Pulmonary hypertension (PH) expert centers have been established in most western European countries during the last 2 decades, since publication of the first randomized trial of drug therapy for pulmonary arterial hypertension (PAH). Western Europe has a variety of different health care systems based on different economic models within countries that vary 18-fold in population size.

The role of these centers was defined in the 2009 PH guidelines of the European Society of Cardiology and the European Respiratory Society and subsequently updated in the 2015 guidelines. These guidelines recognized the need for specialist care and recommended referral of patients with suspected PAH, chronic thromboembolic pulmonary hypertension (CTEPH), or PH with unclear mechanisms to an expert PH center. The purpose of such centers is to obtain best outcomes for patients by providing diagnosis, treatment, and follow-up.

PH expert centers are expected to provide patient care through an interprofessional team consisting of at least 2 consultant physicians, a clinical nurse specialist, a radiologist with PH imaging expertise, and a physician(s) with expertise in echo and right heart catheterization. Twenty-four-hour on-call cover is provided. The centers should have direct links and referral pathways for genetics, connective tissue disease, adult congenital heart disease, pulmonary endarterectomy, lung transplantation, and family planning. To ensure that PH expert centers maintain adequate clinical experience, they are expected to follow at least 50 patients with PAH or CTEPH and should receive at least 2 referrals per month with documented PAH or CTEPH. They should also perform at least 20 vasoreactivity tests during right heart catheterization per annum for idiopathic, heritable, or drug-induced PAH. PH expert centers must participate in collaborative research including phase 2 and phase 3 clinical trials. They are required to audit their patient outcomes.

In 2017 the European Commission established European Reference Networks (ERNs) for rare diseases that included a PH network as part of ERN Lung. The PH network includes 17 PH expert centers whose purpose is to provide consistent cross-border patient care in the European Union. ERN Lung requires and monitors standards for these centers based on the 2015 European guideline recommendations.

This paper describes the models of PH expert centers in 2 European countries—France and the United Kingdom—that contrast with each other and with centers in the United States.

UNITED KINGDOM
The Country and its Health Care System
The current UK population is 65.6 million, and for the purposes of health care the country is subdivided into England (84% of the population), Scotland (8%), Wales (5%), and Northern Ireland (3%). In England the greatest density of the population is in the southeast around London.

The National Health Service (NHS) is funded through taxation and is free of charge at the point of care for people who ordinarily reside in the UK. The NHS employs 1.7 million staff, manages 15 million hospital admissions per year, and spends approximately £124 billion per year. Spending as a proportion of gross domestic product (GDP) is 9.7%, which is less than the United States, Canada, Germany, France, The Netherlands, and Denmark. One major advantage of health care falling under a single national organization means that it has the ability to designate specialized clinical services within the country.

PH Expert Centers
Following the establishment of a PH expert center in Scotland, the NHS in
England designated 7 PH expert centers in 2001. Seven of the UK designated centers are for adults (Hammersmith Hospital, London; Royal Brompton Hospital, London; Royal Free Hospital, London; Royal Papworth Hospital, Cambridge; Royal Hallamshire Hospital, Sheffield; Freeman Hospital, Newcastle; and Golden Jubilee Hospital, Glasgow) and one center (Great Ormond Street Hospital for Children) manages the pediatric service through outreach clinics held in different parts of the UK. Adult services see patients in outreach clinics and manage patients at the PH expert centers. Some centers have also developed shared care arrangements with more distant hospitals to undertake patient care locally under supervision from the PH expert center. Patients from Northern Ireland and Wales are referred to English centers. Thus, the 8 centers provide comprehensive service for the whole country. In many instances, the NHS provides necessary transportation between patients' homes and PH expert centers.

The main driver for establishing PH expert centers in 2001 was the high cost of intravenous epoprostenol, which was about 4 times the price charged in the US at that time. The designated PH expert centers are the only hospitals where prescription of specialist drug therapies for PH is reimbursed by the NHS. Other hospitals are advised that they must send patients to designated PH expert centers.

The PH expert centers are required to make an accurate and complete diagnosis in new patients. They formulate an individualized plan of clinical management for each patient tailored to their needs. The centers are responsible for initiation of PH drug therapies and subsequent prescriptions of these drugs, since they cannot be prescribed by other hospitals or general practitioners for reimbursement reasons as described above. The centers are responsible for vigilant follow-up and adjustment of treatment of the patients under their care. They also undertake clinical and genetic screening of first-degree relatives of patients with heritable and idiopathic PAH. The designated centers meet the criteria established by the European guidelines including having formal links with adult congenital heart disease services, rheumatology, lung transplantation, and family planning clinics. They participate in a national audit of clinical processes and outcomes, collaborative research including multicenter clinical trials, and deliver a comprehensive educational program to educate referring hospitals, local hospital staff, postgraduates, and undergraduates.

