Pulmonary Hypertension Association UK

Registered Charity No: 1082613

Appraisal of the drug treatments used in Pulmonary Arterial Hypertension (PH)

Submission to the National Institute for Health & Clinical Excellence

May 2007

"Due to the success of the medication I am able to continue my life as normal providing I know my limitations" John aged 49

"Without treatment I would be unable to work" Shana aged 34

EXECUTIVE SUMMARY

1. Few disorders are as potentially devastating as PH. It can progressively disable the body's ability to perform the most basic function of life, effective breathing. The average time from diagnosis to death is only 30 months without effective and appropriate treatment and life long management (1).

2. PH is rarely a disease that is seen in isolation. It is commonly seen in association with many other acute and chronic diseases. These co existing conditions and diseases can by themselves devastate an individual's quality and quantity of life. The reality is that this patient cohort is extremely heterogeneous and thus makes broad generalisations of restricted value.

3. It is likely that the individual would be given their diagnosis of PH when young, most commonly in their 40's or 50's. This is a very important phase of their life with regards to personal relationships, often leading to social isolation, loss of confidence, self-esteem and increased difficulties with the very basic activities of daily living. This impact not only affects the individual with the disease but also their family members, employment abilities' and opportunities. This disease is totally distributive to their families, and importantly careers, causing a loss of income and thus creating a dependency on benefits.

4. Access to the right treatments can diminish greatly the impact of PH, and lessen the dependence on carers and spouses. There will also be less impact on the welfare system. It must also be appreciated that without effective treatment this condition will require frequent acute hospital admissions' related to right sided heart failure and untimely deaths.

5. There is a high degree of willingness amongst PH suffers to submit themselves in to clinical trials in a search for an even more effective treatment and possible cure. Many of today's PH patients in the UK have been involved in the pivotal trials of the new therapeutic agents now being considered in this appraisal. It is in these Randomised Controlled Trials that the cornerstone of therapy for patients with advanced symptoms or rapidly progressive PH can most clearly be defined. This has been the administration of systemic prostacyclin analogues by means of continuous intravenous infusion. It is our strongly held judgment that this cornerstone treatment must be the standard comparator for any NICE appraisal in this disease area.

6. PHA-UK remains firm in the principle that the management and long term care of individuals with PH must remain under the direction of one of the UK designated specialist centres. This ensure that patients, their families and carers have access to a multi disciplinary health care team that is able to support all affected by this life threatening disease. Furthermore it will ensure that the National Standards of Care for these patients is continually scrutinised and maintained. They are a rich clinical environment for high standards of research into this rare disease. Our research has shown (PHA-UK survey 2007) very powerfully that 81% of patients managed at a designated PH centre rated the support /care offered at these centres as 'Excellent' and alarmingly this fell to only 44% at none designated centres.

INTRODUCTION

PHA-UK believes that present day treatment pathways described in the Therapy Review document found in appendix one should be available to everyone who has a clinical diagnosis of PH, which crucially is made at one of the designated (by NSACG) centres in the UK, unless there are specific contra-indications to its prescription.

PH is a rare condition previously associated with an inexorable course and ineffective treatment. Over the past two decades this has changed.

PH has become increasingly recognised in association with other medical conditions and effective therapies have been developed. PH is defined as a mean pulmonary artery pressure (MPAP) ≥25mmHg at rest or 30mmHg on exercise. The third "World Symposium on Pulmonary Arterial Hypertension" in 2003 saw the clinical classification of PH revised to identify five major groups. This is of critical importance as the cause of PH defines its subsequent treatment. Patients with chronic thromboembolic pulmonary hypertension (CTEPH) can potentially be cured by surgery (pulmonary endarterectomy) and medical treatments are available for those with PH. PH is a challenging disease to diagnose accurately and treat. There is often a delay from first symptoms to diagnosis of up to three years and the diagnostic process requires invasive investigations. Before transplantation no specific treatment for PH existed, but the past two decades have seen significant advances. Therapies have been developed which improve the symptoms and survival of patients with PH. Without supportive treatment, those with severe disease had a five-year survival of only 27%, which has been increased to 54% with certain targeted therapies. Some of these treatments are often complicated and their use requires significant expertise. The investigation and treatment of certain forms of PH are currently focused at nationally designated specialist centres. In the UK centres currently exist in Glasgow,

Newcastle, Sheffield, Cambridge and London. There is also a specialist centre in Dublin, Republic of Ireland.

It is impossible to under-estimate the positive impact of decisive action as early as feasible. It is a source of great concern that it can take over 24 months for an individual with PH to arrive at a correct diagnosis (PHA-UK Survey 2007) and 45% of these individuals needed to be seen by 4 or more doctors to be given this devastating diagnosis. Clinical trials in the field of PH show a low incident of side effects for most therapies and our own research shows that amongst patients taking part in them the possibilities of side effects are outweighed by the positive benefits obtained. The vast majority reported leading fulfilling and enjoyable lives despite their condition.

The therapeutic options in this disease area are highly valued by the expert PH clinicians that lead the fight against this disease both in the UK and internationally. Both patients and clinicians are deeply concerned about the possibility that any licensed therapeutic option might be withdrawn. This would have a devastating impact on present and future generations of people affected by the disease.

Research amongst suffers of PH demonstrates the very high value placed on the present day therapeutic options by people affected by the disease. The increased life expectancy they offer is considered priceless. The therapies are perceived to improve quality of life (QoL was identified in this research to be of greater importance than increased life expectancy); they ease the shock of diagnosis and give people real hope.

The overall treatment burden of PH to the NHS in monetary terms is always going to be somewhat low given the rarity of the condition. In the context of our wider society given that the most expensive mono treatment in UK for PH is around £35K per

annum it is beneficial to compare this cost to other burdens carried by the state, for example according to the governments own figures it costs around £35K to keep a criminal in a secure unit (2).

Whilst PHA-UK welcomes this NICE appraisal of the therapeutic agents in PH it does have some major concerns that any negative guidance outcomes of this appraisal may stifle and dramatically slow down the effective treatment of this disease area which we have fought so hard to support and encourage. PH is a part of medical science that has and can continue to see rapid advances. It would be a travesty to see such exciting and life changing developments slowed down.

Our main aim in this submission is to ensure that the views and experiences of people affected by PH are effectively communicated to the NICE Appraisal Committee.

PHA-UK was established in 2000. At any one time, we are in contact with approximately 2,000 people with PH within the UK.

Our mission is to ensure that people with PH can secure the care and support they need, to raise awareness amongst the medical profession and to promote research. We are entirely dependent on voluntary donations and receive no government funding. Our income in 2005/6 was just over £1 million with 80% coming from professional fundraising activities and less than 5% coming from pharmaceutical companies.

In preparing this submission we have divided our evidence into three parts:

- Published an independent review document of the currently available data for the treatment of Pulmonary Arterial Hypertension in the UK appendix one.

- Conducted the largest ever single research project in PH amongst patients with the disease in the UK. An independent researcher was commissioned to conduct a postal survey of UK patients and their families in March 2007 looking at the impact of the disease and (amongst other things) the effects of treatments. This was not limited just to PHA-UK members.

- Produced four short video films (approximately 3 minutes long) allowing very differing PH suffers to tell their stories in their own words of how PH really impacts of daily life.

The ImPAHct Survey 2007

Research Methodology

The task facing PHA-UK at the beginning of this exercise was to gather the views of people affected by PH in the UK. We recognised that the greater the number who took part in this research project the greater confidence we could have in the findings. In a patient population that is heterogeneous in their disease profiles and using multiple treatment options there was a need to ensure that such confounding variables did not prevent the true reality impact of PH and effectiveness of present day treatment regimes being clearly heard.

We therefore undertook to commission an independent researcher to design a questionnaire that was posted to all members on our data base, the data bases of other patient groups and through one of the Home Care Delivery Services. The response rate of returned questionnaires was over 45%. For the purposes of data described in this submission document only those responders over the age 18 years old are included.

The quality of the researcher who undertook this project on behalf of PHA-UK is of the highest quality:

Aline Beresford

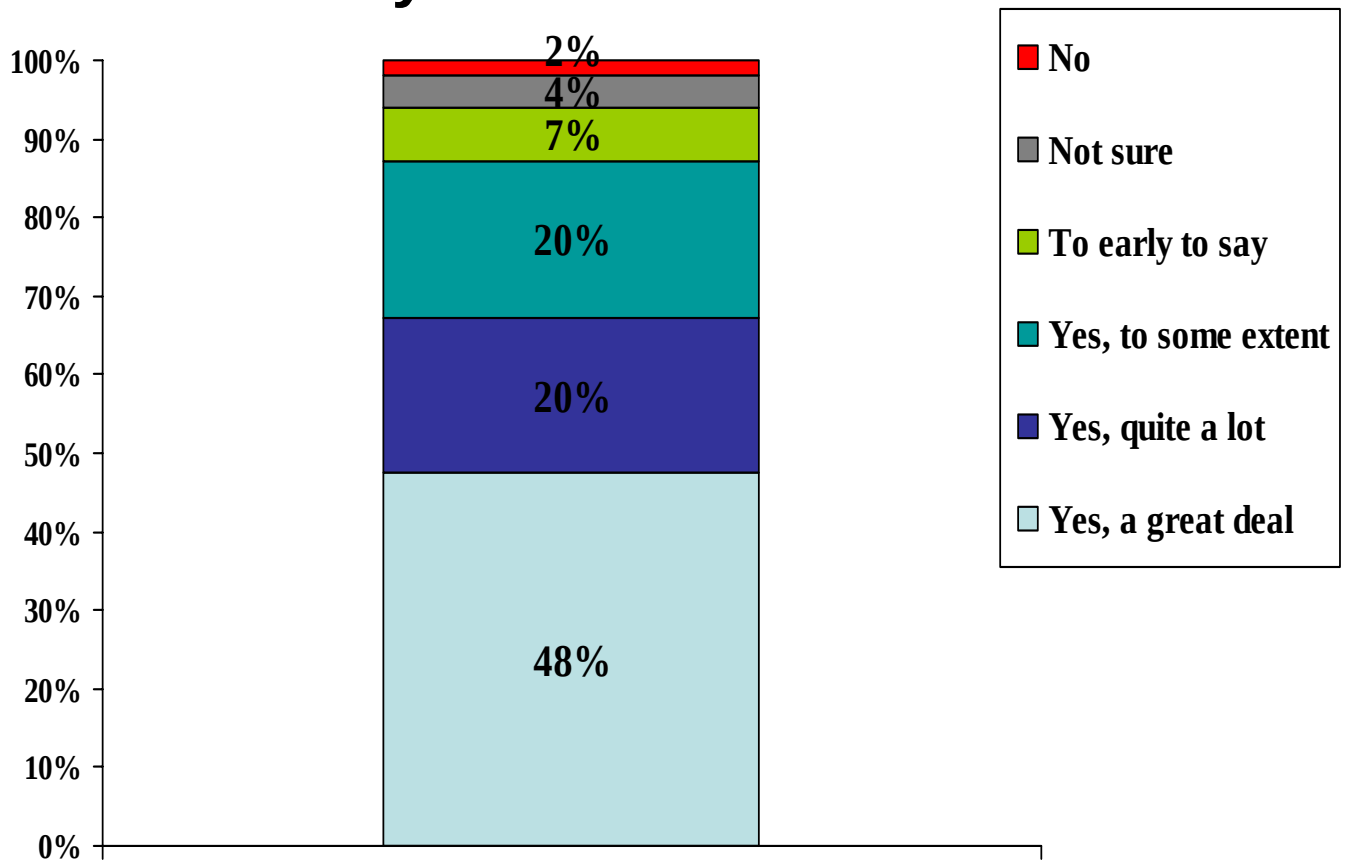
Aline started her career in the healthcare industry in 1986, after graduating from Oxford University with a degree in Biochemistry. For the last 10 years she has worked as a freelance market researcher, with a particular interest in questionnaire design and analysis of quantitative survey data, and has experience across a range of therapeutic areas. She currently holds the position of 'Executive Officer' of the British Healthcare Business Intelligence Association, a professional body that supports healthcare market researchers in upholding the highest ethical and legal standards of working.

A return rate of over 45% was extraordinarily high and clearly describes just how much this patient group want to ensure that their voices are heard and influence the decision makers. The total included in the analysis part of the research process was 540. This number of 540 far exceeds the total number included in any of the Randomised Controlled Trials ever conducted in PH, either in the UK or internationally.

Results

We have taken the decision to offer the reader of this submission the data in a way that we hope allows real clarity to what the patients and their families have said. We have avoided any excess of analysis of the data; it is our intentions to allow the true impact of this devastating disease to speak for itself whilst at the same time illustrate the dramatic effects that having access to the right treatment at the right time managed by the right professionals can have.

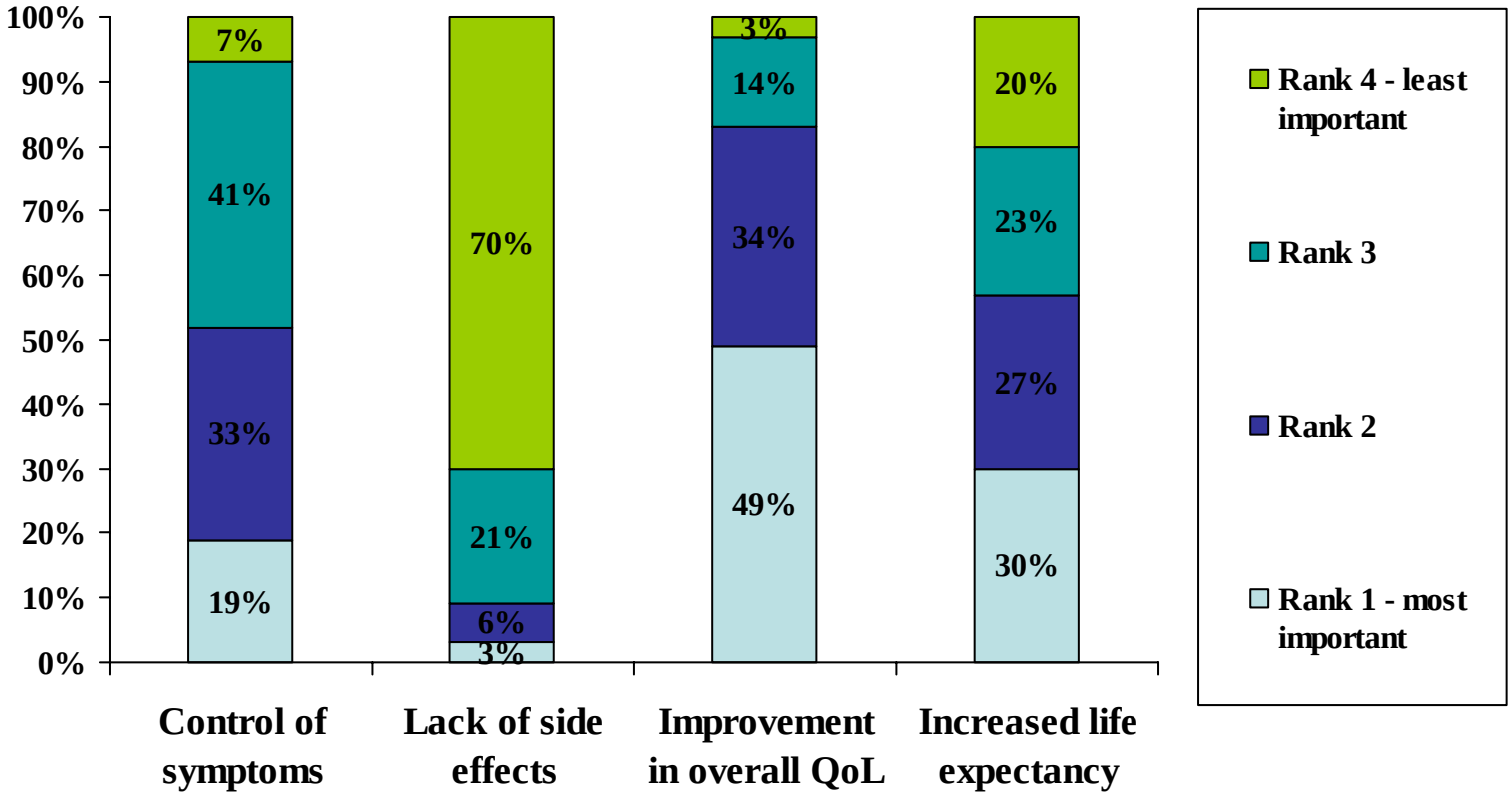
Overall, do you think you have benefited from your current treatment?



