

PHA EUROPE

European pulmonary hypertension association

for the patients



June 2012

Addressing the Unmet Needs of Persons Living with Pulmonary Hypertension: A Call to Action

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Table of Contents

Why action is needed in pulmonary hypertension	5
Call to action (summary)	7
Addressing the unmet needs of persons living with pulmonary hypertension	9
Introduction	9
Types of pulmonary hypertension	10
Symptoms	12
Diagnosis	12
Treatment	13
Prognosis.....	14
Call to action (expanded)	15
1. Improve access to expert care	15
Centres of expertise.....	15
Transplantation	17
Standards of care/clinical guidelines.....	18
Treatment access	19
2. Improve awareness and screening	20
Screening and diagnosis.....	20
Awareness.....	21
3. Encourage clinical research and innovation	23
4. Empower patient groups	26
5. Assure availability of psychosocial support	27
Summary	29
About PHA Europe	30
Pulmonary Hypertension Roundtable members	31
References	35

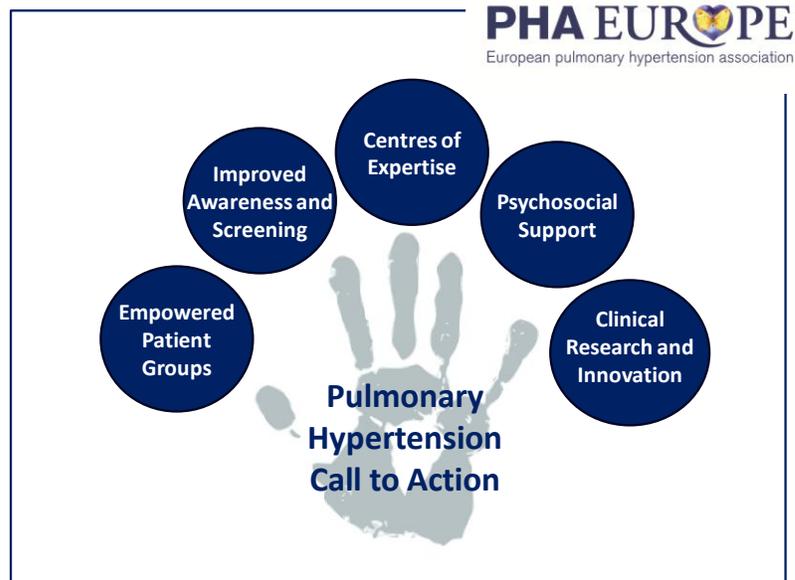
Why Action Is Needed in Pulmonary Hypertension

Most of us take breathing for granted. Persons living with pulmonary hypertension do not. Pulmonary hypertension (PH) is the broad, inclusive name for a group of several chronic diseases that affect the lungs and the heart. Some forms of PH are rare as well as rapidly progressing, debilitating, and deadly. In PH, the arteries that carry blood from the heart to the lungs narrow for reasons that are not yet entirely understood. The heart struggles to pump blood through the narrowed arteries, resulting in high blood pressure in the lungs and enlargement of the heart. Eventually, the overworked heart wears out, and heart failure and death can result.

PH affects more than 25 million people worldwide.¹ It may be caused by any one of a number of other underlying conditions, or it can occur from no identifiable cause. Symptoms usually do not appear until the disease has progressed, meaning diagnosis and treatment may be delayed. PH does not discriminate, but occurs irrespective of age, race, and ethnicity. It can strike our colleagues, our neighbours, our family, ourselves.

Unfortunately, there are approved treatments for only about one percent of persons diagnosed with PH – those who have a rare form of the disease known as pulmonary arterial hypertension (PAH). Even with therapy, the median survival for a person living with PAH is only five to six years, although timely diagnosis and better disease management can significantly improve that timeline.

The struggle to do something as automatic and essential to life as breathing is both frightening and disheartening. That is why this call to action is needed:



- PH must be appropriately diagnosed in a timely manner so that patients can be appropriately treated.
- Centres of expertise having multidisciplinary medical teams that are trained and experienced in the diagnosis and treatment of PH are needed, so that currently available treatments are prescribed only for those patients who will benefit from them, and not for patients in whom PAH treatments can be toxic.
- Researchers must continue to investigate innovative and improved treatments until a cure is found.

I dream that PH becomes a normal illness: you are diagnosed, people know what to do, you are cured!

Melanie, France

CALL TO ACTION

1. IMPROVE ACCESS TO EXPERT CARE

- Establish centres of expertise:
 - High volume centres of expertise, staffed by a multidisciplinary team of physicians who are trained and experienced in pulmonary hypertension (PH) care, should provide for the diagnosis and care of PH patients.
 - Expert centres are necessary to ensure that currently available drugs are prescribed and used appropriately.
- Increase transplants by enacting donor legislation that ensures easier access to transplant. All EU countries should develop and maintain comprehensive and humane organ donation policies.
- Develop and regularly update clinical practice guidelines.
- Ensure that drugs or combinations of drugs for PH patients are prescribed by expert physicians, and that patient access is not arbitrarily limited by national policies.

2. IMPROVE AWARENESS AND SCREENING

- Initiate PH awareness campaigns and training programmes.
- Create national screening and diagnosis programmes, tailored to PH patient subgroups.
- Raise awareness of the potential for curative surgery for chronic thromboembolic pulmonary hypertension (CTEPH) and the need to appropriately evaluate CTEPH patients.

3. ENCOURAGE CLINICAL RESEARCH AND INNOVATION

- Ensure more support and funding for:
 - Fundamental PH research
 - Research that leads to effective treatments for all forms of PH
 - Research to determine non-invasive methods for measuring pulmonary pressure and cardiac output.

4. EMPOWER PATIENT GROUPS

- Facilitate real-life information exchange between PH patient organisations and policy makers through roundtables, working groups, and other activities.
- Include patient groups in health care policy debates and decision-making.
- Increase the capacity of patient organisations to allow them to more effectively serve patients, particularly through the provision of accurate, regularly updated information on websites.
- Encourage financial support for patient associations that ensures their independence.

