 Cost Effectiveness**

- 5.5.1 Few economic analyses have been published and non are available based on current practice. A Trent DEC report of 1997, using an economic model with many assumptions and a level of drug prices that have since reduced, estimated the cost per QALY as £127,000<sup>xxiv</sup> based on a drug cost of £47,000 per patient per annum. In addition clinical practice has changed significantly and IV therapy with its high non-drug costs is now used less frequently. The cost per QALY will therefore be significantly lower now due to the changes in clinical practice and the drugs being cheaper.
- 5.5.2 All prostacyclins and endothelin receptor antagonists are expensive. Non-drug service costs are also high. IV delivery requires implantation of a permanent central venous catheter, use of an external portable infusion pump, careful training of the patient in preparing the medication daily, and comprehensive follow up by fully trained medical staff. This also carries a significant risk of infection leading to prolonged inpatient stays and possible death.

## **5.6 Patient and carer perspective**

- 5.6.1 In 2002 the Pulmonary Hypertension Association carried out a random postal/telephone survey among its members.<sup>xxv</sup> A response rate of around 87% of the 100 members approached was achieved and a fair gender (79% female) and geographical distribution of involved treatment centres (24% from Sheffield). The survey confirmed the delay in diagnosis of more than one year in the majority of the cases. Many patients raised the importance of written information for patients and carers but unfortunately they often felt it to be insufficient. PH impacts on virtually every aspect of daily life and the majority of patients have to give up their job. The specialist nurse of the Sheffield designated centre is the chair and co-founder of the Pulmonary Hypertension Association.

## **6 THE SHEFFIELD SERVICE**

- 6.1 The Sheffield Pulmonary Vascular Disease Unit, based at the Royal Hallamshire Hospital, is one of the 4 NSCAG designated centres. A multi-disciplinary team provides services. It manages all forms of PH excepting children. It has large numbers of patients with IPH, PH in association with connective tissue disease and a large number of patients with chronic thromboembolic disease. In addition it provides a number of specialised services on site allowing a truly multidisciplinary approach to PH associated with HIV infection, liver disease, sickle cell disease and obstetric problems.
- 6.2 Sheffield, in accordance with NHPS service specification, is able to provide the required quality of service by a specialist team. This includes:
- Equitable access to investigation and diagnostic procedures
  - Treatment
  - 24 hours emergency access to care
  - Comprehensive care plan and support for patient and carers, including information package
  - Agreed protocols for patient follow-up
  - Monitoring of agreed outcome indicators
- 6.3 Sheffield collects surveillance data in accordance with NPHS standards. It submits the data to the national database currently funded by NSCAG.
- 6.4 Children are referred to the designated centre currently in London.
- 6.5 Patients with congenital heart disease are managed by the Sheffield PVD Unit in conjunction with a cardiologist with an interest in congenital heart disease. Currently the efficacy of treatment for this group is not known although approximately 20 % of around 2000 patients treated with Bosentan in Europe are treated for this indication.

## **7 PATIENT CRITERIA**

### **7.1 Referral and treatment criteria**

- 7.1.1 Adults with pulmonary hypertension where a diagnosis of pulmonary arterial hypertension, pulmonary hypertension due to chronic thrombotic and / or embolic disease or miscellaneous causes of pulmonary hypertension are suspected / proven, or the cause of pulmonary hypertension is not certain (see classification below) should be referred.
- 7.1.2 Patients who are being referred should normally have undergone routine blood tests, electrocardiogram, chest x-ray, spirometry and echocardiography. Some patients with pulmonary hypertension may deteriorate rapidly: referral should not be delayed in order to complete more extensive investigations.
- 7.1.3 In addition patients with systemic sclerosis should be screened on a yearly basis for pulmonary hypertension due to the high prevalence of disease and referred if they meet the criteria.