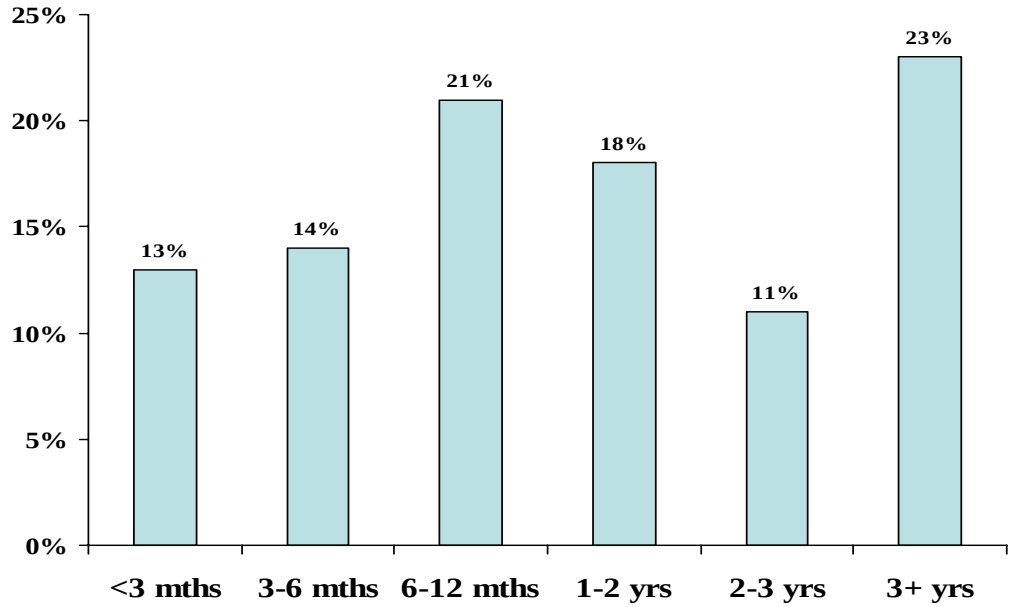
Over two-thirds feel that they have benefited a great deal or quite a lot

Only 2% stated that they derived no benefit for their treatment

How important are the following when considering treatment?



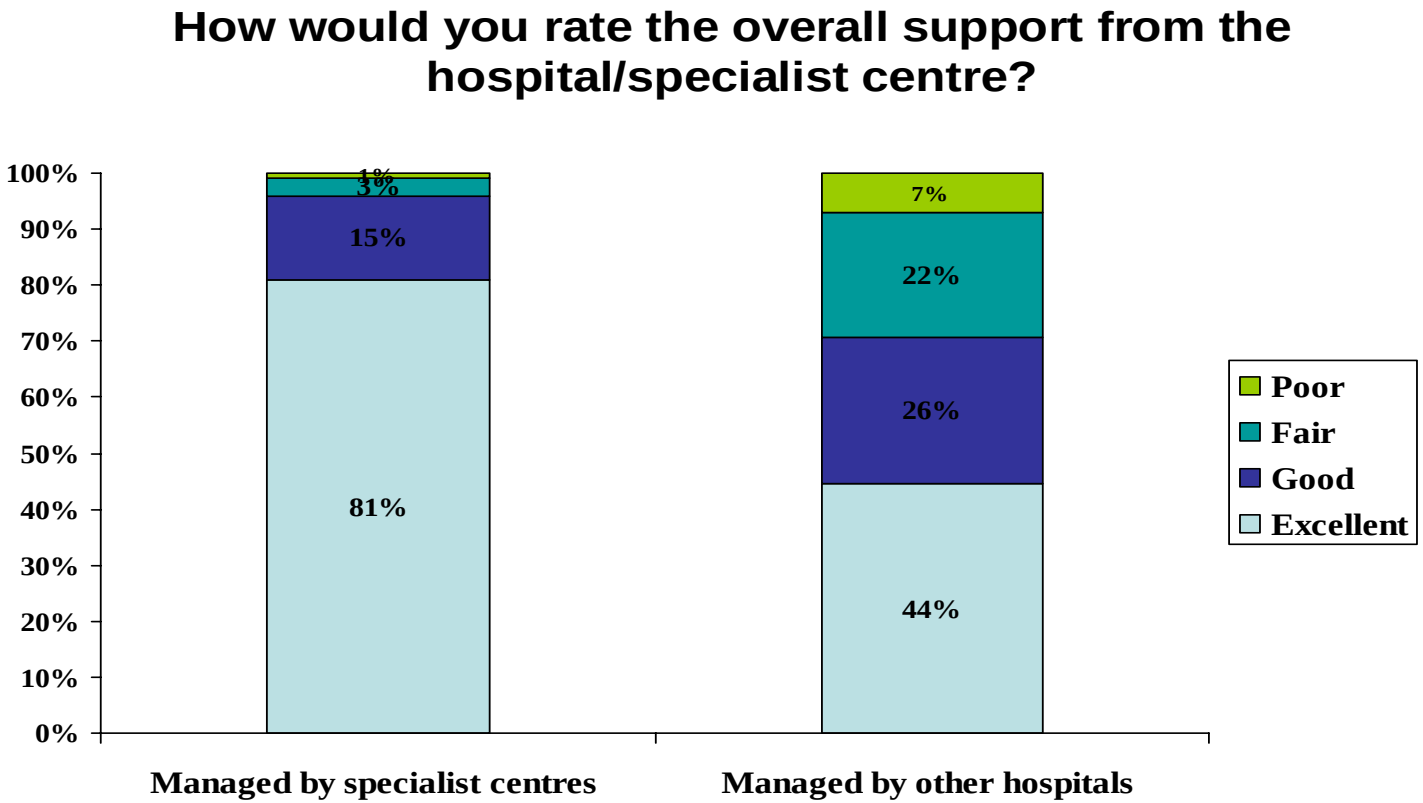
How long was it before seeing the first doctor and being diagnosed with PAH?



Mean time:

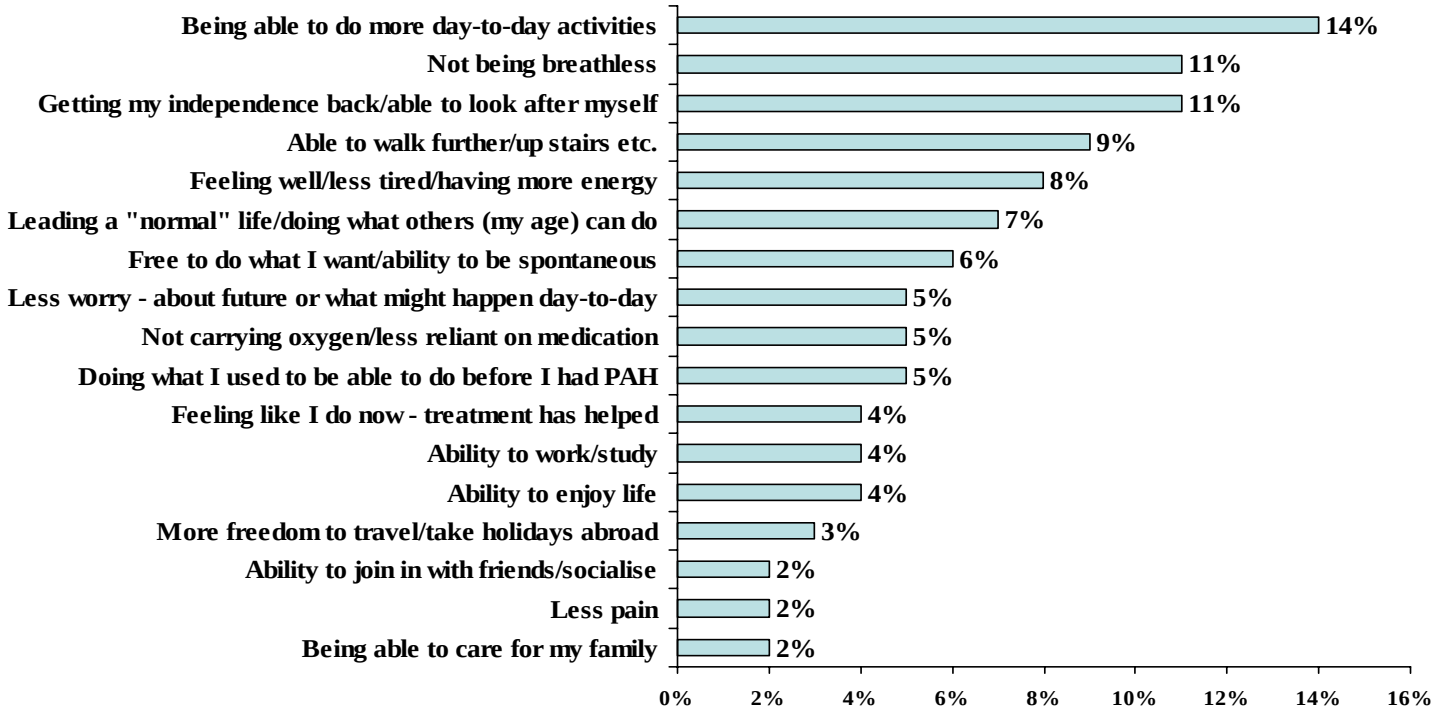
2 years, 2 months

52% waited a year or more for diagnosis; 34% waited 2 or more years, this delay in diagnosis highlights the need for swift access to treatment of this rapidly progressive and aggressive disease.

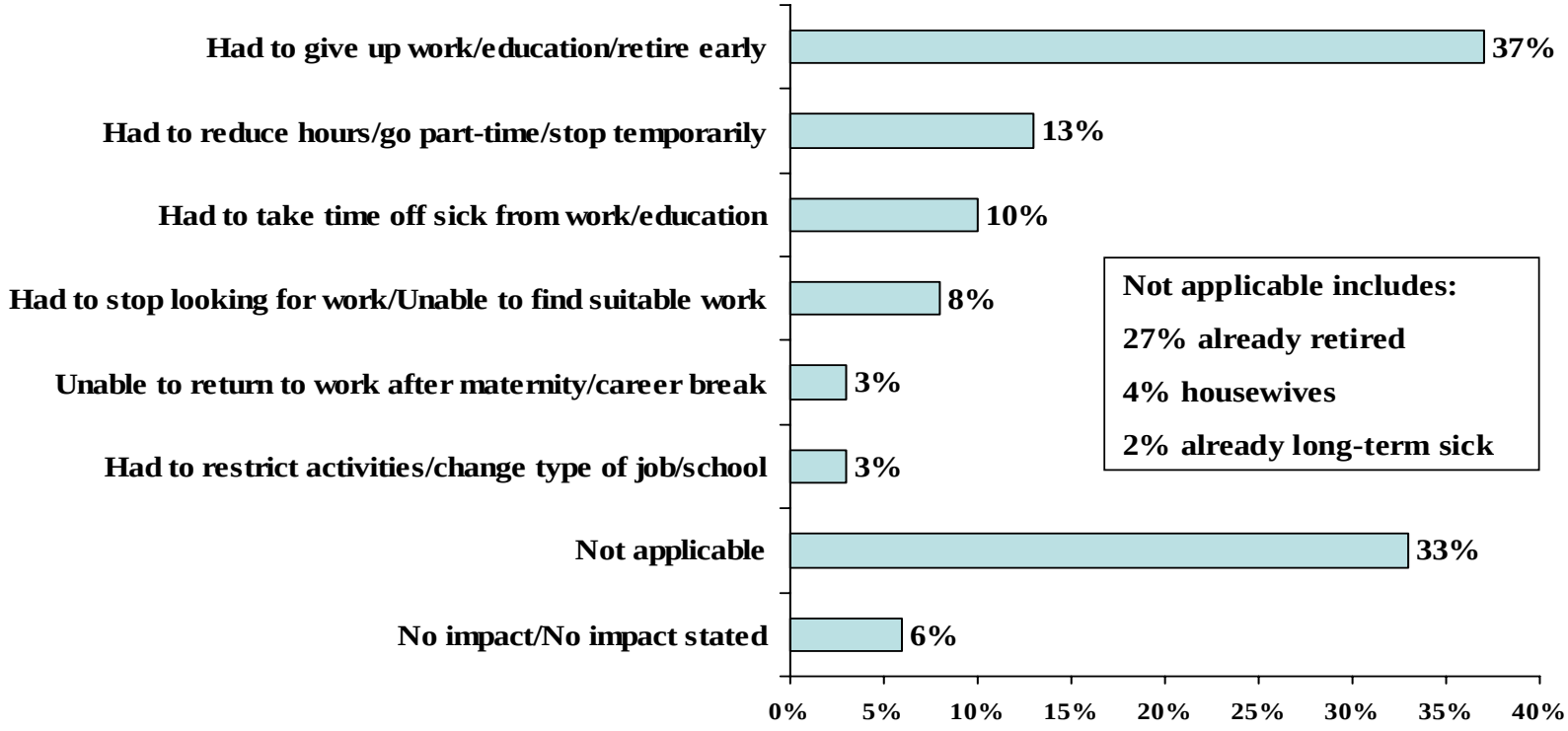


The PHA remains firm in the principle that the management and long term care of individuals with PH must remain under the direction of one of the UK designated specialist centres. This ensure that patients, their families and carers have access to a multi disciplinary health care team that is able to support all affected by this life threatening disease. It will ensure that the National Standards of Care for these patients is continually scrutinised and maintained. They are a rich clinical environment for high standards of research into this rare disease.