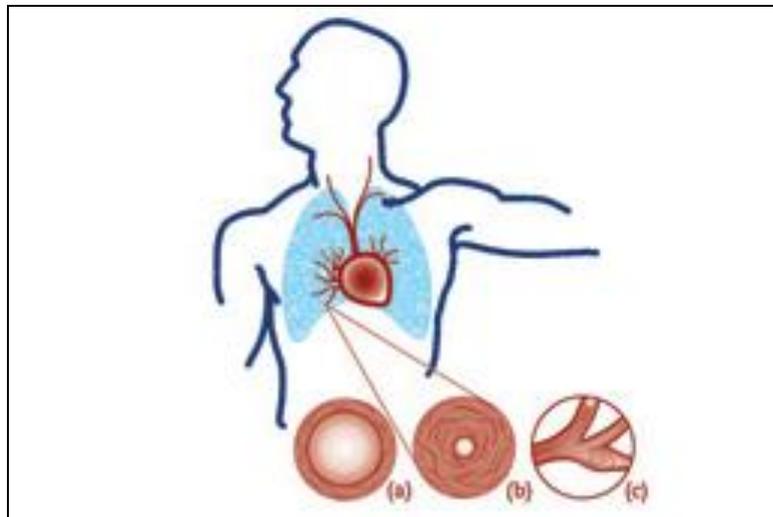
5. ASSURE AVAILABILITY OF PSYCHOSOCIAL SUPPORT

- Ensure that PH treatment encompasses treatment for the “whole” patient. National systems of integrated care must be instituted, encompassing all aspects of medical, psychosocial, nutritional, and rehabilitative support for patients and their caretakers.
- Ensure that patient associations have secure and ongoing sources of funding for patient psychosocial support, including 24-hour telephone help lines and other programmes.
- Afford disabled status to PH patients.

ADDRESSING THE UNMET NEEDS OF PERSONS LIVING WITH PULMONARY HYPERTENSION

Introduction

Pulmonary hypertension (PH) is the broad, inclusive name for a group of several chronic diseases that affect the lungs and the heart. Some forms (or "subtypes") of PH are rare as well as rapidly progressing, debilitating, and deadly. In PH, the arteries that carry blood from the heart to the lungs narrow for reasons that are not yet entirely understood. The heart struggles to pump blood through the narrowed arteries, resulting in high blood pressure in the lungs and enlargement of the heart. Eventually, the overworked heart wears out, and heart failure and death can result.



Grafik: www.rasterfront.de

- a. Cross section of normal pulmonary artery
- b. Reduced lumen of pulmonary vessels due to cell proliferation and remodeling in advanced Pulmonary Arterial Hypertension
- c. Longitudinal section with pathological changes within the vessels (proliferation, deposition of blood clots, thickening) causing difficulties for the heart to pump blood through the lungs

PH does not discriminate. Although more common in young adults and in women, it occurs irrespective of age, race, and ethnicity. Sometimes PH runs in families. Unfortunately, the symptoms of PH, which may include shortness of breath, fatigue, dizziness, and fainting spells, vary from patient to patient, and usually do not occur until the disease has progressed. This delays diagnosis and treatment.

Diagnosis and treatment options are complex. Patients often look well, even when they are deteriorating. In the hands of inexperienced physicians, this may result in missed opportunities for treatment to keep patients relatively well, as well as refusal of social support services from authorities. Current therapies slow disease progression but are not curative. There are many novel drugs which may be effective but require testing in clinical trials.

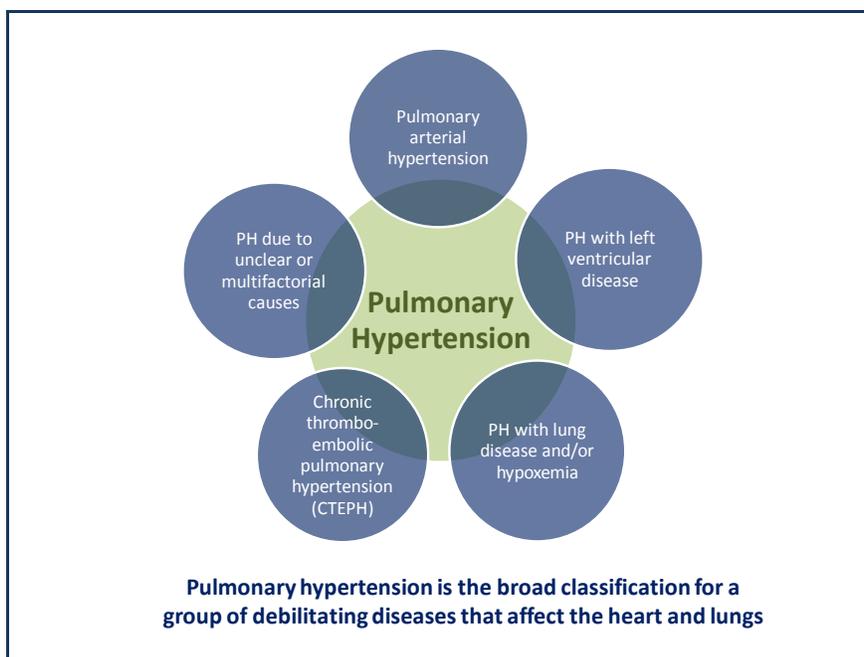
Complicating late diagnosis is the fact that, while pulmonary hypertension affects more than 25 million people worldwide,² the majority of patients are without approved treatment. In fact, the only currently approved therapies are for one of five subtypes of PH: pulmonary arterial hypertension (PAH), which comprises only a small proportion of PH cases. Even with therapy, the median survival for a person living with PAH is only five to six years, although timely diagnosis and better disease management can significantly improve that timeline.

It is critical that people living with PH be properly diagnosed in a timely manner and afforded access to appropriate treatment. There are important economic considerations inherent in this call to action: PAH treatment is costly, and it is sometimes inappropriately prescribed for persons who have other forms of PH (for which there currently are no treatments). Not only does inappropriate treatment escalate health care costs, but currently available PAH treatments can be toxic in patients living with other forms of the disease, so lives are at risk when specific drugs are wrongly prescribed. Inaccurate diagnosis and inappropriate treatment also lead to lost work productivity and increased treatment, hospitalization, and psychosocial support costs.

Only when PH is managed and treated correctly and responsibly will patients' quality of life improve, and the burden on health care infrastructure and society be lessened.