**Box 1: criteria for initiating high cost drug treatment for PH**

**Consider for patients with:**

- 1 **Pulmonary arterial hypertension** as definitive therapy or as a bridge to transplantation.
- 2 **Chronic thromboembolic pulmonary hypertension** as a definitive treatment (if patient not suitable for pulmonary endarterectomy surgery) or as a bridge to surgery.
- 3 **Pulmonary hypertension due to miscellaneous causes** or interstitial lung disease where severity of pulmonary hypertension out of proportion to the severity of parenchymal lung disease.

**Patient Indications (any of below):**

Patients in modified NYHA class III or IV, with a cardiac index , = 2.1 L/min/m<sup>2</sup>  
And/or pulmonary arterial saturation , + 63%, Rt. atrial pressure . 10mm Hg, regardless of acute vasodilatory response.

Lack of response to conventional medical treatment in patients falling within NYHA class III or IV. \*

- Conventional medical treatment includes oxygen, anticoagulants, diuretics and oral vasodilators (calcium channel blockers – these should usually only be used if baseline haemodynamics show a cardiac index . 2.1 L/min/m and pulmonary arterial saturation . 63%, and Rt. atrial pressure , 10mm Hg with a positive vasodilator response).

**Other Issues:**

Combination treatment should be considered in special cases but the rationale for each patient should be explicit.

When a patient does not respond to one form of treatment they may switch to an alternative form of therapy. There may be a transition period when a patient is on more than one drug, which would rarely exceed 3 months.

These criteria will need to be reviewed as the evidence base evolves.

8

**CLASSIFICATION OF PULMONARY HYPERTENSION**

8.1

**Pulmonary Arterial Hypertension**

- Idiopathic
- Familial
- Related to:

Connective tissue disease

Congenital heart disease

Portal hypertension

HIV

Drugs & toxins (definite: fenfluramines, aminorex, toxic rapeseed oil; probable: amphetamines, cocaine and "crack", chemotherapy; possible: phenylpropanolamine, St John's Wort)

- PAH with significant venous and/or capillary involvement (veno-occlusive disease, capillary haemangiomatosis)
- Persistent pulmonary hypertension of the newborn

## **8.2 Pulmonary Hypertension Due to Thrombotic and/or Embolic Disease**

- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries
- Pulmonary embolism (tumour, parasites, ova, foreign material)

## **8.3 Miscellaneous Causes Directly Affecting the Pulmonary Vasculature**

- Sarcoidosis
- Schistosomiasis
- Histiocytosis X
- Lymphangiomatosis
- Compression of pulmonary vessels (tumours, adenopathy, fibrosing mediastinitis)

Patients falling into the two groups below \* (8.4 and 8.5) do not normally require referral since the management of pulmonary hypertension is primarily the management of the underlying condition although in patients with severe PH in the setting of ILD there is some evidence that treating these patients improves outcome and we would be happy to review such patients in Sheffield.

## **8.4 Pulmonary Hypertension With Left Heart Disease\***

- Atrial or ventricular disease
- Valvular heart disease

## **8.5 Pulmonary hypertension With Lung Disease and / or Hypoxaemia\***

- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Sleep disorders
- Alveolar hypoventilation
- Chronic exposure to high altitude
- Developmental abnormalities

## **€ PATIENT NUMBERS FOR NORTH TRENT**

9.1 Establishing an accurate forecast of the number of cases for North Trent is very difficult but current patient numbers suggest that the prevalence locally is towards the upper end of the range referred to in paragraph 2.3.2.

9.2 Using the prevalence figure of 100 per million would give a total of 174 patients for North Trent as compared with the current level of 149 as shown in Table 1 in paragraph 2.3.5.

Of the 174 patients, some 52 could be suitable for targeted drug therapy using the

9.3 rate of 30% suggested in paragraph 2.3.2.