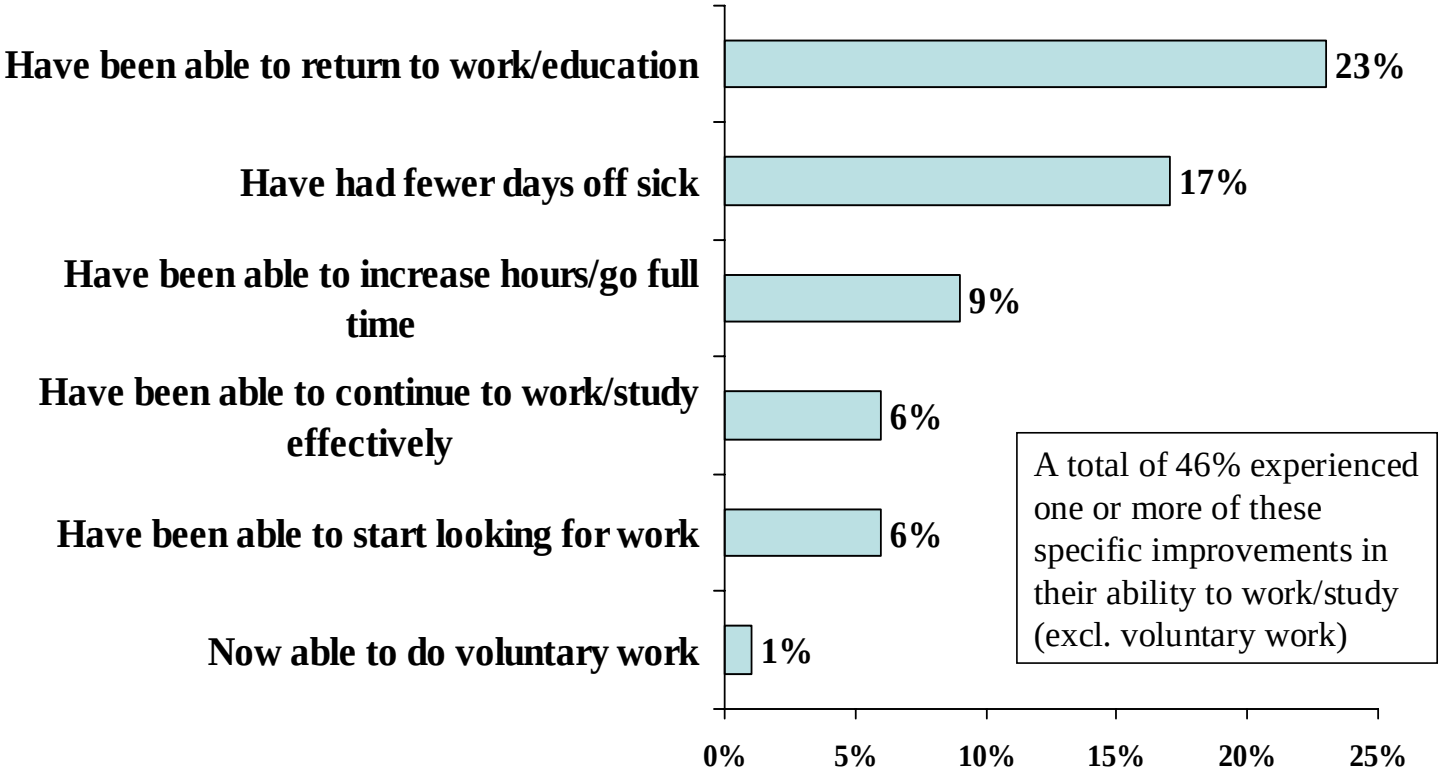
How would you define the term "improved quality of life"



Impact of PAH on work/education

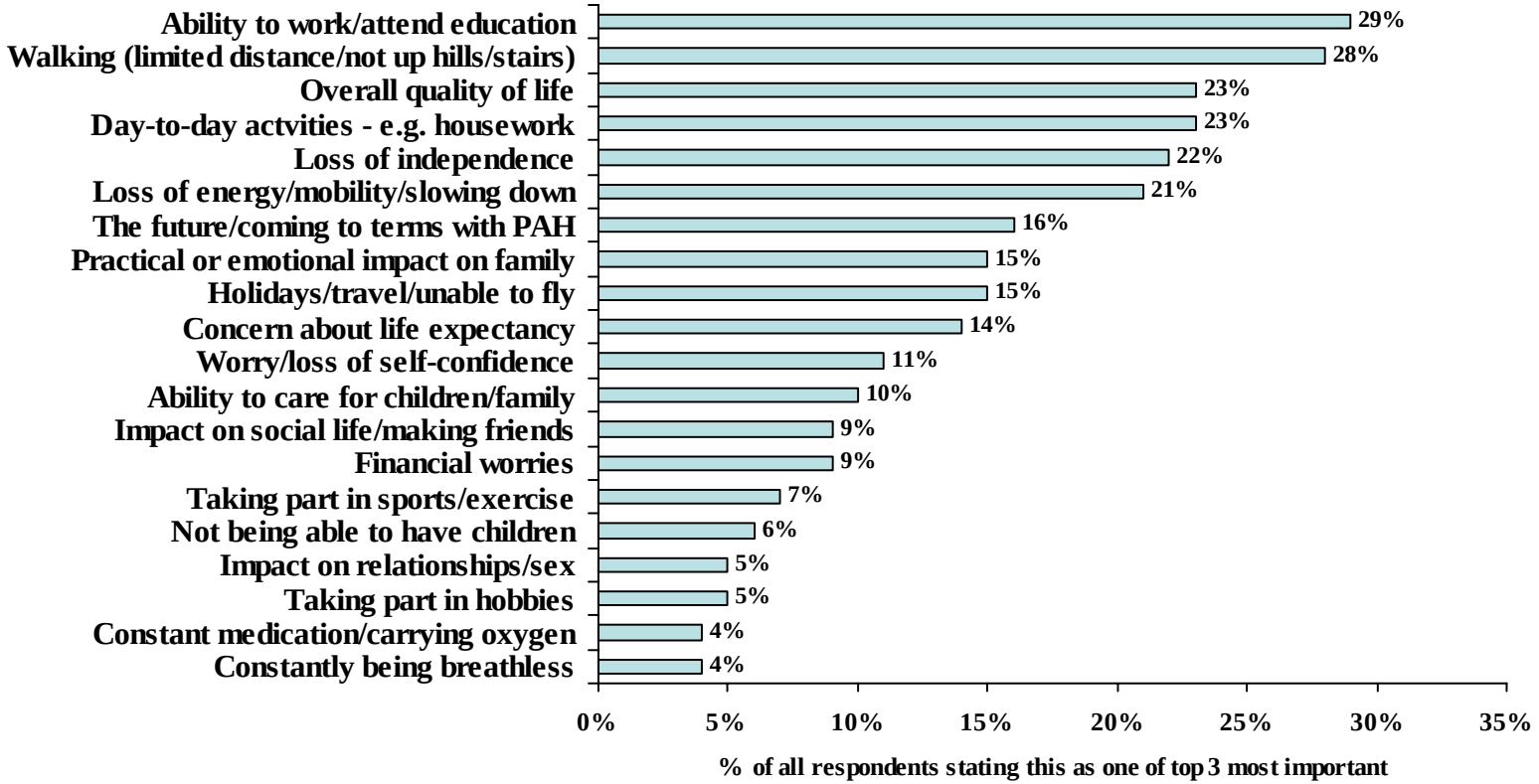


Positive impact of treatment on work/education



Almost half those whose ability to work/study has been affected by PAH, have been able to return to or remain in the workforce/in education as a result of treatment

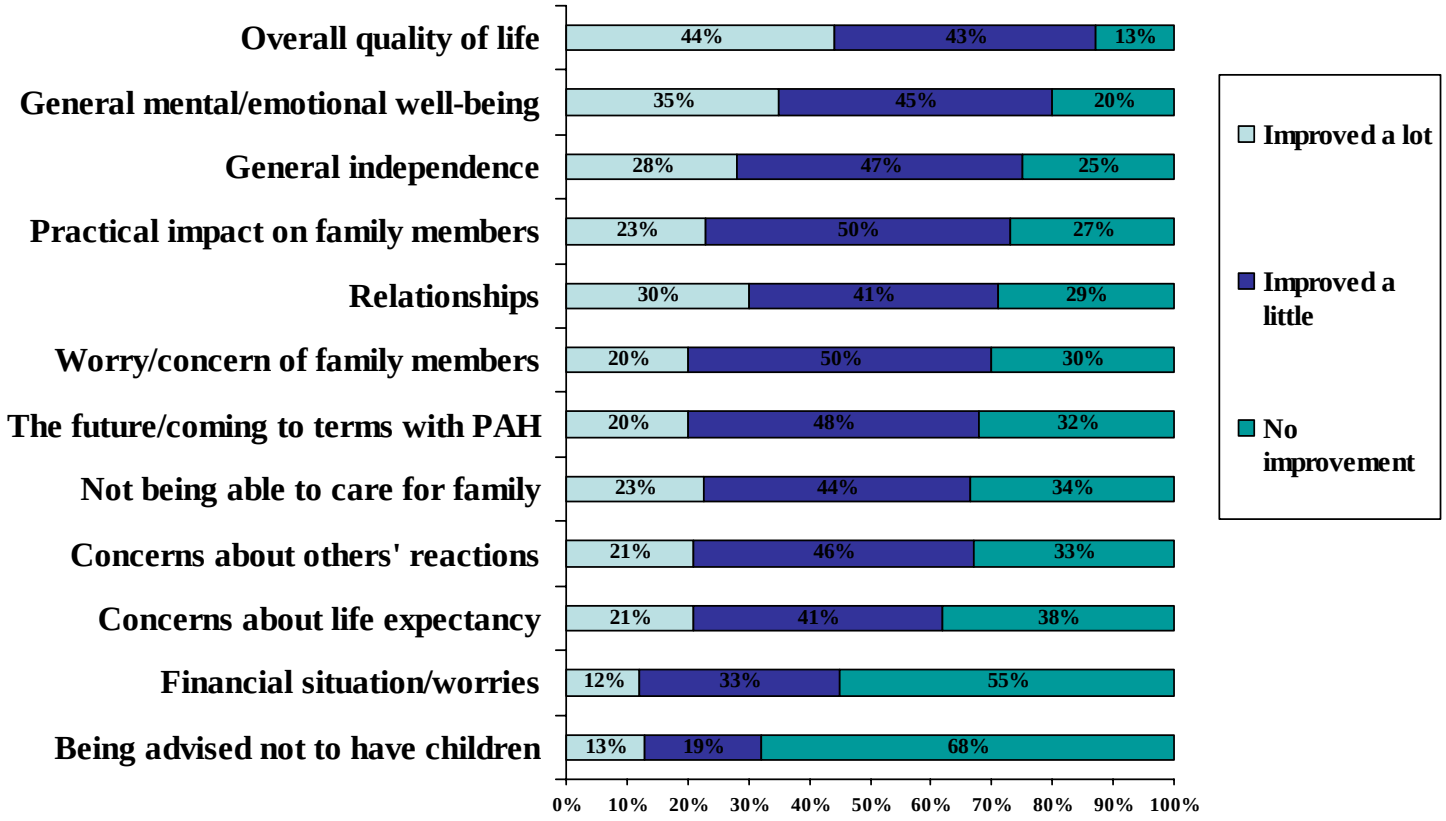
Most important ways in which PAH has had an impact on your life



Impact of PAH on family of sufferers
verbatims

- *Being a burden on family or friends*
- *Had to give up work due to increasing time off sick*
- *The major anxiety and greatly increased workload forced on my wife and family*
- *Impact on family. Children not understanding restrictions*
- *It has just put more worry and stress on my husband and children*
- *Extra work and fewer breaks for my elderly husband*
- *My wife had to take over my role both manually and financially*
- *I am a full time carer for my husband and worry as to how long I'll manage to carry on*
- *Has made my wife depressed*
- *Restricted the activities we can do as a family*
- *I can't pick my little boy up when he's upset*
- *Not able to actively take part in playing with grandchildren*
- *I felt like I was failing my 3 year old son*
- *I wish I could mind my grandchild, then she would not be at Nursery*

Impact of treatment on aspects of life –



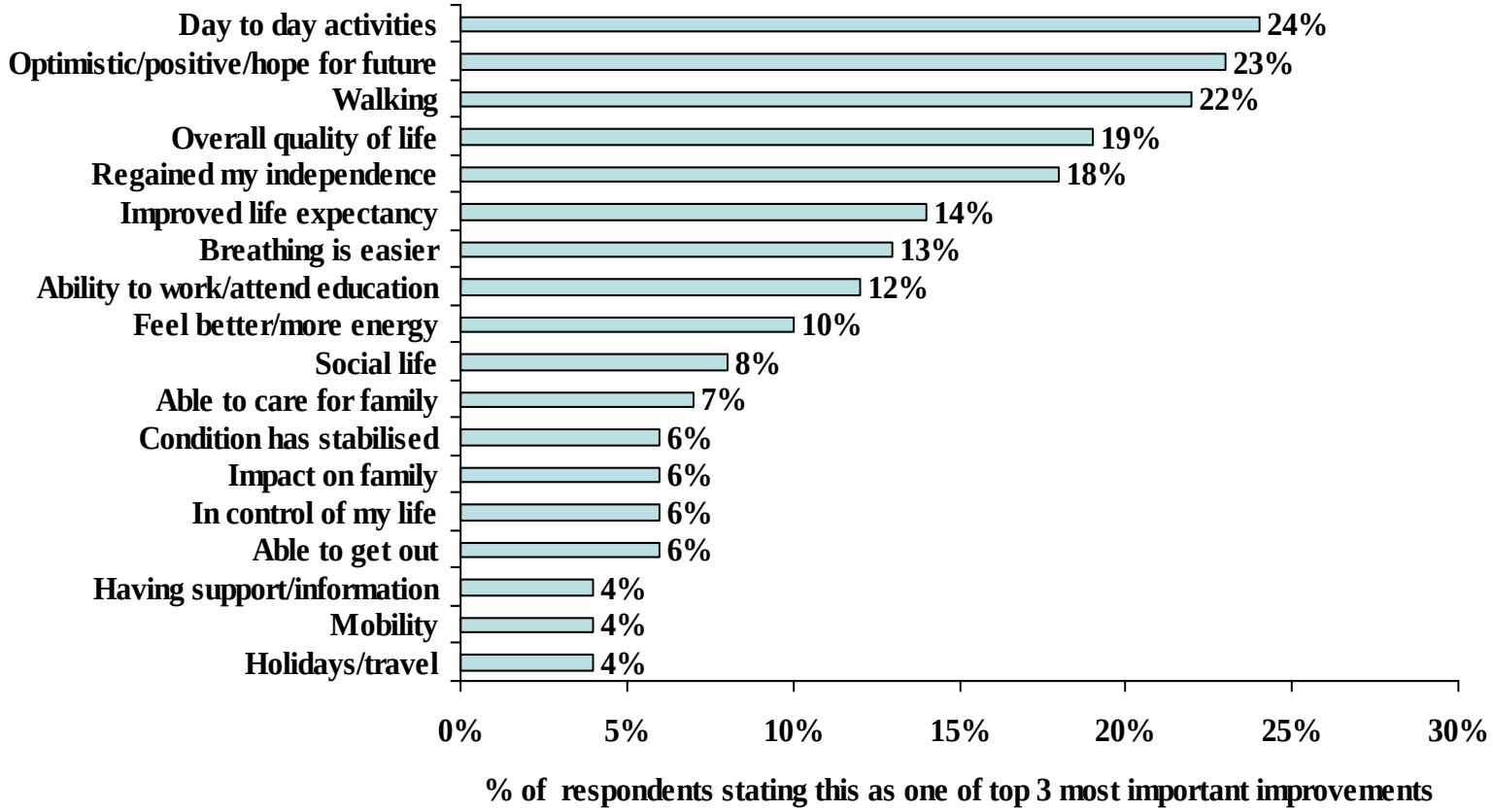
Not being able to care for a family comes higher up the list – although this is not relevant for everyone, treatment has a big impact in helping those who do care for a family

Impact of treatment - verbatims

- ***"Able to do more and have generally been given my life back!"***
- ***"Able to work, run a business, do DIY and be full member of society"***
- ***"Am able to walk short distances and drive short distances, and also return to work part-time"***
- ***"Being able to return to education and study for a degree"***
- ***"Care for myself at home, washing, going to toilet. Dressing and bathing"***
- ***"Changed from zombie back to person"***
- ***"Given hope for future"***
- ***"Has not rendered me housebound"***
- ***"I am able to look after my 11 year old son on my own"***
- ***"Quite simply, I am still alive"***
- ***"Treatment has stopped my condition from deteriorating so it is a case of not getting any worse as opposed to feeling better" therefore able to do much more than without any treatment"***
- ***"I feel able to do more to contribute to running a household"***
- ***"Look forward to do doing things that I wouldn't have done before"***
- ***"Mental attitude - It's a great relief to know what's wrong and to have correct treatment"***
- ***"My outlook upon life so improved because of the care and attention I receive"***
- ***"It has made me more robust and able to walk further and faster"***
- ***"I can now walk upstairs without getting out of breath"***
- ***"Due to success of the medication I am able to continue my life as normal providing I know my limitations"***

- ***"I feel more in control of my life than before treatment"***
- ***"It has improved my quality of life in all aspects"***
- ***"Can now manage at home without other family members helping"***
- ***"Treatment has enabled me to maintain my independence"***
- ***"Being able to return to education and study for a degree"***
- ***"Without treatment I would be unable to work"***
- ***"I now know I have a better life expectancy"***
- ***"I'm alive way longer than expected"***
- ***"Given me an energy boost, can do more than previously"***
- ***"Able to play with my 2 young children"***
- ***"The pressure on my family has eased considerably"***
- ***"My family are able to get on with their lives"***

Most important ways in which treatment has improved your life



Conclusion

The key messages from PHA-UK, and thus from the very people living daily with this disease, is that people with PH place very high value on the drug therapies under review. Not only do they extend life but more importantly they say that these therapies allow for a considerable improvement in quality of that life. PHA-UK has not offered here, a complex 'cost effective argument', just the reality of the patient's voice. The impact of the disease does not just affect the individual but there is an enormous impact on those closest to them. The burden to society can be greatly reduced by the correct use of therapies in this diseases area. It ought not to be forgotten that the answer in PH is not just a pharmacological one, there is a need for access to a highly skilled and motivated health care team that understand their holistic needs.