One advantage of managing patients with a rare disease in high-volume centers is that it has economic benefits in limiting unnecessary prescriptions issued by nonspecialist physicians for expensive PH drugs where they are not clinically indicated. As a consequence, specialist drugs for PH remain rarely used outside PH expert centers in the UK.

A national committee of PH expert center physicians meets twice annually to discuss administrative, clinical, research, and audit issues. Other PH health care professionals from expert centers (clinical nurse specialists, pharmacists, and social workers) meet regularly as well.

National CTEPH Center
Pulmonary endarterectomy for CTEPH is carried out at a single center designated by the NHS at Royal Papworth Hospital. All PH expert centers undertake diagnostic workup for CTEPH. A medical report and imaging for each patient is then reviewed at the weekly CTEPH multidisciplinary team meeting at Royal Papworth where pulmonary endarterectomy is undertaken in suitable patients. More than 160 operations are carried out each year, and this concentration of expertise has ensured excellent clinical outcomes for surgery compared to other major international centers. A program of balloon pulmonary angioplasty has recently commenced.

Lung Transplantation
Bilateral sequential lung transplantation is carried out in designated transplant centers and PH expert centers undertake joint clinics with transplant physicians. The number of transplants for PAH has varied in recent years from 4 to 14 cases per annum. With the advent of extracorporeal life support systems and a recent super urgent lung transplantation program, the number of patients transplanted may increase in the near future.

Referral Criteria for PH Expert Centers
Most patients are referred to PH expert centers by cardiologists, pulmonologists, or rheumatologists. The UK referral criteria recommend referral of patients with suspected PAH, CTEPH, and PH with unclear and/or multifactorial mechanisms to PH expert centers. Patients should also be referred if they are found to have PH where the cause is uncertain, and this is often the most common reason for referral. It is recommended to refer patients with PH related to heart and/or parenchymal lung disease where there is severe PH/right ventricular dysfunction and in particular if there are other PAH-associated diseases (drug- and toxin-induced PAH, connective tissue disease, congenital heart disease, portal hypertension, HIV, or schistosomiasis) present.

Guidelines
While designated PH centers follow European guidelines, the prescription of PH drug therapies is controlled by NHS drug policy. This limits the use of drug therapy to PH expert centers as well as identifying the choice of therapies for patients. The main areas of divergences from European guidelines are in the treatment of PAH in World Health Organization (WHO) functional class II, which is limited to patients with evidence of impaired right ventricular function and permits treatment with phosphodiesterase type 5 inhibitors only. Combination therapy is only permitted in WHO functional classes III and IV and is normally limited to 2 drugs, one of which must be a phosphodiesterase type 5 inhibitor. Triple therapy with a phosphodiesterase type 5 inhibitor, endothelin receptor antagonist, and a prostanoid is only permitted in patients who are suitable for lung transplantation or who are pregnant. At present treprostinil and selexipag are not reimbursed. Treatment for inoperable CTEPH with riociguat is permitted in line with guideline recommendations.
Clinical Outcomes
Individual center data have been collected since 2001, but since April 1, 2009, this has been formalized through the National Audit of Pulmonary Hypertension hosted by NHS Digital. All of the PH expert centers participate in this prospective audit. The audit includes all patients who attend PH expert centers regardless of their final diagnosis. Patient consent is not required according to health care legislation, although patients have the option of withdrawing their data from the national database if they request. The data are the property of the NHS.

The database was originally funded by PHA-UK, the PH patient association and subsequently by NHS Specialized Commissioning. There is no external funding for the audit. Reimbursement of PH drug therapies is contingent on patients being entered into the database. Mortality is ascertained by linking the national database to mortality data collected by the Office of National Statistics in England. The national audit produces an annual report, which in recent years has compared outcomes of audit standards between centers.

National audit has identified the prevalence of PAH to be 46 per million population and for CTEPH to be 23 per million population. Importantly, the number of patients in the service has grown every year since data started to be collected in 2001. In 2016–17, the PH expert centers managed 9576 patients, of whom 5710 (60%) had PAH or CTEPH. Counting the number of patients under PH expert centers on a single day (March 31, 2017) there were 7131 patients, of whom 4170 were treated with specialist drug therapies (phosphodiesterase type 5 inhibitors, endothelin receptor antagonists, and prostanoids).

Patient Association
The national PH expert centers maintain close links with PHA-UK, which was founded at the same time as the English centers were originally designated by the NHS in 2001. Clinicians from all the centers participate in PHA-UK activities including the annual conference. PHA-UK works alongside the clinicians to express the patients’ voice and participate in the future direction of the service. PHA-UK also produces an annual report for patients describing the national audit outcomes and their significance for patients.