Types of Pulmonary Hypertension^{3,4}

There are five subtypes of PH. Some are rare; some occur more frequently. Each has different underlying causes, and may therefore need to be treated differently. Yet currently there are approved treatments for only the first of the five subtypes described below, and that treatment has been demonstrated to have potentially deleterious effects on patients with other forms of PH, underscoring the need for accurate diagnosis in order to ensure optimal rather than life-threatening treatment.



1. **Pulmonary Arterial Hypertension (PAH)** is a rare, chronic, progressive condition that is disabling and costly to society, and which can lead to death. The European Union defines a rare disease as one that affects fewer than five people per 10,000.⁵ Across the globe, PAH has an incidence of 2.4 cases per million per year, and a prevalence of 15 cases per million⁶ (15 to 52 per million in Europe⁷). (*Incidence* refers to the number of people diagnosed within a specific period of time; *prevalence* refers to the number of people living with a disease.) Globally, it is estimated that approximately one percent of PH diagnoses are for PAH.

PAH can be caused by:

- Conditions such as connective tissue diseases, HIV infection, liver disease, congenital heart disease, sickle cell disease, and schistosomiasis (a parasitic infection that is one of the most common causes of PAH in many parts of the world)⁸
- Conditions that affect the veins and small blood vessels of the lungs
- Drugs or toxins, including street drugs and certain diet medicines

PAH may also be idiopathic (having no known cause), in which case the condition is known as idiopathic pulmonary arterial hypertension, or IPAH.^{9,10} PAH may also be inherited.

PAH is treatable. In fact, the only currently approved therapies are for this PH subtype, although PAH comprises only a small proportion of PH cases. Yet even with therapy, the median survival for a PAH patient is only five to six years following diagnosis, and there are no cures. Unfortunately, for the other forms of PH that follow, therapeutic options are extremely limited.

2. **PH with left ventricular disease (PH-LVD)** is caused by disorders that affect the left side of the heart, including mitral valve disease and long-term high blood pressure. Left heart disease is thought to be the most common cause of pulmonary hypertension – about 80% of all PH diagnoses.
3. **PH with lung disease and/or hypoxemia, including PH with chronic obstructive pulmonary disease (PH-COPD) and PH with interstitial lung disease (PH-ILD)**, is associated with lung diseases such as COPD as well as sleep-related breathing disorders such as sleep apnea. It can also be caused by diseases that result in scarring of the lung tissue. Such diseases may stem from long-term exposure to hazardous materials or autoimmune diseases (e.g., rheumatoid arthritis), although in most cases, the cause of ILD is unknown.¹¹ It is thought that ten percent of PH diagnoses are for this subtype.
4. **Chronic thromboembolic pulmonary hypertension (CTEPH)** is caused by blood clots in the lungs or blood clotting disorders. It is often inappropriately treated, and patients do not always have sufficient information about – or access to – indicated surgical options for care. The incidence for CTEPH is believed to be about one to three percent, although the prevalence is unknown, and evidence suggests that the disease is under-diagnosed.¹²
5. **PH due to unclear or multifactorial (i.e., multiple) causes:** Pulmonary hypertension may also be caused by other diseases and conditions including:
 - Blood disorders
 - Systemic disorders, such as vasculitis (inflammation caused by an immune system attack on the blood vessels)
 - Metabolic disorders, such as thyroid disease and glycogen storage disease

- Other conditions, such as tumours that press on the pulmonary arteries, and kidney disease

Approximately eight percent of PH diagnoses fall into this category.

Symptoms

Irrespective of the subtype of pulmonary hypertension, the symptoms of PH tend not to be sufficiently specific to provide a simple diagnosis. Signs and symptoms of PH may include:

- Shortness of breath during routine activity, such as climbing stairs. Difficult or uncomfortable breathing is known as dyspnea, and when PH is severe, the patient may experience this symptom even when at rest.
- Fatigue
- Dizziness or light-headedness
- Racing pulse
- Fainting spells
- Chest pain
- Swelling of the ankles, stomach, and/or legs
- Bluish colour in the lips and skin

As PH worsens, the patient may find it hard to perform any physical activities, inhibiting the ability to perform even the simplest tasks. Patients' daily activities are therefore often curtailed, and when asked by their physicians, they report a substantially reduced quality of life.¹³ In advanced stages of the disease, the patient is both debilitated and dependent.



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Diagnosis

A physician's diagnosis of pulmonary hypertension is dependent on:

- **Medical and family history:** The physician will ask about signs and symptoms, and how and when they began. He or she may also ask whether the patient has other medical conditions that can cause PH, or whether any family members have or have had PH. Persons who have a family history of PH are at higher risk for the condition.

- **Physical Exam:** During the physical exam, the physician will listen to the heart and lungs with a stethoscope, check for fluid in the abdomen, and check ankles and legs for swelling and lips and skin for a bluish colour, all of which are signs of PH.
- **Diagnostic tests:** A physician may recommend tests and procedures to confirm a diagnosis of PH, to look for its underlying cause, and to determine its severity. Tests may include:
 - An electrocardiogram, which can reveal signs of an enlarged right heart or arrhythmia (irregular heartbeat).
 - An X-ray to show the size and shape of the heart and the structure of the lungs. Lung function tests and arterial blood gas readings that may reveal a low uptake of oxygen.
 - An ultrasound of the heart (echo-cardiogram) to assess the structure of the heart, including wall thickness, diameters of cavities, and narrowed heart valves and main vessels. The blood flow can be visualised in some tests, and essential parameters like pulmonary pressure can be calculated. These measurements are, however, indirect and dependent on the skills of the investigator, and so they are not optimal. The echocardiogram should also evaluate whether there are any holes in the heart [indicating congenital heart disease] that may be associated with PH. A cavitation study (i.e., a study to identify cavities, or holes) is often performed to exclude a hole in the heart.
 - Right heart catheterization (RHC) to measure the pressure in the pulmonary arteries and how well the heart is pumping blood to the rest of the body. RHC is performed through a thin tube (catheter) that is inserted into a vein in the neck, arm, or groin and moved through the right heart chambers into the lung artery, most often under X-ray control. Right heart catheterization is the most reliable diagnostic tool for confirming a diagnosis of PH, and it is consequently considered the “gold standard” for PH diagnosis. *According to internationally accepted PH guidelines, every patient should have right heart catheterization to confirm a PH diagnosis.*¹⁴ In some countries (e.g., Germany) RHC is common; in others it is only performed in exceptional cases, largely because of insufficient resources to fund the procedure.