PH is not a respecter of gender, race, status or age. A child of 6 can find themselves battling with the very same life threatening and debilitating disease as a grandma of 65. The only difference is that the child of 6 is not being subjected to the same scrutiny around the 'cost effectiveness' of their therapies. As an Association we are left to contemplate what is to happen as the young people with PH transition to adulthood and adult care.

The arrival of the treatments options now under review by NICE do not cure this terrible disease but they do change despair into hope, prevent untimely deaths, improve quality of life and lessen the burden to society.

"Without treatment I couldn't work"

"Without treatment I would be dead"

"Without treatment I would be unable to work"

"Without treatment I would be very concerned about what the future holds for me and what my overall quality of life would be"

"Without treatment I would suffer both emotionally and financially"

References and suggested other reading

1) British Cardiac Society Guidelines and Medical Practice Committee, approved by the British Thoracic Society and British Society of Rheumatology. Recommendations on the management of pulmonary hypertension in clinical practice. *Heart* 2001; **86 (Suppl 1):** i1-13
2) HMPS Annual Report and Accounts 2004-5 Appendix 1 Statistical Information
3) Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Primary Pulmonary Hypertension. A national prospective study. *Ann Intern Med* 1987; **107:** 216-23
4) Peacock AJ. Treatment of pulmonary hypertension. *BMJ* 2003; 326: 835-836**.**
5) Gaine SP, Rubin LJ. Primary pulmonary hypertension. *Lancet* 1998; **352**: 719-725
6) Barst R J, Rubin L J, Long W A, McGoon M D, Rich S, Badesch D B, et al. A comparison of continuous intravenous epoprostenol with conventional treatment for Primary Pulmonary Hypertension. *New England J Med* 1996; **334:** 296-301
7) SPC Flolan®, GlaxoSmithKline UK, http://emc.medicines.org.uk
8) Rich S, Brundidge B. High-dose calcium channel-blocking therapy for primary pulmonary hypertension: Evidence for long term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy. *Circulation* 1987;**76**:135-141

Insert Appendix one

Pulmonary Arterial Hypertension

Therapy Review

An independent review of the currently available data for the treatment of Pulmonary Arterial Hypertension in the UK

Neil Hamilton

(August 2006)

pha uk
pulmonary hypertension association

Registered Charity No. 1082613

Introduction by Iain Armstrong

Pulmonary arterial hypertension (PAH) is a diagnosis that describes little to the individual, their families and loved ones about its potential prognosis. Often the irony of being given a diagnosis of PAH can be found in the experience told by many of our members. Many with PAH will describe how, on being diagnosed with PAH, they felt somewhat relieved that the cause of their symptoms was not something serious, like a cancer. The irony being that PAH has the potential of having outcomes worse than many forms of cancer. The disease affects both sexes and people of all ages, the mean age at diagnosis being 40 to 50 years.

PAH is a chronic and devastating disease, until the early 1990s PAH was uniformly fatal with a median life expectancy of about 2.5 years. Since the 1990s PAH has become a dynamic and exciting therapeutic arena, most recently the past 5 years have witnessed studies that demonstrate the efficacy of new, longer-acting prostanoids, specifically iloprost and treprostinil, and the arrival of two new strategies for the management of PAH, endothelin receptor antagonism and phosphodiesterase type 5 (PDE-5) inhibitors.

Despite the excitement in therapies for PAH there remains a great deal of work to be done.

All therapies for PAH are costly, £6,000 - £40,000 per annum. In the present climate of the NHS this cost remains one of the biggest challenges in its management. Although the cost of PAH therapy is significant, this is comparable to the cost of therapy for HIV patients[1] and keeping one person in a prison per annum[2]. The information in this review document clearly and independently describes the efficacy of such therapies. Any discussions about the cost effectiveness of such therapies need to take place elsewhere and is not the intention of our review here.

Nonetheless it is the view of the PHA-UK that the patient must be part of that discussion and decision-making process and crucially the expert clinicians (whom can be found at all the designated specialist centres in the UK) must have the authority to prescribe such therapies based on their expert clinical judgement. The management of PAH in the UK, identified by their designation by NSCAG, is the envy throughout the world. In many countries PAH is managed by clinicians acting in isolation with only a handful of patients they believed to have the condition. Of concern are pockets of similar practice that can be found in the UK. They defy the definition of expert and deny their patient access to the best possible care. PAH is a condition requiring not only a pharmacological approach but also intensive and time-consuming support in coping with this life limiting and debilitating disease. Such support requires an infrastructure built around experienced, motivated and qualified healthcare professionals.

We offer this review document with the caveat that a potential weakness for any study with strict criteria is that they can be highly selective and have the possibility of excluding significant sections of the patient population. This can make the generalisability of any results problematic. Studies in the treatments of PAH inevitably have exclusion criteria. This results in some of the complex patients being unable to be included. As a consequence there is limited data to support treatment of PAH patients who have certain co-existing diseases, for example liver disease or those in the older population. This places even more emphasis on the expert clinician to interpret the results in a way that will be used to guide practice in relation to the wider patient group.

This heterogeneous population is the normal patient profile for PAH clinics in the UK. The practice of excluding certain patient types from clinical studies can make them 'scientifically clean' but often not reflective of a day- to-day clinical picture. The PHA-UK firmly believe that it is only at the designated centres that such a transition from clinical trial results to practice can be safely and appropriately implemented.

Iain Armstrong

PHA-UK Chairman

[1] Mandilia S et al. *Cause and time to treatment failure of HAART and cost of care in UK NPMS-HHC clinics, 1996 2002*. HIV Med 7 (supplement 1), abstract 033, 2006

[2] HMPS Annual Report and Accounts 2004-2005 Appendix 1 Statistical Information

Therapy Review

August 2006

Neil Hamilton
Specialist Clinical Pharmacist
Pulmonary Vascular Disease Unit
Royal Hallamshire Hospital
Sheffield

The author of this review is Neil Hamilton Dip Clin Pharm, MRPharmS. Neil is a Specialist Clinical Pharmacist at the Royal Hallamshire Hospital in Sheffield. This is one of the five UK specialist centres managing patients with pulmonary hypertension and associated diseases. He has worked in the Pulmonary Vascular Disease Unit for four years. Neil is a registered Supplementary Prescriber, co-ordinates all of the prescriptions of targeted pulmonary vascular therapies, and provides a dedicated clinical pharmacy service to all patients referred to the centre. Neil has published several abstracts and was recently the author of review articles on Pulmonary Hypertension and its' treatment in the Hospital Pharmacist Journal.

This document has been written to provide an independent review of the currently available data for the treatment of pulmonary arterial hypertension.

Table of contents

Foreword

It is ten years since the first randomised trial of medicinal treatment for idiopathic pulmonary arterial hypertension (iPAH) showed benefit and suggested that efforts should be directed to treating this disease. Treatment was not easy since this first evidence was for the use of a continuous intravenous infusion of epoprostenol with its attendant complexities of administration and huge cost. The last six years have seen randomised trial evidence for two further classes of drugs which can be administered orally: endothelin receptor antagonists and phosphodiesterase 5 inhibitors. Costs have fallen. Furthermore, evidence suggests that other forms of pulmonary arterial hypertension may benefit from treatment with these agents.

Idiopathic pulmonary arterial hypertension is a rare disease, but it strikes at any age, has debilitating symptoms and shortens life expectancy. Observations in the 1970s showed that three quarters of patients were dead after five years, and that median survival at the time of diagnosis was 2.8 years. This series showed it has a predilection from young women. Disease-targeted drug therapies now improve symptoms and quality of life, and registry data shows prolongation of survival. It is now standard practice in the UK to use these drugs in patients in NYHA functional classes III and IV.

To facilitate the best access to treatment for patients, centres for the investigation and management of pulmonary hypertension have been designated in England and Scotland. These centres work closely together and provide best clinical practice through evidence – based care with careful patient selection. The UK published the first guidelines in the world for managing pulmonary hypertension in 2001 and these will be updated towards the end of 2006.

The present treatments slow disease progression but cannot offer cure. The basic mechanism of the disease is not yet fully understood. An increasing interest in pulmonary vascular disease by basic scientists is stimulating the development of new treatments, and the therapy of this disease is going to see dramatic changes over the next ten years.

Dr Simon Gibbs

Senior lecturer in cardiology at the National Heart & Lung Institute, Imperial College London and Honorary Consultant Cardiologist, Hammersmith Hospital

Summary

Pulmonary arterial hypertension (PAH)

Is a rare disease associated with a significantly reduced life expectancy. It is characterised by a progressive rise in pulmonary artery pressure and pulmonary vascular resistance which leads to heart failure and premature death.

Is a debilitating disorder associated with reduced quality of life and life long monitoring co-ordinated from a specialist treatment centre is required.

Diagnosis can be difficult which often results in the diagnosis being delayed for 2-3 years by which time the disease is more severe.

Severe PAH (NYHA class III/IV) has an estimated prevalence of 30-50 cases per million.

Treatment of PAH

Investigations and treatment of PAH can be complex requiring specialist expertise.

Historically PAH was considered an untreatable disease and there is still no cure despite the introduction of new targeted (disease specific) therapies. However, early diagnosis, rapid referral and treatment with targeted therapy can now greatly improve patient outcomes.

Conventional therapies are still used in PAH patients to improve symptoms but they have a limited effect on disease progression. Transplantation is now usually reserved for patients who fail to respond to targeted therapies.

Targeted therapies include prostaglandins (PG), endothelin receptor antagonists (ERA) and phosphodiesterase -5- inhibitors (PDE-5-I). There are currently four targeted therapies licensed for use in PAH patients; intravenous epoprostenol and nebulised iloprost (both PGs), oral bosentan (an ERA) and oral sildenafil (a PDE-5-I).

Clinical trials with targeted therapies in PAH patients have demonstrated improvements in exercise capacity, haemodynamics, symptoms and quality of life. Treatment with bosentan has also been shown to delay clinical worsening.

Survival

Patients with untreated iPAH have a median life expectancy of 2.8 years. This is comparable to the median survival time from diagnosis of certain cancer types (e.g. advanced prostate cancer and advanced breast cancer). Survival rates in untreated PAH patients at 1 and 3 years are reported at 68% and 48% respectively.

Improvements in long term outcomes have been demonstrated in patients with severe PAH (NYHA class III and IV) treated with targeted therapies i.e. PAH patients in randomised trials initiated on monotherapy with i.v. epoprostenol, nebulised iloprost and oral bosentan using recommended UK licensed doses.

In PAH patients with NYHA class II - IV high dose oral sildenafil (four times the recommended dose) has also demonstrated improvements in long term outcomes. In addition, unlicensed subcutaneous treprostinil has demonstrated potential improvements in this group of patients.

Cost of treatment

New and existing patients with PAH can be a significant financial burden to Primary Care Trusts. Treatment with targeted monotherapy (using licensed maintenance doses) can cost up to £47,000 per patient per annum. This is in addition to associated patient care costs.

Section 1: Pulmonary Arterial Hypertension

Disease background

Pulmonary arterial hypertension (PAH) is one of the five different types of pulmonary hypertension classified by the World Health Organisation (WHO) (see page 7).

It is a group of diseases characterised by a progressive increase in pulmonary vascular resistance (PVR) leading to right ventricular failure and premature death. (ESC 2004) Using measurements taken at rest by right heart catheterisation PAH is defined as a mean pulmonary artery pressure 25 mmHg, a pulmonary capillary wedge pressure of 15 mmHg, and raised PVR. (ACCP 2004)

Pulmonary arterial vasoconstriction is thought to be an early factor in the development of PAH although the disease is now known to be more complex. The main vascular changes in PAH are vasoconstriction, smooth-muscle cell and endothelial-cell proliferation, and thrombosis. (Farber 2004, Gaine 1998)

Burden of the disease

PAH is a rare progressive disease associated with reduced life expectancy. Patients with PAH are also susceptible to developing pneumonia (cause of death in 7% of cases). (ESC 2004) Until the mid-1980s iPAH was considered an untreatable disease with a median life expectancy of 2.8 years. (D'Alonzo 1991). This is comparable to the median survival time from diagnosis of certain cancer types (e.g. 2 years in patients with advanced prostate cancer and 1.5 years in patients with advanced breast cancer). (Kato 2001)

Survival rates in untreated PAH patients at 1 and 3 years were 68% and 48% respectively. (BSC 2001) Although mortality is still high, long term outcomes have improved within the last decade since the introduction of targeted therapies (3 year survival rate has increased to 87%). (Sitbon 2005)

PAH can be difficult to diagnose accurately and diagnosis is often delayed (mean interval from onset of symptoms to diagnosis is 2.5 years). (PHA - UK survey 2005) This 'delay' means that by the time patients are diagnosed with PAH, and treatment initiated, they may already have severe disease with compromised quality of life. The impact of exercise limitation on life-style can be considerable and many patients suffer from anxiety and depression, which also affects quality of life. (ESC 2004) Life-long monitoring, co-ordinated from a specialist centre, is also required.

Incidence and prevalence

PAH occurs most commonly in young and middle aged women but recent data from clinical trials suggests that the mean age of presentation, at least for trials, is around 55 years, although it can occur at any age. Race has no bearing on the risk of PAH (Provencher 2006, Gaine 1998)

Idiopathic (previously known as primary) PAH has an incidence of 1-2 cases per million per annum in the general population and the incidence of PAH associated with other causes is believed to account for a further 1-2 cases of PAH per million per annum (BCS 2001, Gaine 1998). Severe PAH (New York Heart Association, NYHA class III/IV) has an estimated prevalence of at least 30-50 cases per million. (Peacock 2003)

The highest number of cases of PAH appear to be in areas close to specialist treatment centres which implies that where awareness is higher more patients are diagnosed. Prevalence estimates should take this factor into account. (Source: UK specialist centres).

Section 2: Disease classification

Pulmonary hypertension (PH) was classified by the WHO into five different types in 2001 (with modifications in 2003) according to similarities in pathophysiological mechanisms, clinical presentation and therapeutic options. This classification groups together the causes of PH that share pathological features and may have similar treatment responses. It also highlights the need for accurate diagnosis and assessment as the treatment for one group would not necessarily benefit another.

WHO classification of PH (BCS Guidelines 2001, Simonneau, 2004)

1) *Pulmonary arterial hypertension (PAH)*
2) PH with left heart disease
3) PH associated with lung disease and/ or hypoxia
4) PH due to thrombotic and/ or embolic disease
5) Miscellaneous group. E.g. sarcoidosis

PAH has been further categorised into five sub-groups (Simonneau 2004, Humbert 2004 and Peacock 2003, Gaine 1998)

a) Idiopathic PAH - previously known as primary PH
b) Familial PAH - caused by germline BMPR2 mutations and accounts for 10% of cases
c) Associated PAH - which includes connective tissue disease (now known as collagen vascular disease), portal hypertension, congenital heart disease, HIV infection and drugs or toxins
d) PAH with significant venous or capillary involvement.
e) Persistent PH of the newborn

PAH is increasingly being recognised in association with other conditions which may predispose patients to PAH i.e. connective tissue disease (10-20%), congenital heart disease (15%), portal hypertension (1-2%) and HIV infection (0.5-2%). (NHamilton 2006)

Section 3: Diagnosis and referral

PAH is a challenging disease to diagnose accurately. Investigation and treatment of PAH can also be complex, requiring specialist expertise.