9.4 The resultant profile of patients within North Trent can then be compared with the current position set out in Table 1 to give some indication of the likely increase in patient number and cost for each of the North Trent health communities as follows:

Table 2: Current and future numbers of patients

<u>Health Community</u>	<u>PCT</u>	<u>Current numbers</u>		<u>Future numbers</u>	
		<u>Patients</u>	<u>Numbers on targeted therapy</u>	<u>Patients</u>	<u>Numbers on targeted therapy</u>
<u>Barnsley</u>		<u>10</u>	<u>4</u>	<u>22</u>	<u>7</u>
<u>Doncaster</u>	<u>Central</u>	<u>6</u>	<u>2</u>	<u>8</u>	<u>2</u>
	<u>East</u>	<u>10</u>	<u>3</u>	<u>11</u>	<u>3</u>
	<u>West</u>	<u>4</u>	<u>1</u>	<u>10</u>	<u>3</u>
<u>Rotherham</u>		<u>9</u>	<u>2</u>	<u>25</u>	<u>8</u>
<u>Sheffield</u>	<u>North</u>	<u>14</u>	<u>4</u>	<u>12</u>	<u>4</u>
	<u>South West</u>	<u>14</u>	<u>2</u>	<u>11</u>	<u>3</u>
	<u>West</u>	<u>20</u>	<u>3</u>	<u>11</u>	<u>3</u>
	<u>South East</u>	<u>32</u>	<u>7</u>	<u>18</u>	<u>5</u>
<u>North Derbyshire</u>	<u>Chesterfield</u>	<u>11</u>	<u>2</u>	<u>14</u>	<u>4</u>
	<u>High Peak</u>	<u>6</u>	<u>1</u>	<u>10</u>	<u>3</u>
	<u>NE Derbys</u>	<u>9</u>	<u>0</u>	<u>16</u>	<u>5</u>
<u>North Notts</u>	<u>Bassetlaw</u>	<u>3</u>	<u>1</u>	<u>10</u>	<u>3</u>
<u>NORCOM Total</u>		<u>148</u>	<u>32</u>	<u>174</u>	<u>53</u>

### **TREATMENT COSTS**

10.1 The projected treatment costs for patients on targeted drug therapies can then be derived from the forecast numbers set out in Table 2 above.

10.2 Using the lower cost figure of £22,500 quoted in paragraph 3.1.3 gives the following cost forecast, which can be compared with current notional spending to show the potential increase in cost for each PCT and health community.

10.3 The notional spending figures in the following table have been derived by multiplying the current numbers of patients on targeted therapy as per Table 2 by the lower cost projection of £22,500 for comparative purposes and therefore they may differ from the actual costs currently being met by individual PCTs although the overall total is in line with the total cost for North Trent health communities of £796,491 as at 15 September 2004.

Table 3: Current and future costs of targeted drug therapies. Based on current treatment we would expect 66% of patients to be on with oral pulmonary vascular targeted therapies (only oral licensed medication is Bosentan current cost £23820

via Clinovia, although if Sildenafil is proven to be an effective treatment the cost of this treatment will be expected to be significantly cheaper than Bosentan) and 33% of patients on Prostaglandin therapy (current cost for Iloprost and treprostinil approximately £37000) This will work out as an average unit cost per patient of £28213.33. This assumes that patients will be treated with sole therapy although it is acknowledged that combination therapy will become increasingly common as the evidence base develops. It may be worthwhile factoring in an additional cost of £2204.33 per patient, this would assume that a third of patients would be on combination therapy with Sildenafil as an add on treatment.

10.4 The above table indicates that the appropriate level of funding for targeted drug therapies could be twice the current level, with the increases falling unequally to individual PCTs and health communities, depending on their current level of commitment.

10.5 In order to address the anomalies in numbers of patients approved for targeted drug therapies highlighted in Table 1 and to reduce the level of bureaucracy associated with the Trust having to write out seeking approval for every patient, it is recommended that PCTs agree to fund a given level of activity each year, funded on a population-based risk share.

10.6 It is recommended that the transition from the current level of 26 patients to the target of 52 should be spread over a four-year period with the PCTs that are not funding the target level at the moment contributing to an increase of £146,250 per annum over that period.

10.7 The Trust would then manage the numbers of patients within the overall financial cap by rigorously applying the agreed clinical criteria.