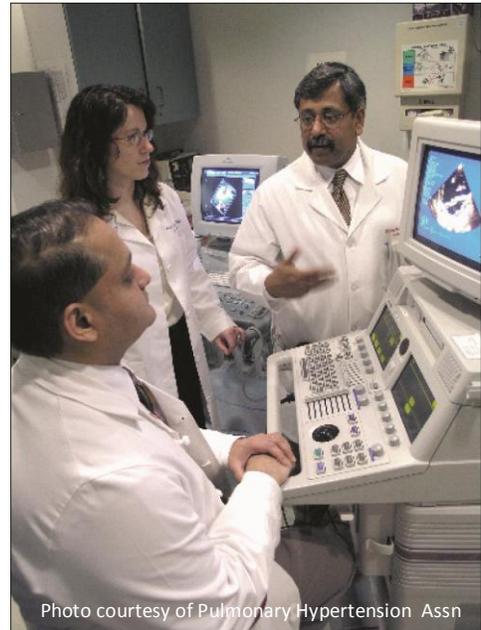


Photo courtesy of Pulmonary Hypertension Assn

Treatment

While there is no approved treatment for most forms of PH, drugs from several classes are available to treat PAH.¹⁵ Currently, treatment tends toward the use of a combination of drugs with different mechanisms of action.^{16, 17} The rationale behind combination therapy is that different disease mechanisms are targeted, which leads to improved treatment outcomes. At present there is no clinical

consensus about whether to utilize all drugs in a combination simultaneously (“hit hard, hit early”),^{18, 19} or to employ them in stepped fashion.²⁰ Clinical trials currently under way are designed to answer this question.

I'd love to work part time, but no one wants to employ me.

Miroslav, Slovakia

It is important to note that medical treatment for PAH is characterized by variable response and, at present, the clinical effect of a selected monotherapy cannot be predicted. This may lead to an insufficient effect on individual patients, and valuable treatment time may be lost. Thus, urgent and regular review of the clinical status is important, to ensure appropriate therapy and the best individual outcome.

Prognosis

PH is severe, debilitating, and life-threatening. It inhibits one’s ability to perform even the simplest daily tasks, and leaves the patient tired and breathless. There are approved treatments for only one subtype (PAH), and there is only one subtype (CTEPH) that is potentially curable without the need to resort to transplantation.²¹ Until about 15 years ago, the prognosis for patients was grim, as there were no PH-specific treatments. Even today, deteriorating quality of life, dependency, and eventual disability and decline are the norm. However, particularly in the last decade, thanks to advances in pharmaceutical research and development, the management of patients has substantially improved as new PH-specific drugs have been discovered, approved, and introduced to market.

[I want to] be less breathless; to not have to always anticipate fatigue.

Martine, France

I hope I will be able to carry my own children because I really want a family of my own. I would be very sad if I couldn't have children of my own.

Lynn, Belgium

I am on a waiting list for lung transplantation and hope that the operation will take place in the next 6 months. I also hope that I won't get ill and will be strong enough to handle everything.

Jana, Slovakia



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CALL TO ACTION

1. IMPROVE ACCESS TO EXPERT CARE

- **Establish centres of expertise:**
 - **High volume centres of expertise, staffed by a multidisciplinary team of physicians who are trained and experienced in PH care, should provide for the diagnosis and care of PH patients.**
 - **Expert centres are necessary to ensure that currently available drugs are prescribed and used appropriately.**
- **Increase transplants by enacting donor legislation that ensures easier access to transplant. All EU countries should develop and maintain comprehensive and humane organ donation policies.**
- **Develop and regularly update clinical practice guidelines.**
- **Ensure that drugs or combinations of drugs for PH patients are prescribed by expert physicians, and that patient access is not arbitrarily limited by national policies.**

Centres of Expertise ²²

High volume expert centres should provide for the clinical care of PH patients. High volume units have recurrently been shown in medicine to obtain best outcomes for patients while maintaining greatest patient satisfaction, lowest complication rates, shortest length of hospital stay, and best value for health care payers. In fact, the European Union Committee of Experts on Rare Diseases (EUCERD) “*recognises the European added-value of networks of expertise in the field of rare diseases, and cites the need to improve ‘universal access to high quality healthcare for rare diseases, in particular through the development of national/regional centres of expertise.’*”²³

I experienced a progressive shortness of breath for about two years. I was prescribed several asthma medications which didn't work. Eventually my physician referred me to a cardiologist. He performed an echo and sent me to [an expert] centre. Then I was diagnosed with PAH and started treatment.

Maria, Slovakia

The call for centres of expertise is also consistent with European Organisation for Rare Diseases (EURORDIS) efforts on behalf of persons living with rare disease. Among many other activities, EURORDIS adopted and disseminated in 2008 a Declaration of Common Principles on Centres of Expertise and European Reference Networks for Rare Diseases²⁴ to improve patient care throughout Europe. The EURORDIS Declaration calls upon National Health Authorities to contribute to the identification of Centres of Expertise and to support them financially. EURORDIS also contributed to the

European Council Recommendation on European Action in the Field of Rare Disease, in which it expressed the “utter need for Centres of Expertise and European Reference Networks for Rare Diseases.”



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Currently structures for the management of PH patients differ substantially across regional and country borders. In some countries, such as France and the UK, centralized structures with selected expert centres are authorized to prescribe drugs for PAH (the one PH subtype for which there are available treatments), while other physicians are not allowed to do so. Conversely, in other countries, such as Germany, expert centres as well as non-specialised health care facilities and practitioners diagnose and treat PH patients.

In a disease such as pulmonary hypertension, some subtypes of which are rare diseases, expert centres should be expected to:

- Be accountable to the organisation or agency that designates their expert centre status (e.g., department of health, other regulatory authority, health care payers).
- Diagnose patients with a medical team including expert staff in echocardiography, imaging, cardiac catheterization laboratory, lung function laboratory, and cardio-pulmonary exercise testing.
- Manage patients with a team comprising physicians who are trained and experienced in the treatment of PH, and incorporating respiratory physicians, cardiologists (including adult congenital heart disease specialists), rheumatologists, haematologists, clinical genetics, critical care, anaesthetics, family planning, palliative care, mental health, and rehabilitative medicine experts – with close links to other clinical services including pulmonary endarterectomy surgery (PEA) and lung/heart-lung transplantation.
- Prescribe disease-targeted drug therapies for PH for the entire duration of treatment.
- Provide printed patient information and have formal links with patient organisations.
- Adhere to pre-specified standards of care/guidelines (see *Standards of Care/Clinical Guidelines*, below).
- Undertake a clinical research programme including entry of patients into randomised controlled trials as a minimum.
- Participate in the development of a network of PH centres within the expert centre’s own country.
- Undertake clinical audits with reporting of outcomes and comparison with other expert centres in the same country.
- Provide a minimum of one to two years’ training in PH for colleagues, junior doctors, and nurses within the expert centre.