This section refers to adults only.

Clinical presentation

Common symptoms include breathlessness, fatigue, angina (chest pain), syncope and abdominal distension. (Gaine 1998, Rich 1987, Guideline 2001, ESC 2004) Although symptoms are cardio-respiratory in nature, they tend to be non-specific and can be present in many other conditions. This can result in a delayed diagnosis and symptoms are often only recognised once haemodynamic and pathological changes are well established i.e. the patient has severe disease.

Patients with PAH often present to their GP with dyspnoea from where they may be referred to secondary care for further examination. An initial diagnosis of PAH can be made following an electrocardiogram and/ or a chest x-ray and a trans-thoracic echocardiogram.

Due to the risk of early death, if PAH is suspected, the patient should be referred to a specialist centre* without delay for a formal diagnosis and treatment initiation where appropriate.

*There are 5 nationally designated specialist centres in the UK (Cambridge, Glasgow, London, Newcastle and Sheffield) and also one in Dublin.

The diagnosis of PAH in a specialist centre involves a series of investigations to confirm the condition, the type of PAH, and to evaluate the severity of the disease in terms of functional and haemodynamic impairment. (BSC 2001, ESC 2004)

Assessments

Investigations used to assess patients with suspected PH include the following (BSC 2001, NHamilton 2006)

Imaging:	Chest x-ray, ventilation/ perfusion scanning, high resolution computed tomograph (CT) of the lungs, contrast helical CT of the pulmonary arteries, magnetic resonance angiography^{+}, pulmonary angiogram^{+}
Respiratory:	Arterial blood gases, lung function, nocturnal oxygen saturation monitoring, exercise test (six minute walk test, 6MWT^{++} / incremental shuttle walk test, ISWT^{++})
Cardiology :	Electrocardiogram, echocardiogram, cardiac catheterisation
Blood tests:	Routine haematology and biochemistry, thrombophilia testing, autoimmune testing, HIV testing

$^{+}$ In selected cases only

$^{++}$ See appendix A for further details

Symptom severity

Symptom severity is assessed by exercise testing (e.g. 6MWT, ISWT or cardiopulmonary exercise testing with gas exchange measurement). (BSC 2001, NHamilton 2006) The absolute value of the 6MWT is predictive of survival in idiopathic PAH and also correlates inversely with modified NYHA functional status severity (Barst 2004a, Rubin 2002). The ISWT is also predictive of a poor prognosis. (Elliot 2004)

Patients are then graded according to the degree of functional disturbance according to New York Heart Association, NYHA, functional classification levels I – IV (ESC 2004). See appendix B for definitions.

Section 4: Treatment of Pulmonary Hypertension

The aims of treatment are to address the underlying cause, improve exercise capacity and symptoms, improve quality of life (QoL) and improve survival. (Langleblen 2004, Gaine 1998, McKenna 2006). Treatment should only be initiated under the care of specialist centres by clinicians experienced in the management of PAH. This may occur in the specialist centre or in an out-reach clinic. An example of the latter are those held specifically for children by specialist clinicians from Great Ormond Street.

To date only limited QoL data is available from published clinical studies in PAH patients. A new measurement tool known as the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) scales has, however, recently been specifically developed to measure health-related QoL (symptoms and functioning) and QoL in patients with PH. (McKenna 2006) The new CAMPHOR scales are intended for use in future clinical trials and also on an individual basis in routine clinical practice.

The following treatments are reviewed;

A. Conventional therapy

B. Transplantation

C. Targeted therapy

Guidelines (British, European and American) are available on the management of PAH (BCS 2001, Simonneau 2004, EHJ 2004, ACCP 2004). However, PAH is a rapidly evolving area in terms of the knowledge and understanding of the disease and the development and introduction of new therapies. Existing guidelines and recommendations may therefore require regular updates over the next few years.

A: Conventional therapy

Conventional therapies are used in all PAH patients to improve symptoms but they have a limited effect on disease progression. (Wilkins M 2005) For patients with severe PAH (NYHA class III/IV) conventional therapy alone is no longer considered adequate treatment. (ACCP 2004)

Table 1. Conventional PAH treatment

Conventional therapy	Uses
Anti-coagulants (e.g. warfarin)	To reduce the risk of venous thromboembolism (Humbert 2004, ESC 2004, BCS 2001)
Diuretics (e.g. frusemide, amiloride or spironolactone)	To treat oedema or fluid retention associated with right heart failure (ESC 2004, ACCP)
Digoxin	Frequently used to improve cardiac output but now only considered useful in the rare patients with atrial fibrillation or atrial flutter to slow ventricular rate (ESC 2004)
Oxygen therapy	Considered useful in patients with hypoxaemia (Gaine 1998, ACCP 2004)
Vasodilator therapy i.e. calcium channel blockers (e.g. nifedipine or diltiazem)	To reduce pulmonary vascular resistance (in the absence of right heart failure) in the small subset of patients (10-15% of PAH patients) who demonstrate an acute vasodilator response. (Peacock 2003, ESC 2004). Limitations include side effects due to the high doses needed. (Gaine 1998, ESC 2004).

B: Transplantation

Until the 1990's transplantation was considered the only option for some PAH patients in the UK. Now transplantation is only considered for patients with severe symptomatic and progressive PAH (advanced NYHA class III/ IV) who fail to respond to targeted therapies. Transplantation options include lung (single or double) or heart-lung with 3 and 5 year survival rates of 55% and 45% respectively. (ESC 2004).

C: Targeted therapy

Historically PAH was considered an untreatable disease. Considerable advances in the understanding of PAH within the last decade have lead to the introduction of new targeted (disease specific) therapies which are now considered standard therapy for patients with severe PAH (NYHA class III/IV).

Most clinical studies using targeted therapies include PAH patients with modified NYHA functional class II – IV and efficacy is evaluated initially over 12 to 16 weeks. (Peacock 2003) A recognised clinical trial primary end point is the measurement of exercise capacity. The 6MWT is often used since it is a reliable tool for the measurement of exercise capacity and it is also an independent predictor of mortality.(Rubin 2002) Secondary end-points include improvements in pulmonary haemodynamics, symptoms and time to clinical worsening. Long term outcome data has also been evaluated for some products in open label extension studies from randomised controlled studies. The latter is increasingly being recognised as essential efficacy data.

It has also been recognised that early diagnosis, rapid referral and treatment with targeted therapy can greatly improve patient outcome. (NHamilton 2006)

The following targeted therapies are discussed in detail

- Prostaglandins (epoprostenol*, iloprost*and treprostinil)
- Endothelin receptor antagonists (bosentan*, sitaxsentan and ambrisentan)
- Phosphodiesterase - 5 - inhibitors (sildenafil* and tadalafil)

*Products licensed for use in PAH patients in the UK (SPC Flolan, Ventis, Tracleer, Revatio)

PROSTAGLANDINS (PGs)

Table 2. PGs – Clinical summary table (see appendic C for clinical trial details)

PG	Epoprostenol	Iloprost	Treprostinil
Route of administration and licensed use	The only prostaglandin licensed for intravenous (i.v.) use in idiopathic PAH patients with NYHA class III/IV.	Administered via a nebuliser. Licensed for use in idiopathic PAH patients with NYHA functional class III.	Administered via subcutaneous (s.c.) infusion into the abdomen. Not licensed for use in PAH patients.
PAH efficacy summary	Epoprostenol i.v. is an established treatment for patients with PAH although no randomised double blind controlled studies (RCT) have been undertaken in PAH patients. Treatment with epoprostenol improves exercise capacity, haemodynamics and QoL in PAH patients. Prolonged improvement in long term outcomes has also been demonstrated (Barst 1996, McLaughlin 2002, Sitbon 2002 & 2005).	Nebulised iloprost has been shown to improve exercise capacity, haemodynamics and QoL in PAH patients in RCTs. (Olshewski 2002, Hoeper 2000)	Moderate improvements in exercise capacity have been demonstrated in RCTs. Improvements in haemodynamics and QoL have also been shown. (Simonneau 2002, Oudiz 2004).
Long term use	Long term data, involving large patient numbers with severe disease, is available and improvements in long term outcomes have been demonstrated. See table 3. (McLaughlin 2002, Sitbon 2002)	Long term efficacy and improvements in long term outcomes have been demonstrated but only a minority of patients with severe PAH remained on inhaled iloprost monotherapy over time. See table 3 (Olschewski 2003 & 2005, Opitz 2005)	Long term efficacy has been demonstrated in PH patients with NYHA class II-IV. A retrospective analysis (of a heterogenous group) demonstrated potential improvement in long term outcomes (Lang 2006).

PG – long term outcome data

Table 3. Summary of PG long term outcome data

Epoprostenol i.v.	Baseline characteristics	Predictive survival[a]	Observed survival[b]	Remained alive on monotherapy[c]
Historical data (Sitbon 2005)	N= 346 Idiopathic PAH, NYHA class III		Year % 1 = 91%, 2 = 84% 3 = 75%	N=253 (73%) after 3 years.
Observational study - database collection[d] (Nov 1991 to Dec 2001) (McLaughlin 2002)	N= 162 Primary PH[e], NYHA class III (46%) and IV (54%)	Year % 1 = 59% 2 = 46% 3 = 35%	Year % 1 = 88% 2 = 76% 3 = 63%	N= 78 (48%) after 3 years.
Observational study - data collection (Dec 1992 to Jan 2001) (Sitbon 2002).	N= 178 Primary PH[e], NYHA class III (67%) and IV (33%)	Year Historical control 1 = 58% 2 = 43% 3 = 33% 5 = 28%	Year % 1 = 85%, 2 = 70%, 3 = 63% 5 = 55%	N=93 (52%) after 5 years.
Iloprost nebulised				
Multi-centre study - initial three month RCT followed by a two year open label study (Olschewski 2003)	N=63 (40 primary PH and 23 secondary PH) NYHA class II/III/IV (33% class II and 67% III/IV)	Over 2 years = 63%	Over 2 years = 85%	N=37 (59%) after 2 years.
Single arm open label study (Opitz 2005)	N=76 Idiopathic PAH, NYHA class II (24%), III (67%) and IV (9%)	Year % (b) 1 = 68%, 2 = 55%, 3 = 46% 4 = 38% 5 = 32%	Year % 1 = 79%, 2 = 70%, 3 = 59% 4 = 59% 5 = 49%	Year % 1 = 42%, 2 = 18%, 3 = 11% 4 = 8% 5 = 6%
Treprostinil s.c.				
Multi-centre open label retrospective study in a heterogeneous group over 3 years (Lang 2006)	N=122 (99 PAH and 23 with inoperable chronic thromboembolic PH) NYHA class II/III/IV (7% class II, 66% III and 27% IV)	Not possible due to inclusion of heterogeneous group	Year % 1 = 89%, 3 = 71%	N=91 (75%) after 11 to 16 months

Key

a. Based on the National Institute of Health (NIH) registry formula (d'Alonzo equation)

b. Reported as Kaplan Meier estimates

c. Patients alive, but no longer on monotherapy, either had a transplant, electively discontinued treatment or received alternative or combination therapy.

d. Clinical data extracted from medical records (including results from exercise testing and cardiac catheterisation details)

e. Now referred to as PAH

f. Major limitation: morbidity associated with chronic indwelling catheter

PG - side effects

Common side effects associated with PG treatment includes headache, flushing, jaw pain, diarrhoea and nausea. Backache, foot and leg pain and abdominal cramping may also occur and rarely hypotension. (ESC 2004, Goldsmith 2004). Nebulised iloprost is generally well tolerated. (Goldsmith 2004)

Use of i.v. epoprostenol (or i.v. iloprost) requires the insertion of a permanent central venous catheter and is associated with a high morbidity. Adverse events directly related to the central catheter tend to be severe and include sepsis (reported incidence 0.14 per patient per year), catheter obstruction (0.02 per patient per year) and local site infection (0.24 per patient per year) (McLaughlin 2002, ESC 2004)

Treprostinil s.c. use is associated with a high incidence of infusion site pain. In a large 12 week RCT (Simonneau 2002) 85% of treprostinil patients (220/233) versus 27% of placebo patients (62/236) reported this side effect ($p<0.0001$) which resulted in discontinuation in 18 treprostinil patients (8%) compared with only one placebo patient. Infusion site reactions were also common (83% treprostinil versus 27% placebo, $p<0.0001$).

PG - other issues

Parenteral use of PGs can be inconvenient for patients requiring hospitalisation (in-patient stay approximately 10 to14 days) for treatment initiation. It can also be associated with a negative body image in young and middle aged women in addition to a number of other issues. (NHamilton 2006) Simple screening regimens are used for patients with i.v. PG therapy to allow early identification of line infections and may prevent the development of decompensated right heart failure often seen in the context of Hickman line related infection in patients with severe PH. (Armstrong 2003)

Epoprostenol has to be administered via continuous i.v. infusion due to its short half life (2-3 minutes). Once reconstituted the product is only stable for 8 to 12 hours at room temperature which means interruption to the infusion for a syringe change. Whilst the use of cold packs allows the infusion to be changed once daily there are still issues associated with infusion interruption and the risk of infection (ESC 2004). In the short term the product may be administered (off-license) via nebulisation.

Iloprost also has a short half life which means that patients need to nebulise around 6 to 9 times a day (Peacock 2003). The I-neb (hand held) powered delivery system is breath activated and the correct amount of medication required is delivered to the patient regardless of size or breathing pattern. Pumps need to be provided for use in conjunction with this device. loprost may also be administered via continuous i.v. infusion (un-licensed use) but this is associated with a high risk of infection.(NHamilton 2006).

Treprostinil administration is associated with pain at the site of infusion, a common side effect, which can limit dose increases and lead to discontinuation of treatment in some patients. (Simonneau 2002, ESC 2004, Lang 2006). Long term s.c. use has also been associated with the occurrence of haematomas at the infusion site. (Vachiery 2002) Alternatively, treprostinil may be administered via i.v. infusion (un-licensed) but this is associated with a high risk of infection.

Table 4. Limitations associated with the use of PGs

PG Limitations		
Epoprostenol i.v.	**Iloprost nebulised**	**Treprostinil s.c.**
- Patient inconvenience associated with administration - Negative body image - High risk of infection associated with administration of the drug	- Patient inconvenience associated with frequency of administration - Negative body image	- Not licensed for use - Negative body image - Side effects associated with administration of the drug

ENDOTHELIN RECEPTOR ANTAGONISTS (ERA)

Table 5. ERA –Clinical summary table (See appendix D for clinical trial details)

ERA	Bosentan [a]	Sitaxsentan	Ambrisentan
Route of administration and licensed use	Administered orally (twice daily[b]). The only ERA licensed. For use in PAH patients with NYHA class III.	Administered orally. Not licensed.	Administered orally. Not licensed.
PAH efficacy summary	An established first line oral treatment for PAH. RCTs have shown that treatment with oral bosentan improves exercise capacity, haemodynamics, symptoms, functional class and QoL in PAH patients with NYHA class III. Bosentan also delays clinical worsening. (Channick 2001, Rubin 2002)	In RCTs improvements in exercise capacity and haemodynamics have been demonstrated in PAH patients with NYHA functional class II/III/IV. (Barst 2004b, Cleland 2005).	There are no placebo controlled studies evaluating the efficacy and safety of ambrisentan in PAH patients. A single double blind dose ranging study in PAH patients (NYHA class II/ III) demonstrated improvements in exercise capacity, haemodynamics, symptoms and QoL. (Galie 2005a)
Long term use	Long term efficacy and tolerability data is available (>1 year) in patients with NYHA class III/ IV(Sitbon 2003). Improvements in long term outcomes up to three years have been demonstrated (see table 6) (Sitbon 2003 & 2005, Joglekar 2006, McLaughlin 2005, Provencher 2006)	Long term data is limited (n=10 patients with NYHA class II/ III)) and further evaluation is required. (Langleben 2004) There is no published long term outcome data.	Long term efficacy (from a 1 year dose ranging study) has been demonstrated in patients with NYHA class II/ III (Galieb 2005) Improvements in long term outcomes up to one year have been demonstrated (see table 6)

Key

a. Bosentan is a dual acting ERA (i.e. inhibits both ETA and ETB receptors) unlike sitaxsentan and ambrisentan which inhibit the ETA receptor only. [The ETA receptor is located on the surface of smooth muscle cells and is involved in vasoconstriction. The ETB receptor can be found mainly on the surface of endothelial cells and is involved in both vasoconstriction and vasodilation] (NHill 2005).

b. Recommended dose: Starting dose bosentan 62.5mg twice daily (bd) for four weeks, then increased to the maintenance dose of 125mg bd

ERA – long term outcome data

Improvements in long term outcomes have been demonstrated in PAH patients with first line use of bosentan (up to three years) and ambrisentan (up to one year). (Sitbon 2005, McLaughlin 2005, Provencher 2006, Galie 2005b) No data is available for sitaxsentan.