FRANCE
The Country and its Health Care System
The current population in France is 67.2 million; the country is subdivided into 18 administrative regions, including 13 metropolitan and 5 overseas regions. In France, the greatest density of the population is in the area of Paris (“Île-de-France”), accounting for 12 million inhabitants (1000 per km²).

The French health care system is one of universal health care largely financed by government national health insurance (Social Security System). For funding this insurance, each French individual is required to contribute by withdrawing part of his/her salary. Expenses related to the health care system in France represent about 11% of the country’s GDP and 15% of its public expenditure. Global health care expenses represented €198.5 billion in 2016. Each individual living in France is about 77% covered with the national health insurance. The remaining must be covered by non-mandatory additional private insurance. However, for people with chronic severe diseases (eg, diabetes, hypertension, heart failure, and others including PH), health care expenses are 100% covered by the national health insurance. In 2000, the WHO found that France provided “close to the best overall health care” in the world.

PH Expert Centers
Individual center data have been collected since the 1990s, and more extensively in the Paris-Sud University center, which was located initially at Antoine Béclère Hospital (Clamart) then at Bicêtre University Hospital (Le Kremlin-Bicêtre) since 2012. In 2002–2003, a first national network was created in 17 university hospitals following at least 5 newly diagnosed patients per year. This PH expert center network launched the first national registry that included 674 patients with all forms of PAH, and first described patient characteristics and current practice in France. Centers within this first network were certified by the French Health Authorities in 2004, the year of the first National Rare Diseases Plan (“Plan National Maladies Rares”). Health authorities designated Paris-Sud University/ Antoine Béclère Hospital as the National Reference PH Center and also certified 23 Regional PH Centers (called “Competence Centers”) according to specific considerations (consistent with current guidelines requests).

Certification of the PH network was confirmed in 2010 and 2016 (second and third National Rare Diseases Plans).

Today, the PH network includes the National Reference Center located at Bicêtre University Hospital (medical care) and Marie-Lannelongue Hospital (surgery), both components of Paris-Sud University, and 23 Regional Competence PH Centers widespread across France, including 2 overseas centers in “La Réunion” island (Indian Ocean) and “La Martinique” island (French Indies in the Atlantic Ocean).

All PH centers are composed of a multidisciplinary team including pulmonologists, cardiologists, and internal medicine specialists. Some centers also include a dedicated pediatric team. Some centers have also developed shared care arrangements with more distant hospitals to undertake patient care locally under supervision from the Regional Competence Center. Patient transportation between patients’ homes and Reference or Competence PH Centers are covered by the government national health insurance. Although PAH–targeted medications can be prescribed by all pulmonologists, cardiologists, and internal medicine specialists working in public hospitals, such therapy is usually initiated by dedicated PH centers. The centers organize the initial management plan, follow-up, and adjustment of treatment of the patients under their care. Clinical and genetic screening of first-degree relatives of patients with heritable and idiopathic PAH is the responsibility of the National Reference PH Center. Also, Competence Centers meet the criteria established by the European guidelines including having formal links with adult congenital heart disease services, connective tissue disease...
specialists, hepatologists, and lung transplantation specialists. They are expected to participate in collaborative research including multicenter clinical trials and to deliver an educational program to educate referring hospitals, local hospital staff, postgraduates, and undergraduates.

**National CTEPH Center**

Pulmonary endarterectomy for CTEPH is carried out at a single center in Marie-Lannelongue Hospital that is part of Paris-Sud University. All PH Competence Centers from the French PH Network perform diagnostic workup for CTEPH. A medical report and imaging for each patient is then reviewed at the weekly CTEPH multidisciplinary team meeting at Bicêtre Hospital (Paris-Sud University). More than 150 pulmonary endarterectomy procedures are carried out each year, and this concentration of expertise has ensured excellent clinical outcomes for surgery, similar to other major international centers. A program of balloon pulmonary angioplasty began in July 2014 at the 2 centers from Paris-Sud University (Marie Lannelongue and Bicêtre hospitals), and today more than 250 patients with CTEPH have benefited from the technique.

**Lung Transplantation**

Lung and heart-lung transplantation is conducted in designated transplant centers. However, few surgical centers are performing lung transplantation for PAH and CTEPH in France. The biggest surgical center is Marie-Lannelongue Hospital, which works in close collaboration with the French PH Reference Center in Bicêtre Hospital; PH physicians conduct joint clinics with transplant physicians. The possibility for decompensated PH patients to be listed on a highly urgent allocation program has markedly increased the number of patients listed and dramatically decreased the mortality on waiting list. The number of transplants for PAH is relatively stable in recent years from 40 to 50 cases per year.