- Undertake an educational programme for health care professionals to raise awareness about appropriate patient referrals to expert centres.
- Perform thoracic surgery and organ transplants, as necessary and indicated.
- Actively participate in international exchanges of research and other data.

The size of an expert centre should depend on the population demographics of the country in which it is located. In general:

- Each country should have at least two adult expert centres.
- Each country should have at least one paediatric expert centre.
- The ideal number of patients seen by an adult centre each year should be no fewer than 200, of which at least half should have a final diagnosis of PAH. (Paediatric centres should see 30 to 50 patients per year.) In countries with a population greater than 10 million, adult centres should ideally expand to accommodate more than 300 patients annually.

I dream about seeing my girls find their paths in life and them being safe and sound. I dream of a cure for PH or for the continuing development of good medications to treat it. Vivian, Norway

Transplantation

Heart-lung transplantation and bilateral lung transplantation are last resort measures in PH and PAH. Transplanted organs provide a long-term survival benefit for patients with advanced PH. Benefits of lung transplantation include improvement in haemodynamics (blood flow), exercise tolerance, alleviated shortness of breath, and long-term survival. Studies indicate that “early referral to a centre with expertise in the management of PAH and transplantation increases the chances of achieving the best possible long-term outcome for patients with this devastating disease.”²⁵

For this reason, transplant for PH patients should be performed only in specialised treatment centres having high expertise. Expert centres should allow for the possibility of trans-border referrals and concentration of expertise that transcends geographic borders.



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Transplant is, however, associated with major shortcomings, including the need for lifelong immune-suppression (suppression of the body's immune system to reduce the likelihood of rejection of a transplanted organ) and the morbidity associated with increased risk for infection and allograft

rejection. (An allograft is the transplant of an organ or tissue from one person to another, other than from an identical twin.)

I am already on borrowed time; [I was] given two to four months in 2010 when I had heart failure. I am listed for a heart/double lung transplant. I hope to have that transplant and survive it in order that I may spend more time with my daughter (now 2). Kristy, United Kingdom

Because organ transplant is a last resort measure for patients who have exhausted other treatment options and whose life may hang in the balance, the need for organ donation is important. Organ procurement can be increased across the European Union by a simple change in policy that assumes that people will be organ donors unless they specifically opt out.

Moreover, PH patients awaiting transplantation often experience rapid disease progression and are therefore in more critical need of donor organs than are patients with other diseases. Unfortunately, this urgent need currently is not sufficiently reflected in the different organ allocation systems across Europe. Adaptation of organ allocation algorithms to meet the needs of patients with advanced PH should therefore be initiated.

Standards of Care/Clinical Guidelines²⁶

Among the Council of the European Union Recommendations on action in the field of rare diseases,²⁷ one important goal is to “gather expertise at the national level and support the pooling of that expertise with European counterparts” to encourage “sharing of best practices on diagnostic tools and medical care” and improve standards of care for patients with rare diseases.

Whatever the health care system, physicians should focus on obtaining the best outcomes for their patients. A document describing national standards of care for pulmonary hypertension centres should consider inclusion of standards about:



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- Patient-centred care
- Referral
- Diagnosis and assessment
- Care and treatment
- Patient monitoring, review, and follow-up
- Shared care
- Psychosocial support and palliative care
- Communication with health care professionals outside the expert centre
- Education and training of expert centre staff

- Research and development
- Transition of patients from paediatric to adult services
- Thoracic surgery and transplant

European scientific societies including the European Society of Cardiology and the European Respiratory Society have published evidence-based guidelines for PH care (<http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-PH-FT.pdf>), which are regularly reviewed and updated as necessary. These can and should serve as a guide and model for national standards of care.

Treatment Access

In a rapidly advancing disease area such as PH, expert providers should have sufficient flexibility to provide the right combination of drugs in the right sequence for their patients. National policies that limit the number of drugs to be used, or that impose “fail first” restrictions, do not support the evolving standard of PH care and may lead to poor outcomes for patients.

Moreover, many orphan drugs (treatments for rare diseases) remain unreimbursed at the national level for unacceptably long periods of time after they are approved for use. As should be the case with all drugs that treat serious, life-threatening conditions, where access to appropriate care can save lives, PH drugs should be reimbursed as soon as is practicable after approval.

My wistful dream is easy breathing, [but] however much I should like it, I can't realize this without a combination of drugs. But there is no access to combination therapy because of limits that legislation in our country places on the number of drugs that can be used. Zane, Latvia

2. IMPROVE AWARENESS AND SCREENING

- **Initiate PH awareness campaigns and training programmes.**
- **Create national screening and diagnosis programmes, tailored to PH patient subgroups.**
- **Raise awareness of the potential for curative surgery for chronic thromboembolic pulmonary hypertension (CTEPH) and the need to appropriately evaluate CTEPH patients.**

Screening and Diagnosis

PAH is a rare disease for which there are several established treatment options. Unfortunately, there are no approved therapies for other, more frequent forms of PH, and PAH treatments may be lethal in other subtypes of the disease. For these reasons, systematic screening programmes for at-risk groups are essential to diagnose patients as quickly as possible – before disease progression – in order to substantively improve patient prognoses.

Given that PH symptoms are often non-specific (i.e., symptoms do not necessarily point to a PH diagnosis), a public at-large screening campaign would be unaffordable and ethically questionable: patients would need to undergo invasive diagnostic procedures and incur the risk of false positive diagnoses. Thus, screening programmes should be initiated only to ensure timely diagnosis of PH in patient groups at high risk. All at-risk patients should undergo a physical examination at regular intervals, incorporating ultrasound, to look for the early signals of PH.