Table 6. ERA long term outcome data

Bosentan	Baseline characteristics	Predictive survival [a]	Observed survival [b]	Remained alive on monotherapy [c]
Prospective analysis of bosentan clinical trial data (Sitbon 2005)	N=139 PAH, NYHA class III		Year % 1 = 99%, 2 = 91% 3 = 87%	Year % 1 = 87%, 2 = 75%
Prospective study of observed survival[d] Clinical trial data (bosentan for 3 months followed by open label/ other treatment if required) (McLaughlin 2005)	N=169 Idiopathic PAH, NYHA class III/IV	Year % (b) 1 = 69% 2 = 57% 3 = 48%	Year % 1 = 96% 2 = 89% 3 = 86%	Year % 1 = 85% 2 = 70%
Retrospective analysis of bosentan treated patients. (Nov 1999 to May 2004). Treatment strategy included PG treatment if necessary[e]. (Provencher 2006)	N=103 Idiopathic PAH, NYHA class III/IV	Year % (d) 1 = 71% 2 = 61% 3 = 51%	Year % 1 = 92% 2 = 89% 3 = 79%	Year % 1 = 56%
Ambrisentan				
Open label extension study (Galie 2005b)	N=54 PAH, NYHA class II (36%) and III (64%)	Year % (d) 1 = 77%	Year % 1 = 93%	Year % 1 = 93%

Key

a. Based on the NIH registry formula (d'Alonzo equation)

b. Reported as Kaplan Meier estimates

c. Patients alive, but no longer on monotherapy, either had a transplant, discontinued treatment due to side effects (or voluntarily) or received alternative or combination therapy

d. Data from two placebo controlled studies followed by open label extensions.

e. Reasons for PG initiation included persistent or worsening NYHA class IV on treatment and persistent NYHA class III after at least 4 months on bosentan monotherapy with a mean 6MW distance <250m, a >10% decrease in 6MW distance or a cardiac index <2.2 L/min/m^2

ERA - side effects

Common side effects associated with ERA treatment includes syncope and flushing. Abnormal hepatic function (identified by elevated levels of alanine aminotransferase and/or aspartate aminotransferase) may also occur. Abnormal hepatic function is dose dependant, reversible on withdrawal, and a recognised class effect associated with ERAs. (ACCP 2004) Regular (at least monthly) monitoring of liver enzyme levels is recommended in bosentan treated patients and levels should also be measured two weeks after any dose increase. (Tracleer SmPc).

In a European post marketing surveillance programme the long-term safety of bosentan was assessed. Data from May 2002 to May 2004 represents 2,036 patient years of exposure to bosentan in PAH patients (NYHA class III).

Mean exposure to bosentan was 30.6 weeks (20% >1 year). Effects on the liver (i.e. elevated aminotransferase levels) were noted in 7.4% of patients, with the majority (55%) of the reported elevations being no greater than five times the upper limit of normal. This is consistent with data from RCTs. (Humbert 2005)

Sitaxsentan and ambrisentan side effects evaluated in RCTs were as expected for ERAs. Due to the effect of sitaxsentan on the inhibition of the cytochrome p450 enzyme, patients on warfarin treatment require monitoring of the warfarin dosage and the dose of sitaxsentan adjusted. (Steinbis SP 2005, ACCP 2004).

Table 7. Limitations associated with the use of ERAs

ERA Limitations		
Bosentan	**Sitaxsentan**	**Ambrisentan**
- Dose limiting (reversible) side effects associated with elevations in liver enzyme levels. - Regular (monthly) monitoring of liver enzyme levels required (SmPc).	- Not licensed for use. - Dose limiting (reversible) side effects associated with elevations in liver enzyme levels. - Monitoring and dose adjustment necessary when co-administered with warfarin. - Long term efficacy data is limited. - There is no published long term outcome data for monotherapy.	- Not licensed for use. - Clinical data is limited (no RCTs). - Abnormal hepatic function noted.

C: PHOSPHODIESTERASE - 5 - INHIBITORS (PDE-5-I)

Table 8. PDE-5-I – Clinical summary table (See appendix D for clinical trial summary details)

PDE-5-I	Sildenafil	Tadalafil
Route of administration and licensed use	- Administered orally (three times daily)[a]. - The only PDE-5-I licensed. - For use in PAH patients with NYHA class III.	- Administered orally (once daily). - Not licensed for use.
PAH efficacy summary	In RCTs in PAH patients (majority NYHA class II/III) improvements in exercise capacity, NYHA class, haemodynamics and QoL have been demonstrated using doses up to 80mg tds (Sastry 2004, Galie 2005c)	The efficacy and tolerability of tadalafil in PAH patients has yet to be evaluated in a RCT (PHAwebsite).
Long term use	Long term efficacy (up to 1 year) has been demonstrated with sildenafil 80mg tds (four times the recommended dose) alone or in combination. (Galie 2005d) There is currently no long term efficacy or outcome data for sildenafil 20mg tds[a] used alone or in combination.	No data available.

Key

a. Recommended dose: 20mg three times daily (tds)

PDE-5-I - long term outcome data

Survival data for PAH patients (97% NYHA class II or III) receiving sildenafil 80mg tds (four times the recommended dose) is available. (Galie 2005d) Additional treatment with PG or ERA was also allowed if required. Results are shown in table 9 below.

Table 9. PDE-5-I long term outcome data

Sildenafil	Baseline characteristics	Predictive survival [a]	Observed survival [b]	Alive on monotherapy [c]
RCT of sildenafil 20mg (n=69),40mg (n=n=68) or 80mg (n=71) tds or placebo (n=70) for 12 weeks, followed by open label extension of sildenafil 40mg tds for six weeks followed by 80mg tds thereafter. (Galie 2005d)	N=278 (I n=141) 63% idiopathic PAH, NYHA class I (1%), II (39%), III (58%) and IV (3%)	Year % 1 = 71%,	Year % 1 = 96%[d]	80% (n=222)[d]

Key

a. Reported as Kaplan Meier estimates.

b. Based on the NIH registry formula

c. Patients alive, but no longer on monotherapy, either withdrew from treatment or additional treatment

d. All patients received sildenafil 80mg tds (four times the licensed recommended dose). Patients demonstrating tolerance issues on 80mg were given a lower dose of 40mg.

PDE-5-I - side effects

Sildenafil is usually well tolerated. In RCTs, using doses up to 100mg tds, side effects included headache, flushing, dyspepsia, diarrhoea and myalgia (Sastry 2004). The safety profile of tadalafil is yet to be evaluated in a RCT.

Table 10. Limitations associated with the use of PDE-5-I

PDE-5-I Limitations	
Sildenafil	**Tadalafil**
- No long term efficacy and outcome data is available for sildenafil 20mg tds (recommended dose)	- Not licensed for use - No RCT to confirm efficacy in PAH patients.

Section 5: Clinical practice

Home delivery

Treatment for PAH can be time consuming, painful, inconvenient and anxiety generating. It is therefore important for the clinician to take into account the patients wishes and QoL when choosing a suitable treatment. (McKenna 2006)

With this in mind, most of the UK specialist centres use a home delivery service to efficiently deliver targeted therapy and any associated ancillary products (syringes, pumps etc) to the patient's home.

The benefits are;

1. Patient convenience
2. Risk Management: Safe exchange and disposal of sharps and medication
3. Cost: Medication dispensed through home delivery agents will not incur VAT associated with a hospital or FP10 prescription.

Patients are closely followed up at a specialist centre with careful periodic reassessment and adjustment of therapy.

Choice of therapy will depend on response to treatment, tolerability and patient's preference for the route of administration.

Shared care

Management of PAH patients is currently co-ordinated from the specialist centre where patients' disease and treatments are regularly reviewed. GPs and hospital consultants more local to the patients are encouraged to have ownership of co-existing morbidities. Some out-reach clinics have been established where staff from the specialist centre hold clinics in the local hospitals. Formalised shared-care arrangements for managing PAH may evolve further but currently no fixed model exists.

Combination therapy

In clinical practice combination targeted therapy is sometimes given to PAH patients in whom initial treatment fails to bring about the required response/ improvement or when deterioration occurs following an initial favourable response. (Hill 2006)

Open label clinical studies have evaluated the efficacy and tolerability of combination therapy using targeted therapies with different mechanisms of action. In some studies the addition of bosentan or sildenafil to on-going treatment with PGs, in patients deteriorating despite chronic therapy, has demonstrated improvements in pulmonary haemodynamics, exercise capacity and long term outcomes. (e.g. Hoeper 2003, Ghofrani 2003, McLaughlin 2005, Kataoka M 2005, Provencher 2006) However, none of the available targeted therapeutic agents are specifically licensed for use in combination and published data is limited in terms of patient numbers.

Section 6: Budget impact

Annual cost of targeted therapies

The annual cost of treating a PAH patient with a single targeted therapy, on a recommended maintenance dose, is within the range of £4,200 to £47,000 (see table 11). This excludes the cost of caring for a PAH patient in a specialist centre.

In clinical practice recommended maintenance doses may be exceeded e.g. sildenafil dosage titrated up to 100mg tds (associated with an annual cost of £20,916). (Source: UK specialist centre). Combination treatment is increasingly being used, which further increases the cost.

Additional costs to be taken into consideration include those associated with parenteral PG such as hospital admission costs for treatment initiation, screening for infection and infection related costs.

To help manage the cost of targeted therapies some manufacturers have introduced annual purchasing schemes with fixed costs. In such schemes, quarterly "subscription" fees may be payable per patient per year for unlimited supplies to meet patient's requirements over a 12 month period.

Table 11. Annual cost of PAH treatments licensed in the UK

Targeted therapy	Licensed maintenance dose[SPC]	Monthly treatment cost (28 days treatment) [MIMS]	Annual cost/ patient[a]
Epoprostenol	See infusion rate recommendation (1 vial per day)	£3,902.10	£46,825.20
Iloprost	7 cycles (7 amps per day)	£2,773.40	£33,280.80
Bosentan	125mg bd	£1,541.00	£18,492.00
Sildenafil	20mg tds[b]	£348.60[c]	£4,183.20

Key

a. Assumes PAH patient is kept on licensed maintenance dose

b. Higher doses (up to 100mg tds) are often used in clinical practice.

c. Sildenafil monthly pack: 30 days (90 x 20mg tablets) = £373.50 (ref: MIMS). 28 days treatment calculated as £348.60

N.B. Treprostinil is not shown here because it is not licensed for use in the UK. It is available on a named patient basis only and the annual cost of treprostinil treatment (inclusive of pump rental) = £35,680.00 (Source: UK specialist centre).

Estimated number of UK PAH patients

Table 12. Estimated number of UK PAH patients potentially eligible for targeted therapy.

UK population+	60 million	
Prevalence Severe PAH prevalence at least 30 - 50 cases/ million	Assume 50 cases per million	3,000
Incidence Idiopathic PAH = 1 - 2 cases/ million/ annum PAH secondary to other causes = 1 - 2 cases/ million/ annum	Assume total of 4 cases per million per annum	240
Estimated total number of UK patients (prevalent and new) potentially eligible for treatment		**3,240**

Key

+ National statistics. UK population 59.8 million. Available at http://www.statistics.gov.uk/cci/nugget.asp?id=6 accessed on 9.5.06

Use of targeted therapies in England

Limited data from specialist centres in England is available (see table 13). National data is not yet available and there is no data currently on the usage of different types of treatment or combination treatment.

Table 13. Patients receiving targeted therapy in England[a]

	Patient numbers
Total number of PAH patients receiving targeted therapy in England[a]	N = 1,114

Key

a. Data (from centres in England only) supplied by National Specialist Commissioning Advisory Group (NSCAG) time period: 31st March 2005/ 2006

PCT approval

Due to the limited number of treatments available, the low numbers of PAH patients in the UK receiving targeted therapy and the high cost associated with treatment, approval from the referring PCT is currently required before treatment can be initiated for PAH patients.

Given the incidence of the disease compared to the size of a typical PCT contracts to share the risks with other PCTs may also help to manage the burden of care of a patient with PAH.

Section 7: Discussion

PAH is a rare and complex condition that requires management by specialists in nationally designated specialist centres. Increased awareness of PH and its associations should enable diagnosis to be made more readily. Early referral to a specialist centre will improve diagnosis, facilitate early treatment and thus improve survival outcomes.

Until recently this condition was considered untreatable and there is still no cure. Considerable progress has, however, been made within the last decade due to a significant advance in the understanding of the disease and the development and introduction of targeted (disease specific) therapies. Following the identification of the gene for familial PAH future treatment may include gene therapy or other treatment options. (Peacock 2003).

Targeted therapies (i.e. PGs, ERAs and PDE- 5 -Is) are now considered standard treatment in patients with severe PAH (NYHA class III/IV). Improvements in haemodynamics, functional capacity, symptoms and quality of life have been demonstrated in PAH patients with all products licensed for use in PAH (i.e epoprostenol, iloprost, bosentan and sildenafil). Bosentan has also been shown to delay clinical worsening.

Improvements in long term outcomes have been demonstrated in patients with severe PAH (NYHA class III/ IV) receiving targeted therapies. For example i.v. epoprostenol, nebulised iloprost and oral bosentan initiated as monotherapy at recommended licensed doses. In PAH patients with NYHA class II-IV high dose oral sildenafil (i.e. four times higher than recommended) has also demonstrated improvements.

The cost of treating and caring for a PAH patient can be considerable (particularly if using doses higher than recommended or if using combination treatment). A PCT risk shared approach might therefore be a cost effective consideration.

Management of the PAH patient is currently co-ordinated from a specialist treatment centre. As knowledge and clinical experience have developed in this area, a shared care approach is evolving.

In summary, despite recent therapeutic advances PAH remains a life threatening disorder and the discovery and development of new PAH treatments is still on-going.

Section 8: Other sources of useful information

1) Pulmonary Hypertension Association UK (PHA-UK)

PHA-UK is a registered charity that provides information to patients, caregivers and medical professionals.