10.8 The numbers of patients for whom targeted therapies would be available would then rise by 6 or 7 per annum from the current number of 26 to 52 by 2007/08 giving the following capped level for each year:

<b><u>2004/05</u></b>	<b><u>33</u></b>
<b><u>2005/06</u></b>	<b><u>39</u></b>
<b><u>2006/07</u></b>	<b><u>46</u></b>
<b><u>2007/08</u></b>	<b><u>52</u></b>

10.9

The cost implications for each PCT arising from this recommended approach can be summarised as follows:

Table 4: Recommended levels of increased financial contribution

---

<u>Health Community</u>	<u>PCT</u>	<u>2004/05</u>	<u>2005/06</u>	<u>2006/07</u>	<u>2007/08</u>
		Additional funding	Additional funding	Additional funding	Additional funding
		<u>£</u>	<u>£</u>	<u>£</u>	<u>£</u>
<b><u>Barnsley</u></b>		<b><u>0</u></b>	<b><u>0</u></b>	<b><u>0</u></b>	<b><u>0</u></b>
<b><u>Doncaster</u></b>	<b><u>Central</u></b>	<b><u>5,625</u></b>	<b><u>5,625</u></b>	<b><u>5,625</u></b>	<b><u>5,625</u></b>
	<b><u>East</u></b>	<b><u>0</u></b>	<b><u>0</u></b>	<b><u>0</u></b>	<b><u>0</u></b>
	<b><u>West</u></b>	<b><u>5,625</u></b>	<b><u>5,625</u></b>	<b><u>5,625</u></b>	<b><u>5,625</u></b>
<b><u>Rotherham</u></b>		<b><u>39,375</u></b>	<b><u>39,375</u></b>	<b><u>39,375</u></b>	<b><u>39,375</u></b>
<b><u>Sheffield</u></b>	<b><u>North</u></b>	<b><u>16,875</u></b>	<b><u>16,875</u></b>	<b><u>16,875</u></b>	<b><u>16,875</u></b>
	<b><u>South West</u></b>	<b><u>11,250</u></b>	<b><u>11,250</u></b>	<b><u>11,250</u></b>	<b><u>11,250</u></b>
	<b><u>West</u></b>	<b><u>11,250</u></b>	<b><u>11,250</u></b>	<b><u>11,250</u></b>	<b><u>11,250</u></b>
	<b><u>South East</u></b>	<b><u>0</u></b>	<b><u>0</u></b>	<b><u>0</u></b>	<b><u>0</u></b>
<b><u>North Derbyshire</u></b>	<b><u>Chesterfield</u></b>	<b><u>11,250</u></b>	<b><u>11,250</u></b>	<b><u>11,250</u></b>	<b><u>11,250</u></b>
	<b><u>High Peak</u></b>	<b><u>11,250</u></b>	<b><u>11,250</u></b>	<b><u>11,250</u></b>	<b><u>11,250</u></b>
	<b><u>NE Derbys</u></b>	<b><u>16,875</u></b>	<b><u>16,875</u></b>	<b><u>16,875</u></b>	<b><u>16,875</u></b>
<b><u>North Notts</u></b>	<b><u>Bassetlaw</u></b>	<b><u>16,875</u></b>	<b><u>16,875</u></b>	<b><u>16,875</u></b>	<b><u>16,875</u></b>
<b><u>NORCOM Total</u></b>		<b><u>146,250</u></b>	<b><u>146,250</u></b>	<b><u>146,250</u></b>	<b><u>146,250</u></b>

11  
11.1

## **POLICY STATEMENT**

The following statement sets out the position of NORCOM in respect of future referrals and funding requests for PH.

- As from 1 April 2004, all new referrals for PH of North Trent residents should be made to the Sheffield designated Unit based at the Royal Hallamshire Hospital.
- Patient criteria for PH treatment are listed in section 7 and 8.
- NORCOM will not fund drug treatment of PH conditions outside the agreed criteria and with drugs not approved in this agreement.
- Funding for PH will be covered for patients under the responsibility of those PCTs, which have signed up for a risk-sharing scheme, which is managed by NORCOM.
- The treatment regimens of individual patients that have already been agreed and funded by NHS commissioners prior to the adoption of this policy will be honoured.