Photograph courtesy of Pulmonary Hypertension Association

The following patient groups should be specifically targeted for screening:

- Persons having shortness of breath for no apparent reason.
- Patients with connective tissue disease (CTD): Some diseases – such as systemic sclerosis, lupus erythematoses, and, to a lesser extent, rheumatoid arthritis, dermatomyositis, and Sjögren’s syndrome – bring an increased risk for PH.^{28,29,30} PAH associated with CTD is the second most prevalent form of PAH.
- Patients with HIV/AIDS: The prevalence of PAH in HIV patients is about 0.5 percent (i.e., one in 200 people living with HIV also has PAH). Many of these patients are already at an

advanced stage of PAH when diagnosed,³¹ and they consequently have very poor prognoses.

- Patients with portal hypertension (portal hypertension is an increase in pressure in the vein that carries blood from the digestive organs to the liver): PAH is a well-established complication in patients with established liver disease (occurring in one to two percent of such patients). In patients with severe liver disease, such as those scheduled for liver transplantation, the incidence of PAH rises to approximately five percent.³²
- Patients with congenital heart disease: Systemic-to-pulmonary shunts (congenital heart defects) are among the most frequent congenital heart diseases, and an estimated five to 10 percent of this large patient group³³ have PAH. Clinical research in this population, even in the most severe forms of PAH, shows that available drug therapies are effective.³⁴ Although surgical repair of the congenital heart defects within the first year of life prevents progressive PAH in the vast majority of patients, early repair does not preclude the development of progressive PAH later in life after successful surgical repair in infancy or early childhood. Thus, all patients who are repaired should be followed long-term with one of the aims being to evaluate for the possible development of PH post-repair.



Photograph courtesy of Sociedad Latina de Hipertensión Pulmonar

Chronic thromboembolic pulmonary hypertension (CTEPH) deserves particular attention because it is the only form of PH that can be cured other than by transplantation.^{35,36,37} CTEPH has been observed in 0.1 to 4 percent of patients who have survived pulmonary embolism.³⁸ Embolism often leads to death, but patients may survive even as their blood clots persist. The clot impedes blood flow, which in turn leads to right ventricular failure, causing death. If the blood clot is removed, a normal blood flow can be restored.

Blood clots can be removed with pulmonary endarterectomy (PEA)³⁹. Unfortunately, some 50 percent of patients are ineligible for this surgery, and inoperable CTEPH patients as a group face one of the worst PH prognoses.⁴⁰ Even after undergoing PEA, roughly 10 percent of patients continue to suffer from PH and need other treatment. Pulmonary embolism (PE) is an emergency condition, and virtually all intensive care units treat the condition. However, systematic screening programmes for CTEPH in patients who have survived PE are currently limited because of insufficient data regarding subpopulations at risk and the rate at which CTEPH is occurring after PE.

Awareness

Improved awareness about PH is essential among primary health care providers to ensure correct and appropriate diagnosis. Only when general practitioners are adequately educated about PH will they know how to recognize disease symptoms and to refer patients for expert care at a centre of expertise.

PH can be won simply with awareness. I hope that in the future doctors will identify this disease in a short time, and research will find new therapies for us.

Giuliana, Italy

Awareness campaigns have been launched in various countries by patient associations and pharmaceutical companies. One such campaign in 2006 highlighted breathlessness as an indicator for PAH and was directed to cardiologists, pulmonologists, and internists.

Awareness campaigns are also needed for patients at risk for PH so that they can be made aware of the condition and provided with information that lets them know where to find educational material and sources of support, including PH patient groups. As is the case with all rare disorders, these campaigns should be targeted to locations where they will be most effective – for PH, in cardiology, pulmonology, infectious disease, hepatology, and internal medicine clinics and offices, as well as to the general public.

As one example, PHA Europe launched the *Breathtaking* public awareness campaign in conjunction with Rare Disease Day in 2011, and redoubled its efforts in 2012, with awareness-raising activities in 17 countries.



3. ENCOURAGE CLINICAL RESEARCH AND INNOVATION

- **Ensure more support and funding for:**
 - **Fundamental PH research**
 - **Research that leads to effective treatments for all forms of PH**
 - **Research to determine non-invasive methods for measuring pulmonary pressure and cardiac output**

To develop new treatments for PH, more translational research is needed. Translational research moves from theoretical studies to practical application, beginning with basic research in the laboratory and ultimately progressing to clinical research at the patient's bedside. Translational research has proven to be a powerful process that drives clinical research. Encouraging translational research in PH will not only strengthen the research infrastructure, but also potentially accelerate the discovery of new, safe, and effective treatments for all forms of PH.

My dream, and I think I speak for many people with PH, would be to find a cure that makes living with PH easier, [and] that treatment is available to all. Kateřina, Czech Republic

While funding for basic research and clinical trials has increased understanding of PH and resulted in a number of approved drugs, compelling research questions remain, covering:

- **Clinical trials in PH subtypes other than PAH:** While PAH has been the subject of a substantial number of investigations, clinical studies in other PH subgroups are far less frequent. PH resulting from left heart disease or lung disease, for example, occurs frequently, yet no treatments have been developed. Investigation of currently approved PAH drugs for use in other PH subtypes must also be supported.⁴¹
- **Treatment outcome goals:** Research is needed to clarify desired outcomes (tailored to severity of disease, age, and other factors), covering enhanced quality of life, improved functional capacity, and greater independence, among other outcomes.
- **Clinically relevant endpoints and extended duration for clinical trials:** The great majority of PH studies employ the six-minute walk test as a measure of the ability to exercise. Its validity as an endpoint is compromised because age and orthopaedic conditions may interfere with one's ability to walk six minutes. New, more clinically relevant endpoints must be identified. Also, to date, clinical trials have been nearly uniform with respect to duration of treatment. Extending treatment duration would better reflect real life conditions and more realistically measure disease progression.
- **Quality of life:** Quality of life is a pivotal concern for all patients. Consequently, quality of life data should be available for all approved drug treatments.
- **PH health technology assessment (HTA):** At present, the only approved treatment for pulmonary hypertension is for one of the five forms – pulmonary arterial hypertension

(PAH) – and there currently has been only one HTA for PAH treatment, which assessed the “clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for pulmonary arterial hypertension within their licensed indications.”⁴² Because new drugs are now available, and given the increasing use of combination therapy, an update of this HTA is necessary.