Address: The Brampton Centre, Brampton Road, Wath Upon Dearne, Rotherham, S63 6BB

Telephone/Fax: 01709 761450

Website: http://www.pha-uk.com

2) Guidelines

a) British Cardiac Society Guidelines and Medical Practice Committee, and approved by the British Thoracic Society and the British Society of Rheumatology. Recommendations on the management of pulmonary hypertension in clinical practice. Heart 2001; 86 (suppl 1): i1-i13.

b) European Society of Cardiology (ESC) Guidelines on diagnosis and treatment of pulmonary hypertension. The Task Force on diagnosis and treatment of pulmonary arterial hypertension of the ESC. European Heart Journal 2004; 25: 2243 – 2278.

c) American College of Chest Physicians (ACCP) Evidence-based clinical practice guidelines for pulmonary arterial hypertension. Chest 2004;126 (supplement): 1-77. http://www.chestjournal.org/cgi/content/full/126/1_suppl/4S

Section 9: References

American College of Chest Physicians (ACCP) Evidence-based clinical practice guidelines for pulmonary arterial hypertension. Chest 2004;126 (supplement): 1-77. http://www.chestjournal.org/cgi/content/full/126/1_suppl/4S

Armstrong I, Martin L, Taylor AE et al. Screening for Hickman line related infection in patients with severe pulmonary hypertension. European Respiratory Society Meeting. September 2003.

Badesch DB, Tapson VF, McGoon MD et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized controlled trial. Annals of Internal Medicine 2000; 132(6): 425-434.

aBarst RJ, McGoon M, Torbicki A et al. Diagnosis and differential assessment of pulmonary arterial hypertension. Journal of American College of Cardiology 2004;43(12): 40S – 47S.

bBarst RJ, Langleben D, Frost A et al. Sitaxsentan therapy for pulmonary arterial hypertension. American Journal of Respiratory and Critical Care Medicine 2004;169: 441-447.

Barst RJ, Rubin LJ, Long WA et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. New England Journal of Medicine 1996; 334: 296 – 302.

British Cardiac Society Guidelines and Medical Practice Committee, and approved by the British Thoracic Society and the British Society of Rheumatology. Recommendations on the management of pulmonary hypertension in clinical practice. Heart 2001; 86 (suppl 1): i1-i13.

Channick RN, Simonneau G, Sitbon O et al. Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo controlled study. Lancet 2001; 358: 1119-1123.

Cleland JGF, Coletta AP, Lammiman M et al. Clinical trials update from the European Society of Cardiology meeting 2005; CARE-HF extension study, ESSENTIAL, CICIS-III, S-ICD, ISSUE-2, STRIDE-2, SOFA, IMAGINE, PREAMI, SIRIUS-II and ACTIVE. European Journal of Heart Failure 2005;7: 1070-1075.

D'Alonzo GE, Barst RJ, Ayres SM et al. Survival in patients with primary pulmonary hypertension. Annals of Internal Medicine 1991; 115: 343-349.

Elliot CA, Armstrong IJ, Billings C et al. Incremental shuttle walking test distance predicts poor prognosis in pulmonary hypertension. European Respiratory Society Meeting. European Respiratory Journal 2004;24 (supplement 48); 138.

ESC Guidelines on diagnosis and treatment of pulmonary hypertension. The Task Force on diagnosis and treatment of pulmonary arterial hypertension of the European Society of Cardiology. European Heart Journal 2004; 25: 2243 – 2278.

Farber HW and Loscalzo J. Mechanisms of disease. Pulmonary Arterial Hypertension. New England Journal of Medicine 2004; 351 (16): 1655-1665.

Flolan (epoprostenol) Summary of Product Characteristics. GlaxoSmithkline UK. Last updated 30 December 2004.

Gaine SP and Rubin LJ. Primary pulmonary hypertension. Lancet 1998; 352: 719-725.

aGalie N, Badesch D, Oudiz R et al. Ambrisentan therapy for pulmonary arterial hypertension. Journal of American College of Cardiology 2005;46 (3): 529 – 535.

bGalie N, Keogh A, Frost A et al. Ambrisentan long term safety and efficacy in pulmonary arterial hypertension - one year follow up. American Thoracic Society, San Diego May 23 2005. (Mini Symposium). B16 Abstract page A299.

cGalie N, Ghofrani HA, Torbick A et al. Sildenafil citrate therapy for pulmonary arterial hypertension. New England Journal of Medicine 2005;353: 2148-2157.

dGalie N, Burgess G, Parpia T et al. Effects of sildenafil on 1-year survival of patients with idiopathic pulmonary arterial hypertension. American Thoracic Society, 24th May 2005. C88. Abstract page A802.

eGalie N, Beghetti M, Gatzoulis M et al. BREATHE-5: Bosentan improves hemodynamics and excercise capacity in the first randomised placebo contriolled trial in eisenmenger physiology. Chest 2005;128(4): Abstract page 496S.

Ghofrani HA, Voswinckel R, Reichenberger F et al. Differences in haemodynamic and oxygenation responses to three different phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension. A randomized prospective study. Journal of American College of Cardiology 2004;44 (7):1488-96.

Ghofrani HA, Rose F, Schermuly RT et al. Oral sildenafil as long term adjunct therapy to inhaled iloprost in severe pulmonary arterial hypertension. Journal of American College of Cardiology 2003;42(1): 158-164.

Goldsmith DR and Wagstaff AJ. Inhaled Iloprost in primary pulmonary hypertension. Drugs 2004;64(7): 763-773.

Hamilton N and Elliot C. Pulmonary hypertension – the condition and specialist assessment. Hospital Pharmacist 2006; 13 (special feature): 7-9.

Hamilton N and Elliot C. Pulmonary hypertension – treatment options. Hospital Pharmacist 2006; 13 (special feature): 13-14.

Hoeper MM, Taha N, Bekjarova A et al. Bosentan treatment in patients with primary pulmonary hypertension receiving nonparenteral prostenoids. European Respiratory Journal 2003; 22: 330-334.

Hoeper MM, Schwarze M, Ehlerding S et al. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. The New England Journal of Medicine 2000;342: 1866-70.

Humbert M, Keily DG, Carlsen J et al. Long-term safety profile of bosentan in patients with pulmonary arterial hypertension: Results from the European Surveillance Program. American Thoracic Society, San Diego, May 23 2005, Abstract B16 page A300.

Humbert M and Simonneau. Pulmonary arterial hypertension. Orphanet 2004: 1-7. http://www.orpha.net/data/patho/GB/uk-PulmArterHypert.pdf

Joglekar A, Tsai FS, McCloskey DA et al. Bosentan in pulmonary arterial hypertension secondary to scleroderma. Journal of Rheumatology 2006;33: 61-68.

Kataoka M, Satoh T, Manabe T ET AL. Oral sildenafil improves primary pulmonary hypertension refractory to epoprostenol. Circulation 2005;69: 461-465.

Kato I, Severson RK, Schwartz AG. Conditional median survival of patients with advanced carcinoma. Cancer 2001;92: 2211-2219.

Keogh A, Macdonald P, Williams T et al. Tracleer (Bosentan), for the treatment of pulmonary arterial hypertension (PAH) 6 month quality of life data. The International Society fro Heart and Lung Transplantation 24th Annual Meeting and Scietific Sessions. (April 21-24) 2004. San Francisco, USA.

Lang I, Gomez-Sanchez M, Kneussl M et al. Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension. Chest 2006;129 (6): 1636-1643.

Langleben D, Hirsch AM, Shalit E et al. Sustained symptomatic, functional, and hemodynamic benefit with the selective endothelin-A receptor antagonist, sitaxsentan, in patients with pulmonary arterial hyper tension. A 1 year follow up study. Chest 2004; 126(4): 1377-1381.

McKenna SP, Doughty N, Meads DM et al. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): A measure of health-related quality of life and quality of life for patients with pulmonary hypertension. Quality of Life Research 2006;15: 103-115.

McLaughlin VV, Sitbon O, Badesch DB et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. European Respiratory Journal 2005;25: 244-249.

McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonar y hypertension: the impact of epoprostenol therapy. Circulation 2002; 106; 1477-1482.

National statistics. UK population 59.8 million. Available at http://www.statistics.gov.uk/cci/nugget.asp?id=6, accessed on 9.5.06

Olschewski H, Hoeper MM, Behr J et al. Safety, dosing and clinical benefit of 2 year therapy with inhaled iloprost. American Thoracic Society, San Diego May 22 2005. A57 Poster K29. Abstract page 200.

Olschewski H, Nikkho S, Behr J et al. Long-tern survival in patients with pulmonary hyper tension inhaling iloprost. European Heart Journal 2003; 24(Suppl), p482. Abstract No. 2567.

Olschewski H, Simonneau G, Galie N et al. Inhaled iloprost in severe pulmonary hypertension. New England Journal of Medicine 2002; 347: 322-329.

Opitz CF, Wensel R, Winkler J et al. Clinical efficacy and survival with first-line inhaled iloprost therapy in patients with idiopathic pulmonary arterial hyper tension. European Heart Journal 2005; 26 (18): 1895-1902.

Oudiz RJ, Schilz RJ, Barst RJ et al. Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension with connective tissue disease. Chest 2004;126: 420-427.

Peacock AJ. Treatment of pulmonary hyper tension. Several options exist, but they are expensive and necessitate specialist care. British Medical Journal 2003; 326: 835-836.

Pulmonary Hyper tension Association (PHA). http://www.phassociation.org.

PHA - UK survey 2005

Provencher S, Sitbon O, Humbert M et al. Long term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hyper tension. European Heart Journal 2006;27: 589-595.

Revatio (Sildenafil) Summary of Product Characteristics. Pfizer Limited. (Last updated October 2005).

Rich S, Dantzker DR, Ayres SM et al. Primary Pulmonary Hypertension, Annals of Internal Medicine 1987;107: 216-223.

Rubin LJ, Badesch DB, Barst RJ et al. Bosentan therapy for pulmonary arterial hyper tension. New England Journal of Medicine 2002;346 (12): 896-903.

Sastry BK, Narasimhan C, Reddy NK et al. Clinical efficacy of sildenafil in primary pulmonary hyper tension: a randomised, placebo controlled, double blind crossover study. Journal of American College of Cardiology 2004;43: 1149-1153.

Simonneau G, Nazzareno G, Lewis LJ et al. Clinical classification of pulmonary hypertension. Journal of the American College of Cardiology 2004;43 (12): 5S – 12S.

Simonneau G, Barst RJ, Galie N et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary hypertension. A double blind randomised placebo controlled trial. American Journal of Respiratory and Critical Care Medicine 2002; 165: 800-804.

Sitbon O, McLaughlin VV, Badesch DB et al. Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol. Thorax 2005;60: 1025-1030.

Sitbon O, Gressin V, Speich R et al. Bosentan for the treatment of human immunodeficiency virus-associated pulmonary arterial hypertension. American Journal of Respiratory Critical Care Medicine 2004;170: 1212- 1217.

Sitbon O, Badesch DB, Channick RN et al. Effects of the dual endothelial receptor antagonist bosentan in patients with pulmonary arterial hypertension: A 1 year follow up study. Chest 2003;124; 247-254.

Sitbon O, Humbert M, Nunes H et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension. : prognostic factors and survival. Journal of American College of Cardiology 2002;40: 780 – 788.

Steinbis SP. New developments in the treatment of PAH. Chest 2005: 71st Annual Meeting of the American College of Chest Physicians Pulmonary Vascular Disease. http://www.medscape.com/viewprogram/4791_pnt

Tracleer (bosentan) Summary of Product Characteristics. Actelion Pharmaceuticals UK. (Last updated Sept 2004).

Vachiery JL, Hill N, Zwicke D et al, Transitioning from iv epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension. Chest 2002; 121:1561-1565.

Ventavis (iloprost) Summary of Product Characteristics. Schering Health Care Limited. Last updated 5 September 2005.

Wilkins MR, Paul GA, Strange JW et al. Sildenafil versus endothelin receptor antagonist for pulmonary hypertension (SERAPH) study. American Journal of Respiratory and Critical Care Medicine 2005;171: 1292-1297.

Section 10: Appendices

Appendix A: Glossary of Terms

Term	Definitions
Pulmonary Hypertension (PH)	PH is a condition characterised by increased pressure in the pulmonary arteries and is defined as a mean pulmonary artery pressure >25 mmHg at rest or >30 mmHg during exercise (Gaine 1998)
Pulmonary arterial hypertension (PAH)	A group of diseases characterised by a progressive increase in pulmonary vascular resistance leading to right ventricular failure and premature death. (ESC 2004) Using measurements taken at rest by right heart catheterisation PAH is defined as a mean pulmonary artery pressure 25 mmHg, a pulmonary capillary wedge pressure of 15 mmHg, and raised PVR. (ACCP 2004)
Primary pulmonary hypertension	Now known as idiopathic pulmonary arterial hypertension (Simonneau 2004)
Six minute walk test (6MWT)	The distance (measured in metres) a person can walk on a flat surface over a period of 6 minutes. (Peacock 2003)
Incremental shuttle walk test (ISWT)	In shuttle walk tests, patients walk back and forth between two cones placed a set distance apart on flat ground at a pace that is controlled by audiotape bleeps. Walking speed can be increased incrementally, which gradually stresses the cardio-respiratory system to a symptom-limited maximum.

Appendix B: NYHA/ WHO classification of functional status of patients with PH

(Adapted from ESC 2004)

Class	Description
Class I	Patients with PH without limitation of usual physical activity, does not cause increased dyspnoea, fatigue, chest pain or pre-syncope.
Class II	Patients with PH with mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain or pre-syncope.
Class III	Patients with PH with marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain or pre-syncope.
Class IV	Patients with PH who are unable to perform any physical activity and whom have signs of right ventricular failure at rest. Dyspnoea and/ or fatigue are present at rest and symptoms are increased by almost any physical activity.

Appendix C: Summary of PG clinical trial data

Epoprostenol

In a long term observational study (McLaughlin 2002) 162 PAH patients (46% NYHA functional class III and 54% class IV) treated with i.v. epoprostenol over a mean period of 36.3 months (±27.1 months) showed a significant improvement in NYHA class (from a mean of 3.5 to 2.5, $p<0.001$) and a significant improvement in haemodynamics.

Results from another long term observational study (data collected December 1992 to January 2001), involving 178 PAH patients (NYHA functional class III/IV) treated with i.v. epoprostenol have also been reported (Sitbon 2002). Patients were followed for a mean period of 26 months (±21 months). The 6MWT and right sided cardiac catheterisations were performed at baseline, after 3 months epoprostenol treatment and then once a year thereafter. At three months NYHA class improved in 75% of patients (n=125) and the 6MWT improved in 90% of patients (n=149) with a mean increase of 147m. After one year 115 patients remained stable, five improved and 10 worsened in terms of their functional class. Improvements in haemodynamics were also demonstrated.

QoL improvements were demonstrated in a 12 week prospective, randomised open trial comparing the effects of i.v. epoprostenol (plus conventional therapy) with conventional therapy alone in patients (n=81) with NYHA class III/IV. Indexes of QoL were improved only in the epoprostenol group ($p<0.01$). (Barst 1996)

Efficacy data (randomised open label study) is also available for 111 patients with PH secondary to the scleroderma spectrum of diseases. (Badesch 2000).

Iloprost

In a 12 week RCT patients (n=203) with PAH and chronic thromboembolic PH (NYHA class III/ IV) received nebulised iloprost (15-45mcg/ day). The primary end-point (combined) was met if after 12 weeks the NYHA class improved by one class and the 6MWT distance improved by >10%. (Olshewski 2002). The primary end-point was met by 16.8% of patients receiving iloprost compared with 4.9% of placebo patients ($p=0.007$). In the sub-group of patients with primary (idiopathic) PAH the 6MWT distance increased overall by 58.8m. Significant improvements in the iloprost treated patients (compared with placebo) were noted in terms of haemodynamics ($p<0.001$), NYHA class ($p=0.03$), dyspnoea ($p=0.015$) and QoL ($p=0.026$).

The long term efficacy and safety of inhaled iloprost has also been studied (Hoeper 2000 and Olschewski 2005).

Hoeper MM et al studied the compassionate use of inhaled iloprost in 24 PAH patients (NYHA class III/IV) who received treatment for at least one year and completed exercise testing (6MWT) and catheter studies. After three months treatment the 6MWT distance increased significantly (by 75+67m) compared with baseline ($p<0.001$) and this was sustained after 12 months. Haemodynamic improvements were also noted at three and 12 months. (Hoeper 2000).