NORCOM will only fund treatment at centres that have been accredited by NSCAG. It requires the Royal Hallamshire Hospital, Sheffield to comply with minimum standards laid out in the Service Specification for the National Pulmonary Hypertension Service (NPHS).

The Quality of Life criteria under development by Papworth Hospital is expected to become the national standard for assessing quality of life and will be considered in a next review of this policy.

The Sheffield Centre will inform NORCOM of all patients put on treatment in accordance with this policy, supplying the following information:

- The patient's NHS number or where not available the patient's name
- DOB and postcode
- The GP practice code
- The name of the drug
- The expected maintenance dose
- The cost of the drug
- The starting date for treatment
- The projected cost to end of year

- Clinical information:
  - Primary diagnosis (i.e. underlying condition)
  - NYHA functional classification
  - Cardiac index
  - Pulmonary arterial oxygen saturation
  - Right arterial pressure
  
- **Providers must notify NORCOM if:**
  - There is any change in dosage
  - If there is any change in the drug prescribed
  - If the patient is transplanted, dies or comes off treatment.

New drugs coming onto the market may be added to the list in year via NORCOM under the following circumstances:

- If they have the same or greater efficacy than current drugs
- and
- If they have an equivalent or lower cost to current treatment.

New treatments will not otherwise be considered in year unless there is evidence of very substantial benefit (which it should be noted is extremely uncommon throughout the whole spectrum of health interventions).

Equity in access and treatment should be an important principle in considering the treatment for individual patients.

New treatment regimens (combination regimens or dosage schedules which significantly increase costs) or new indications for treatment will only be considered in the context of the normal commissioning process.

NORCOM will not pick up the funding of patients coming off trials unless prior arrangements have been made at the time the patient is entered into the trial. It is seen as the responsibility of clinicians entering patients into trials to ensure that there is a proper exit strategy for the trial and that patients understand what that is.

This policy will be reviewed when further significant information becomes available, either from the Sheffield designated centre, clinical trials or NSCAG.

## **APPENDIX A**

### **SERVICE SPECIFICATION FOR THE NATIONAL PULMONARY HYPERTENSION SERVICE (NPHS)**

#### **1. PURPOSE OF THE SPECIFICATION**

- 1.1 Regulation of the commissioning of the investigation and management of pulmonary hypertension following the designation of the service by NSCAG.
- 1.2 The specification has been developed to enable PCTs, Specialised Services Commissioning Groups(SSCGs)/LSCGs and the lead commissioners for Consortia to make service level agreements in 2003/4 for NPHS. The specification should be used by all commissioners to ensure consistency in agreements.
- 1.3 This specification will be used by the PCTs and SSCG's to monitor the performance and quality of the providers of NPHS.
- 1.4 The commissioners of the service will make decisions about funding prostaglandin and other related drug treatments for individual patients within five working days of the request having been made by one of the centres.
- 1.5 The specification has been developed to take account of agreements, related to:
  - management of pulmonary hypertension based on the *Recommendations on the Management of Pulmonary Hypertension in Clinical Practice* by the British Cardiac Society (publication in Autumn 2001 in Heart)
  - draft European guidance (in press)
  - clinical outcomes: mandatory for specialised services as part of each SSCG's monitoring programme
  - discussions with NPHS centres on benchmarking of prices and content of pulmonary hypertension care packages.
  - standards and accreditation for NPHS

#### **2. CLINICAL PRACTICE: INDICATIONS AND VOLUME**

- 2.1 Indications for assessment and treatment of pulmonary hypertension have been developed to guide referring clinicians and for the purpose of service level agreements. Appropriate referrals are based on current international evidence, taking account of changes in clinical practice and changes in clinical indications for specific diseases after discussion with the designated providers of the service.
- 2.2 The categories are as follows:
  - 2.2.1 Patients referred for investigation to establish or exclude a diagnosis of pulmonary hypertension.
  - 2.2.2 Treatment and follow-up of pulmonary hypertension which is:
    - Pulmonary arterial including familial, primary, and PH associated with connective tissue diseases, exposure to toxins, portal hypertension, shunts associated with congenital heart disease and HIV