- **Non-invasive diagnostic tests:** Currently, the only definitive way to diagnose PAH is through right heart catheterization (RHC). This is a costly and highly stressful procedure for the patient – particularly for infants and children – that carries risks if performed by inexperienced clinicians. Research must focus on the refinement of non-invasive diagnostic measures. That said, for the time being, RHC is the gold standard for diagnosing PH and assessing response to therapy. In an experienced center, the benefit-to-risk profile strongly favors performing an initial RHC for diagnosis and subsequent RHCs to assess disease severity and patient response to treatment.
- **Real life data:** While results from approximately 30 randomised controlled clinical trials have been published on various PAH drugs and their combinations, data on patient management in clinical conditions is limited. Observational data are needed. Information from the management of PH patients in expert centres will yield useful data (and as the number of expert centres increases, more data will be available), and registries should follow individual PAH patients over several years.
- **More paediatric studies:** The prevalence of pulmonary hypertension in children is not known, but it does occur, most commonly because of premature birth, prolonged mechanical ventilation, certain types of heart disease, diaphragmatic hernia, or family history.⁴³ Paediatric patients often have comorbidities (i.e., other diseases or disorders) that make the definite etiology (i.e., cause) of PH difficult to determine. More studies are needed to understand the causes of paediatric PH and to identify optimal diagnostic tests and treatments. There are far fewer paediatric PH centres than there are adult centres. Because of the frequent need for anesthesia during right heart catheterization (necessary for an accurate PH diagnosis), children with suspected PH should only receive care at paediatric PH centres of expertise having dedicated paediatric cardiologists and paediatric anesthesiologists.



Photograph courtesy of Pulmonary Hypertension Association

I want to be cured.

Sara (child), Switzerland

Finally, given the paucity of currently available treatments for most forms of PH, patients who qualify for clinical trials should not find their participation barred by policies that do not allow reimbursement for clinical trials and “experimental” treatment. Rather, insurance companies and reimbursement agencies must understand that these studies are often the only treatment option available for many patients, and therefore facilitate their enrolment in appropriate trials.

My dream for the future is to finish a major in economics and work in a government-related job. Being able to contribute to medical research, and ultimately find a cure for PH through government funding, is one of my main motivations for pursuing this career. Niklas, Norway



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My dream for the future is to see my little boy grow up.

Diane, Netherlands

4. EMPOWER PATIENT GROUPS

- Facilitate real-life information exchange between PH patient organisations and policy makers through roundtables, working groups, and other activities.
- Include patient groups in health care policy debates and decision-making.
- Increase the capacity of patient organisations to allow them to more effectively serve patients, particularly through the provision of accurate, regularly updated information on websites.
- Encourage financial support for patient associations that ensures their independence.

Health care providers need to be well informed about patient organisations and the services they offer so that they are able to direct patients to these vital sources of information and support that can help them navigate the often bewildering maze that follows a PH diagnosis. Many patient groups are staffed by people living with or affected by PH, and they offer peer support networks that can provide a wealth of experiential and knowledge-based counsel, advice, and direction. They can be a tremendously helpful adjunct to busy physicians who may not have sufficient time to adequately discuss patient concerns and needs.



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Patient groups are also well positioned to provide invaluable counsel to policy makers. When considering important issues that may impact the lives of PH patients, policy makers should actively seek and incorporate patient perspectives. Patients and their advocates should therefore always be represented on HTA panels, guidelines panels, clinical trial investigational review boards, regulatory advisory committees, clinical trial design and oversight committees, and other advisory bodies.

I dream of a world where PH Associations are strong and present in each and every country, so that we can all work for the ultimate goal of finding a cure for PH.

Juan, Spain

For patient groups to be as effective and efficient as possible, empowerment is required on numerous levels. Awareness must be enhanced within the health care community so that physicians are more likely and able to refer patients to these organisations. Policy and regulatory officials need to better understand the value of their counsel. Tax deductibility of contributions to not-for-profit organisations and other incentives must be in place so that more people are encouraged to support patient organisations, thereby helping to broaden their base of support.

5. ASSURE AVAILABILITY OF PSYCHOSOCIAL SUPPORT

- Ensure that PH treatment encompasses treatment for the “whole” patient. National systems of integrated care must be instituted, encompassing all aspects of medical, psychosocial, nutritional, and rehabilitative support for patients and their caretakers.
- Ensure that patient associations have secure and ongoing sources of funding for patient psychosocial support, including 24-hour telephone help lines and other programmes.
- Afford disabled status to PH patients.
- Encourage financial support for patient associations that ensures their independence.

Many patients feel isolated and alone after a PH diagnosis. Not only may they face complex treatment management issues, but also inevitable disruptions in their professional and personal lives as they experience a decreased capacity to work (in the office and at home) and to be involved in normal daily social and recreational activities. Some patients become so discouraged by their disability that they consider suicide. Because PH is debilitating and prognoses can be bleak, psychosocial support is critical. Health care teams should include social workers and psychological counselors as core members.



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I have PAH. I was diagnosed for it four years ago. My house is located in the countryside comparatively far from cities and district centres. I have no family and I live alone. For the present I can go to shop and pharmacy, but I don't know how long I will be able to do it myself. I am afraid I won't be self-dependent anymore, but there is no social support for PH patients in Latvia.

Marta, Latvia

Psychosocial assessment should be a routine component of medical treatment. Psychosocial screening tools are needed to identify patients and families at risk for emotional and mental distress. Studies show that such tools do not take much time to develop and deploy, and that patients are willing to participate in such evaluations.⁴⁴

Even if health care teams provide state-of-the-art treatment, failure to address the psychological and social issues associated with PH can lead to problems such as lack of adherence to treatment, additional suffering, and delayed return to good health. Psychosocial problems can be exacerbated by a number of issues, including insufficient skills and information that help a patient successfully cope with illness;

anxiety, depression, or other emotional concerns; lack of resources such as transportation to treatment; and interruptions in family life, work, and school.⁴⁵

Patients also need more and improved information about their disease and the availability of psychosocial support services. A National Alliance for Rare Diseases study in the UK found that just over half (52 percent) of patients surveyed felt they were given insufficient information about their condition at the time of diagnosis. Even when patients receive optimal medical treatment, a lack of information combined with feelings of insecurity or isolation can lead to a perception of inadequate care.⁴⁶ And because family members and care givers are an important source of patient support, more information must be made available to families and carers.