In an open label extension study (following an initial randomised controlled 12 week period) 52 PAH patients (70% idiopathic and 30% familial) with NYHA class II-IV received iloprost treatment for up to 2 years. (Olschewski 2005). A total of 36 patients with idiopathic PAH completed at least 630 days of treatment. The Hodges-Lehmann estimate showed an increase by 89m in the 6MWT (from baseline up to 2 years) in 31 patients. A >10% increase in 6MWT plus improvement in NYHA class (primary end-point) was sustained after 3 months and up to 2 years in 4/30 patients who received iloprost from week 1. Improvements in Mahler Dyspnoea Index were also demonstrated (4.8 at baseline and 5.8 at 2 years). The authors noted that treatment effects were maintained with only minor dose increases over two years.

Treprostinil

The efficacy of treprostinil was evaluated in a 12 week RCT study involving 470 PAH patients (with idiopathic or connective tissue disease, CTD or congenital systemic-to-pulmonary shunts) with NYHA class II/III/IV (Simonneau 2002). After 12 weeks the difference in median distance walked between the treprostinil and placebo groups was 16m ($p=0.006$). Treprostinil treated patients (compared with placebo) also demonstrated significant improvement in the Borg Dyspnoea Score ($p<0.0001$) and the QoL physical dimension score ($p=0.0064$) with a trend towards improvement in the global dimension score ($p=0.17$). Cardiopulmonary haemodynamics also improved in the treprostinil treated group.

A sub-set of 90 patients (with PAH associated with CTD from the latter study have been evaluated (Oudiz 2004). At baseline most patients had NYHA class III. The results demonstrate that treprostinil improves exercise capacity (with a placebo corrected median improvement in 6MWT from baseline of 25m, $p=0.055$), symptoms and haemodynamics in PAH patients with CTD. In a retrospective long term study efficacy has been demonstrated with s.c. treprostinil for up to 3 years in 122 patients with class I-IV PH (n= 99 with PAH and n= 23 with inoperable chronic thromboembolic PH). Potential improvements in long term outcomes have also been shown. (Lang 2006)

Appendix D: Summary of ERA clinical trial data

Bosentan

In a RCT 32 patients with PAH (idiopathic or associated with scleroderma) and NYHA class III received bosentan (62.5mg bd for four weeks and 125mg bd thereafter) or placebo for a minimum of 12 weeks. Exercise capacity and haemodynamics improved in the bosentan treated group (6MW distance improved by 70m compared with baseline in the bosentan group but worsened by 6m in the placebo group, $p=0.021$). This improvement was maintained for at least 20 weeks. Borg dyspnoea index and functional class improved in the bosentan treated patients. The time to clinical worsening also increased significantly in the bosentan group compared with placebo ($p=0.033$). (Channick 2001)

In a large RCT 213 PAH patients, primary or associated with CTD, received placebo (n=69) or bosentan (n=144) 62.5mg bd for four weeks followed by 125mg or 250mg bd for a minimum of 12 weeks. After 16 weeks treatment bosentan improved the 6 MW distance; mean difference between placebo and the combined bosentan groups was 44m ($p<0.001$). Bosentan also improved the Borg Dyspnoea index (mean treatment effect was -0.6 in favour of bosentan) and NYHA class (over 90% of patients had functional class III at baseline which improved to class II after 16 weeks in the groups receiving bosentan 125mg and 250mg, 38% and 34% of patients respectively). A delay in time to clinical worsening was demonstrated in the bosentan group (compared with placebo) with clinical benefits maintained for up to 28 weeks ($p=0.002$). (Rubin 2002).

Long term treatment with bosentan (> 1 year) demonstrated sustained improvements in haemodynamic parameters and NYHA class III/IV in 29 PAH patients and was well tolerated. (Sitbon 2003)

QoL improvements have also been demonstrated in an open-label single arm study involving 82 PAH patients class III/IV (70% idiopathic and 30% associated with CTD) treated with bosentan. (Keogh 2004) Results from an interim analysis at 6 months showed that bosentan significantly improved NYHA class and all QoL measures (short form, SF-36).

The following additional studies describe the efficacy of bosentan in the treatment of HIV associated PAH, PAH in patients with pre-existing congenital heart disease (CHD) and PAH secondary to scleroderma. (Sitbon 2004, Galie 2005e, Joglekar 2006)

In a RCT 54 PAH patients with pre-existing CHD (a condition known as Eisenmenger physiology) with NYHA class III received bosentan (n=37) or placebo (n=17). Improvements in exercise capacity (6MW distance +53.1m, $p=0.008$) and haemodynamics (reduction in mean pulmonary resistance) were demonstrated. (Galie 2005e)

In a prospective (non-comparative) 16 week study, PAH patients with HIV (n=16) and NYHA class III/IV received bosentan (62.5mg bd for 2 weeks followed by 125mg bd). Improvements in exercise capacity (6MW distance $\pm 91 \pm 60$m, $p<0.001$), NYHA class and QoL were demonstrated as well as improvements in cardiopulmonary haemodynamics, cardiacgeometry and cardiac function. Twelve patients continued treatment for >1 year. (Sitbon 2004)

A retrospective study (Joglekar 2006) of the efficacy of bosentan treatment (62.5mg bd for 1 month followed by 125mg bd) over 18 months was undertaken in patients (n=23) with PAH secondary to scleroderma including patients with restrictive lung disease (NYHA class II-IV). During the first three months of treatment 57% of patients improved functional class and none worsened. Improvement was sustained for three to six months but tended to worsen between 12 and 18 months.

Sitaxsentan

Results from RCTs evaluating the efficacy of oral sitaxsentan (doses 150mg, 100mg or 300mg) once daily involving over 400 PAH patients (NYHA class II/III/IV) demonstrate improvements in 6MWT distance, NYHA class and haemodynamics. (Barst 2004b, Cleland 2005).

In one RCT 178 PAH patients (53% idiopathic, 24% related to CTD and 24% congenital heart disease) class II-IV patients received placebo (n=60) or sitaxsentan 100mg daily (n=55) or 300mg daily (n=63) for 12 weeks. (Barst 2004b) Primary endpoint (% of predicted peak Vo2), Secondary end-points included 6MWT, QoL, time to clinical worsening and haemodynamics. After 12 weeks the primary end-point improved only in the 300mg sitaxsentan group ($p<0.01$ compared with placebo). However, both 100mg and 300mg doses demonstrated an increase in 6MWT distance (22m and 20m respectively) and improvements in haemodynamics. NYHA class improved in 29% and 30% of patients in the 100mg and 300mg groups respectively. No significant differences were seen between treatment groups in time to clinical worsening and QoL.

In a phase III RCT involving 246 PAH patients (NYHA class II-IV) the efficacy of sitaxsentan 100mg or 50mg was compared with placebo or open label bosentan for 18 weeks. The author reports of improvements in 6MWT and NYHA class in the sitaxsentan 100mg group when compared with placebo. (Cleland 2005).

Long term data (from an open label extension study) is also available for 10 patients receiving sitaxsentan 100mg daily up to one year. (Langleben 2004)

Ambrisentan

In a dose ranging study 64 PAH patients (idiopathic or associated with collagen vascular disease, anorexigen use and HIV infection) with NYHA functional class II/III received ambrisentan 1mg, 2.5mg, 5mg or 10mg once daily. (Galie 2005a) Patients were randomised to receive double blind treatment (no placebo) for 12 weeks followed by 12 week open label ambrisentan. After 12 weeks the 6MWT distance improved across all ambrisentan groups by 36.1m ($p<0.0001$). Improvements in the Borg Dyspnoea index, NYHA class, subject global assessment, mean pulmonary arterial pressure ($p<0.0001$) and cardiac index ($p<0.0008$) were also demonstrated. No dose response for efficacy was noted in this study.

The long term (one year) results from the above study are also available. (Galie 2005b) A total of 54 patients (NYHA class II/III) continued treatment in the open label extension and after 48 weeks (double blind/ open label) ambrisentan treatment the mean increase in the 6MWT distance for all combined dose groups ($n=64$) was 54.5m $\pm$54.9m ($p<0.0001$) with a mean improvement in Borg Dyspnoea index of -0.9$\pm$ 2.1 ($p<0.001$). NYHA class improved in 57% of patients and deteriorated in 5%.

Appendix E: Summary of PDE -5- I clinical trial data

Sildenafil

In a large RCT (Galie 2005c) PAH patients ($n=278$) were included regardless of NYHA functional class although the majority were graded class II (39%) or class III (58%). Patients received sildenafil (20, 40 or 80mg) orally three times a day or placebo. After 12 weeks the median distance walked in the sildenafil groups was 45m, 46m and 50m for the 20, 40 or 80mg groups respectively ($p<0.001$ for all comparisons). Improvements in at least one functional class was demonstrated in patients receiving placebo (7%), sildenafil 20mg tds (28%), 40mg tds (36%) and 80mg tds (42%). Results from a further analysis of this study have been presented demonstrating that sildenafil improves exercise capacity in patients with less severe disease (class I/II). (Badesch D Poster 2005)

In another RCT involving 22 PAH patients (NYHA class II-IV) (placebo $n=12$, sildenafil $n=10$) (Sastry 2004) significant improvements in the Dyspnoea ($p=0.009$) and fatigue ($p=0.04$) components of the QoL questionnaire were demonstrated in the sildenafil group ($n=10$) compared with placebo ($n=12$).

Long term treatment of sildenafil 80mg tds used alone or in combination, in PAH patients (NYHA class II-IV) for up to 1 year demonstrates that it is effective and well tolerated when four times the recommended licensed dose is used. (Galie 2005d).

Tadalafil

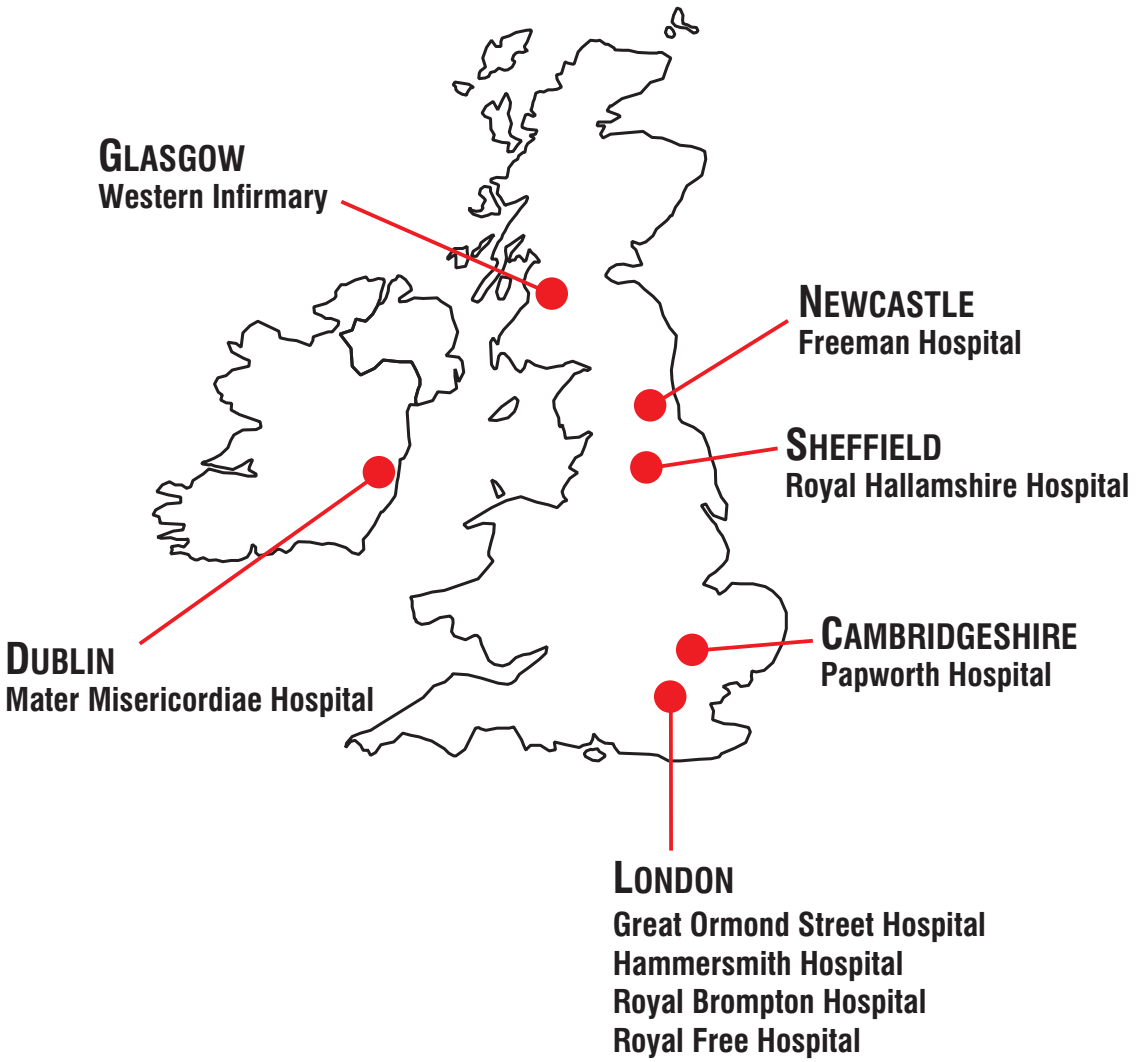
Only the short term impact of tadalafil on haemodynamic and oxygen responses has been evaluated in 60 PAH patients (46 with idiopathic PAH) with NYHA class II-IV in a prospective randomised study. Patients received tadalafil 20mg ($n=9$), 40mg ($n=8$) or 60mg ($n=8$) or other PDE-5 Is (sildenafil, $n=19$ and vardenafil, $n=16$). Tadalafil caused significant pulmonary vasorelaxation (following short term nitric oxide inhalation) and a significant reduction on pulmonary to systemic vascular resistance ratio. No improvement in arterial oxygenation was noted. (Ghofrani 2004)

Appendix F: Clinical trial inclusion criteria

- RCT are included for all efficacy data where available.
- Smaller studies are mentioned only if no RCT data available.
- Long term data includes open label studies.

PH Specialist Centres

There are 8 PH Specialist Centres in the UK as designated by the National Service Committee Advisory Group (NSCAG), with an additional centre in the Republic of Ireland. They are based at the following locations:



PHA-UK: Growing all the time

The PHA-UK is registered with the Charity Commission and it is run independently from the NHS and other affiliated bodies. It is governed by a committee of voluntary Trustees, has a Medical Advisory Group and the support of Patrons that come from different backgrounds. The PHA-UK continues to see steady and, most importantly, sustainable growth in both size and activity. Since its formation in 2000 the membership has grown from 6 original members to over 1,500 today. This expansion has been helped by the trustees, PH specialist centres, pharmaceutical companies and allied trades but most importantly by the members themselves.

Over the years the charity has very successfully strengthened and broadened its links with the PH specialist centres and is well respected at both national and international level.

Here are just some of the things that are now available to all members:

- National Conferences
- Family Weekends
- Regional Support Groups
- Specialist Centre Meetings
- Website www.pha-uk.com
- Educational Materials - Literature / DVD's
- Freephone Helpline for patients and families
- Financial Grants for patients and research
- Newsletters

Other activities undertaken

- All Party Committee for PH at Westminster
- PH Awareness Week
- Targeted Media Campaigns
- Member of PHA Europe
- Member of the Heart Care Partnership
- Member of the Specialist Healthcare Alliance

The list of activities goes on and is expanding at an amazing rate. Over the years many people have given and continue to give huge amounts of time freely to ensure that this organisation continues to make a positive difference in the world of PH. Without these people these aims and achievements would never have happened.

Notes

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