- Thromboembolic where surgical pulmonary thromboendarterectomy is not immediately indicated
- Miscellaneous causes such as sarcoidosis which may respond to current drug therapies for pulmonary hypertension

2.2.3 The providing centres will be those detailed in 3.1

2.3 The clinical protocol is based on the British Cardiac Society guidance and will provide the basis for selection of patients for whom management by the NPHS is judged appropriate.

### **3. REFERRAL OF PATIENTS**

3.1 The PCTs/SSCGs will expect and encourage their local consultants to refer to those provider units that the Consortium/collective commissioning teams have contracted with in 2003/4):

- **Newcastle**
- **Cambridge**
- **Sheffield**
- **London**

3.2 Referral of patients may be elective or non-elective.

### **4. PATIENT PATHWAY**

4.1 Unless agreed otherwise between PCT and Provider a typical sequence of care will include an initial outpatient assessment, admission for investigation, admission for initiation of treatment, after care, and routine follow-up in outpatients, including re-admission if necessary.

4.2 Patient care may be transferred back to the referring hospital, but pulmonary hypertension care will need to continue at the NPHS centre.

**Note: Rare clinical exceptions to this approach must be agreed in advance with lead purchasers.**

The lead purchaser will monitor with support from referring clinicians lengths of stay and the outcomes detailed in section 5.

4.3 The NPHS consultant must report back to the referring consultant and GP on the progress of the patient. They should be informed at all stages of the patient's treatment and on how to access advice. The quality of communication between NPHS providers and referring consultants will be monitored.

4.4 There should be arrangements for direct 24 hour emergency access after discharge.

4.5 The follow-up process must run for the life time of the patient, until lung transplantation or for a period of time agreed with the referring clinician. A clinical review will be required after treatment is established between referring and provider clinicians to enhance communication, to plan further treatment and to agree on any transfer arrangements.

- 4.6 Delays in planned or agreed transfers should be audited. The clinical quality, timing and effect in terms of cost to secondary care hospitals of these transfer arrangements will be monitored.

## **5. CLINICAL OUTCOMES, INFORMATION AND AUDIT, AND CLINICAL GOVERNANCE**

- 5.1 A national database has been co-ordinated by Dr Simon Gibbs, Hammersmith Hospital and is currently funded by NSCAG. Pulmonary hypertension data for England and Wales will be analysed by one centre, working with the other centres to produce clinical outcome comparisons (with casemix analysis).
- 5.2 As a minimum, for the purposes of the SLA the consortia will want to monitor outcomes by each provider separately but duplication of data collection will be avoided. Rapid progress on outcome analysis using the database with risk modelling to follow will avoid the need for separate direct reporting to the consortia.

Note: These outcome measures include:

- Pulmonary Function Tests
- Six minute walk (distance in metres)
- Echocardiography – reduction in peak pulmonary artery pressure
- Chest X-Ray – reduction in cardiothoracic ratio.
- Quality of Life measures (v Papworth protocol)
- Survival at 6 months and 1 year on prostaglandins and analogues

Definitions and further detail on timing (i.e. interim reports on NPHS outcomes) and additional within centre data requirements to be agreed by NPHS clinicians and SSCGs.

- 5.3 Regular and documented clinical audit should be carried out and results reported to the lead PCTs/SSCGs.

Note: Proposed audit topics for 2004/5 should be agreed with the commissioners and will focus on monitoring of clinical demand, and the use of the specific clinical outcome measures outlined in 5.2.

- 5.4 A database of all NPHS activity will be maintained. Information on casemix, activity, and the agreed results of the programme should be transferred to the commissioners every quarter no later than 21 days after the end of the previous quarter.
- 5.5 Note: Each provider must share the clinical results of the NPHS programme with all referring clinicians including them in annual education and audit reviews (with emphasis on improving communication and collaboration between secondary care and NPHS units).
- 5.6 There should be arrangements in place for continuous review of patients by the Provider on a long-term basis.