**Referral Criteria for PH Expert Centers**

Most patients are referred to the National Reference Center and Regional Competence Centers by pulmonologists, cardiologists, internal medicine specialists (connective tissue diseases), hepatologists (portopulmonary hypertension), and more rarely by specialists of infectious diseases (HIV) or rheumatologists. The French referral criteria recommend referral of patients with suspected PAH, CTEPH, and PH with unclear and/or multifactorial mechanisms to centers belonging to the French PH Network.

It is also recommended to refer patients with PH related to heart disease and PH with lung disease where there is severe PH or right ventricular dysfunction. Patients should also be referred if they are found to have PH where the cause is uncertain, and this is often the most common reason for referral.

**Guidelines**

While designated PH centers usually follow European guidelines, the prescription of PAH-targeted drugs is not restricted to physicians from those dedicated centers. All pulmonologists, cardiologists, and internal medicine specialists working in a public hospital may prescribe PAH therapies. Only general practitioners, private-practice cardiologists or pulmonologists, and other specialists are not allowed to prescribe them. This rule is less restrictive than that from the UK, but it restrains the prescription of PAH drug therapy. Physicians may prescribe all available drugs as monotherapy or as a combination (initial or sequential, dual, or triple) irrespective of the type or the severity of PAH. There is no rule about the first class of drug to use as initial therapy (endothelin receptor antagonist, phosphodiesterase type 5 inhibitor, or prostanoit). Lung transplantation is considered in eligible PAH patients failing on triple combination therapy or in patients with pulmonary veno-occlusive disease irrespective of the treatment received. At present macitentan is not available as it is not reimbursed, and riociguat is reimbursed only for patients with CTEPH.

**Clinical Outcomes**

The first national registry, initiated in 2002-2003 in 17 university hospitals, calculated the low estimates of prevalence and incidence of PAH in France, which were 15.0 cases per million of adult inhabitants and 2.4 cases per million of adult inhabitants per year, respectively. This first national cohort followed for 3 years, estimating the 1-, 2- and 3-year survival to be 82.9%, 67.1%, and 58.2%, respectively. After the labeling of the first “Rare Diseases Plan” by the health authorities, a new national registry was launched in 2007. This registry, which is still ongoing, collects the data from all the PH centers of the National Network. All newly diagnosed patients (ie, incident patients) with PAH, CTEPH, or Group 5 PH are included in the registry. For patients with Group 2 or Group 3 PH, only those with “severe” PH are included (ie, with diastolic gradient >7 mm Hg or pulmonary vascular resistance >3 Wood units for Group 2 PH, and with mean pulmonary artery pressure >35 mm Hg for Group 3 PH, according to the European guidelines definitions). The national registry currently contains the data for 11,669 patients, including 6640 (57%) with PAH (Group 1) and 2487 (21%) with CTEPH. As in the UK, patient consent is not required according to health care legislation, although patients have the option of withholding their data from the national database if they request. The database is the property of the National Reference Center (Bicêtre University Hospital, “Assistance Publique–Hôpitaux de Paris”). French health authorities requested that the Reference Center launch and manage the national registry, but no funding was provided. We collect demographics, clinical signs and symptoms, exercise capacity, echo, biomarkers, and hemodynamics and treatments prescribed at the time of PH diagnosis (initial visit) and at subsequent follow-up visits. Follow-up ends when a patient dies or undergoes lung transplantation. Analysis of outcomes of patients included in the registry in the last 10 years showed that survival markedly improved since 2002-2003. Today, the 1- and 3-year survival estimates of patients with PAH are 90% and 73%, respectively (unpublished data).

**Patient Association**

The National Reference PH Center and the competence centers from the...
PH Network maintain close links with “HTaPFrance,” the patient association that was founded in 1996. Clinicians from all centers participate in “HTaP-France” activities including the annual general assembly and the patient association conference that is held every 2 years. “HTaPFrance” works with the clinicians to express the patients’ voice and participate in the future direction of the service. “HTaPFrance” also produces a regular publication for patients (“Cap Vers”) describing the progress of clinical and basic research in the field of PAH and including stories and testimonies from patients and relatives.

Conclusion
France and the United Kingdom both aimed to concentrate PH expertise and patient care on a national scale in a small number of designated hospitals. They have achieved this in a rare disease within disparate health care systems by adopting different approaches tailored to their respective national health care system. Maintaining these intentions and improving patient care is a considerable task, which will remain challenging as health care evolves. While countries can share common objectives for best clinical practice, how these are achieved will remain unique to each health care system.

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