PH patient organisations and health care providers must work collaboratively to produce a comprehensive, standardized PH information package. PH patient organisations are in need of secure sources of ongoing funding so that they can produce new and update existing informational materials and websites. An “information prescription” developed by UK Rare Disease can serve as a model. It includes:

- Medical information, including treatment options
- Care plan timelines
- Information needed by carers and family members
- Psychosocial, financial, educational, and palliative care information and sources of support
- Tools to help access information and conduct research about PH

I hope I'll pass my exams in January and in June. I also hope that I can walk for longer without having to stop because of breathing problems.

Lynn, Belgium



Given the physically debilitating nature of the disease, affecting the ability to walk for even short distances, PH patients should be understood to have a serious disability and should be afforded disabled status. Handicapped status would allow PH patients to have access to special parking, reduced transit fares, leave from work, and other services that are made available to persons with physical impairment. Loved ones and family members who help care for PH patients should also be encouraged to provide appropriate care through work leave policies, which will help reduce PH patients’ reliance on government agencies and other institutional services.

I was denied a parking permit. The local authority sent me a statement that my diagnosis of ischemic heart disease is not a sufficient reason. But I don't have ischemic heart disease, I have pulmonary arterial hypertension.

Julia, Slovakia

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Finally, activities and events sponsored by patient associations must be encouraged and supported. Such programmes strengthen the PH community and are a vital and essential source of support for patients, their families, and caretakers, and even the physicians and other medical staff who treat them.

Summary

Pulmonary hypertension is a life-threatening disease that severely impacts one's ability to perform the most routine daily life activities. It is a condition that manifests in several different forms, of differing ranges of prevalence and severity. Some of its subtypes are rare conditions that have seriously debilitating consequences. Although currently there are approved treatments for only one subtype of PH, innovative research offers the potential for new and improved treatments for all subtypes – and hopefully, one day, a cure.

Pulmonary hypertension can affect any of us. The struggle to do something as automatic and essential to life as breathing is both frightening and disheartening. Persons who live with PH are challenged on a regular basis by this simple activity, which most of us take for granted and do not even think about.



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What is critically needed now is for persons living with PH to be appropriately diagnosed and treated in a timely manner, for currently available treatments to be prescribed only for those patients who will benefit from and not be harmed by those treatments, and for innovative research to continue to investigate new and improved treatment until a cure is found. These needs can be addressed by two relatively simple solutions that will not only enhance PH patient outcomes, but will also result in cost savings for society and health care systems.

Having PH is difficult because nobody takes it seriously and you are the only one who understands it. Just keep fighting - there are going to be many ups and downs in your life but you have to keep going!

Raja, Belgium

The **establishment of centres of expertise for the diagnosis, treatment, and management of PH** will ensure that persons at risk of and living with PH are seen, properly diagnosed, and appropriately treated by clinicians with significant experience in PH, who will also help ensure that costly medications are not over-prescribed. And the **support and funding of innovative research** will help ensure that new therapies are developed for those PH subtypes for which there currently are no treatments, and that improved treatments are developed for PAH, until such time that a cure is found.

Breathing is not an activity that persons living with PH take for granted. Centres of expertise and innovative research can help restore normalcy to their lives. Let us not hold our breath, but move forward now.

My dream is a cure for PH . . . maybe someday I will say "I had PH, but now I am a healthy person!"

Agnieszka, Poland

About PHA Europe

PHA Europe is a patient organisation that works to enhance awareness of pulmonary hypertension across Europe, promote optimal standards of care for people living with the disease, ensure the availability of approved treatments, and encourage research for new medicines and therapies. To accomplish its mission, PHA Europe helps its 25 affiliated national patient groups located throughout Europe to collaborate effectively with health care professionals, specialised clinics, governmental and regulatory agencies, and industry, so that all work together productively toward mutual goals.

Its regular interactions with patients and patient advocates uniquely position PHA Europe to understand the high unmet needs of people living with PH. Accordingly, PHA Europe decided in 2011 to convene a pulmonary hypertension roundtable to provide a forum for the sharing of PH knowledge and expectations across diverse stakeholders and geographic boundaries.

The 35 roundtable members are drawn from across the globe – from Africa, Asia-Pacific, Canada, Europe, Latin America, the Middle East, and the US. The membership reflects a wide range of clinical, patient, research, and industry interests, and includes numerous key opinion leaders at the forefront of PH care and treatment. (See page 27 for a list of members.)

The multidisciplinary nature of the roundtable helps members translate their unique understandings of patient, professional, and policy maker perspectives on PH treatment and care into direct action. Among the aims of the roundtable are a) to equip health policy makers with the information they need to make decisions that reflect the best interests of PH patients, and b) to ensure a scientific basis for informed treatment decision-making.

At a meeting in Amsterdam in September 2011, roundtable members discussed the need for all PH patients to have access to optimal screening and diagnosis, appropriate treatment, psychosocial support, and integrated care through centres of expertise. Members subsequently agreed upon the framework for a call to action to enhance public awareness about the personal and societal burdens imposed by pulmonary hypertension, and to improve the care of persons living with the disease.

The messages in this document are universal and transcend geographic boundaries, because PH patients around the globe share similar concerns and face the same challenges relative to diagnosis, treatment, and care. Our call to action identifies areas of most urgent need and recommends effective ways to address those needs. Implementation of these strategies will afford PH patients access to high quality services, treatment, and support, whilst ensuring the most efficient and effective use of limited health system resources.

It should be noted that our recommendations do not necessarily imply the need for a significant increase in funding for treatment and care as much as a *reallocation* of existing resources. Currently funding is often inefficiently allocated, largely due to delays in diagnosis, misdiagnosis, and delayed, inappropriate, and fragmented treatment. Our call to action suggests appropriate methods to address these critical shortcomings so that *existing* resources are effectively and efficiently allocated for improved patient outcomes.

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This report was made possible by unrestricted educational grants from Actelion Pharmaceuticals LTD, AOP Orphan Pharmaceuticals AG, Bayer HealthCare Pharmaceuticals, GlaxoSmithKline, Novartis Pharma, Pfizer, and United Therapeutics Corporation.

The content of the report has been determined independently of all donors by PHA Europe.