## **6. STANDARDS**

- 6.1 The NPHS committee has agreed standards of care for pulmonary hypertension with NSCAG . A programme of data collection, analysis and accreditation has been developed by NSCAG with the NPHS national committee in 2001/2.

Centres should prepare for re-assessment/review of accreditation and will need to pay close attention to key areas where there may be difficulty in compliance with the national standards.

- 6.2 Standards for staffing and facilities are laid down by the Standards of Care and amendments will be agreed by the SSCGs with the NPHS National Committee for incorporation within this service specification (after the current 2003/4 commissioning intentions round).
- 6.3 NPHS centres must meet the minimum standards for specialist units. The purchaser will monitor against these standards and expect providers to provide evidence in support.
- 6.4 Each pulmonary hypertension centre should manage at least 40 patients per year to encourage a high standard of care in investigation, treatment and follow-up of patients.
- 6.5 The Provider will treat only those patients for whom the condition is included in the service agreement. (see sections 2 and 3).

## **7. STAFFING AND FACILITIES**

- 7.1 NPHS centres must provide 24-hour on-call cover. There should be appropriately trained specialised medical and nursing staff.
- 7.2 Each centre should have a named designated person acting as lead clinician.
- 7.3 There should be a full range of support staff including radiologists, pathologists, cardiac and lung function technicians, social workers, paramedic support, physiotherapy, pharmacy and palliative care.
- 7.4 Strategies for prevention, control and treatment of complications of pulmonary hypertension should be defined and updated.

Note: Supportive therapies are included in all NPHS packages and are subject to audit.

- 7.5 Beds in NPHS centres should be in a designated ward with dedicated beds. This could be part of a larger facility for the treatment of patients with cardiothoracic disease.
- 7.6 Children should be treated at Great Ormond Street Hospital for Children and, where judged appropriate and only after assessment at GOSH, treated through shared care arrangements at other centres only with a joint clinical care plan.
- 7.7 The NPHS centre should be able to perform on-site all procedures connected to the management of pulmonary hypertension or confirm to the lead purchaser that alternative appropriate arrangements have been made with another centre.

## **8. QUALITY ASSURANCE**

- 8.1 The Provider must work to written quality standards and provide monitoring information to the lead purchaser.
- 8.2 The Provider unit must fulfil the requirements of Your Guide to the NHS.
- 8.3 The centre must enable the patient's, carer's and advocate's informed participation and to be able to demonstrate this. Provision should be made for patients with communication difficulties and for children.
- 8.4 Good quality information should be made available to patients. Written information (which has been evaluated by patients) should be available at the point of referral in NPHS centres and should be used to reinforce clinical communication and to inform patients about all aspects of the condition and treatment and its effects on daily living.
- 8.5 The patient's contact with the unit in terms of attendance for day care and local shared care should be planned in consultation with the patient. The care plan should include the likely timescale for treatment.
- 8.6 The Pulmonary Hypertension Association provides a national patient-run support group and should be informed by commissioners of significant difficulties with the provision of a clinical service at any NPHS centre.
- 8.7 The environment of the NPHS centre should afford privacy.
- 8.8 The NPHS centre should have a policy on death and bereavement which is culturally sensitive and considers the needs of staff as well as patients.
- 8.9 A clearly defined after-care programme should be developed with the patient and the referring provider unit.
- 8.10 Discharge should be planned and agreed with all parties concerned, though responsibility for effective discharge lies with the consultant.
- 8.11 Post-discharge care should be agreed with the GP and secondary services.

## **9. RESEARCH**

- 9.1 National analysis and audit including outcome data analysis, coordinated through the NPHS Database in collaboration with SSCGs will be essential.
- 9.2 All experimental treatments with future funding implications should be agreed with the commissioners as pilot studies and will require prior approval. The proposed treatment protocol must have received the approval of the relevant ethical committees.

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