Characterization of the epidemiology, treatment patterns and burden of Pulmonary Hypertension Group 1 and 3 in France, Germany and the UK: a real-word evidence study

Study protocol final v2.0

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Abbreviations

Abbreviation	Label
6MWD	6-minute walk test
ACE	External technical procedures and visits (Actes et consultations externes)
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BNP	Brain natriuretic peptide
AU	German certificate of incapacity for work (Arbeitsunfähigkeitsbescheinigung)
CCAM	Common classification of medical procedures
CépiDC	Centre for Epidemiology of Medical Causes of Death (Centre d'Epidémiologie sur les Causes médicales de Décès)
CHD	Congenital heart diseases
CI	Confidence interval
CLD	Chronic lung disease
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise testing
CPFE	Combined pulmonary fibrosis and emphysema
CPRD	Clinical Practice Research Datalink
CT	Computed tomography
CTD	Connective tissue disease
CTPH	Chronic thromboembolic pulmonary hypertension
DCIR	Inter-regime consumption data (Données de Consommation Inter-Régime)
DLCO	Diffusing capacity of the lungs for carbon monoxide
DM+D	Dictionary of Medicines and Devices
DRG	Diagnosis-related group
ECG	Electrocardiogram
ED	Emergency department
EMR	Electronic medical record
ERA	Endothelin receptor antagonist
ERS	European Respiratory Society

ESC	European Society of Cardiology
FC	Functional classification
FRC	Follow-up and rehabilitation care (SSR – Soins de suite et réadaptation)
GHM	Homogeneous groups of patients
GHS	DRG tariff – "Homogeneous Group of Stay" (Groupe Homogène de Séjour)
GP	General Practitioner
HAD	Home care (Hospitalization à domicile)
HES	Hospital Episode Statistics
HPAH	Heritable pulmonary arterial hypertension
ICD-10	International Classification of Diseases 10th Revision
IHD	Ischaemic heart disease
IIP	Idiopathic Interstitial Pneumonias
ILD	Interstitial lung disease
IPF	Idiopathic Pulmonary Fibrosis
IPAH	Idiopathic pulmonary arterial hypertension
IV	Intravenous
LD	Lung disease
LHD	Left heart disease
LPP	List of products and services qualifying for reimbursement
LTD	Long-term disease
mPAP	Mean pulmonary arterial pressure
MRI	Magnetic resonance imaging
MSO	Medicine, Surgery, Obstetrics
NABM	Clinical pathology test nomenclature (Nomenclature des actes de biologie)
NGAP	General nomenclature of professional procedures (Nomenclature générale des actes professionnels)
NHS	National Health Service
NT-proBNP	N-terminal pro B-type natriuretic peptide
ONS	Office for National Statistics
OPCS	Office of Population, Census and Surveys
PA	Pulmonary arterial

PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
PAWP	Pulmonary artery wedge pressure
PCA	Prostacyclin analogues
PCWP	Pulmonary capillary wedge pressure
PD	Principal diagnosis
PDE5i	Phosphodiesterase-5 inhibitor
PFT	Pulmonary function test
PH	Pulmonary hypertension
PMSI	French National Hospitals Database (Programme de médicalisation des systèmes d'information)
PRA	Prostacyclin Receptor Agonists
PT	Pulmonary thromboembolism
PVR	Pulmonary vascular resistance
PZN	Pharma central number
RD	Related diagnosis
RHC	Right heart catheterization
RV	Right ventricle
SAD	Significantly–associated diagnosis
SC	Subcutaneous
SD	Standard deviation
SDS	Standardised discharge summary
sGC	Soluble Guanylate Cyclase Stimulator
SHI	Statutory health insurance
SNDS	French Healthcare Database (Système National des Données de Santé)
sPAP	systolic pulmonary artery pressure
TTE	Transthoracic echocardiogram
UK	United Kingdom
US	United States
WHO-FC	World Health Organization-functional classification
WSPH	World Symposia on Pulmonary Hypertension
WU	Wood units

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1. BACKGROUND

1.1 Pulmonary Hypertension

1.1.1 Clinical Definition

Pulmonary hypertension (PH) is a rare, highly complex and progressive disease which defines a group of clinical conditions with abnormal elevation in the pulmonary circulation pressure. Pulmonary hypertension may involve multiple clinical conditions and can complicate most of the cardiovascular and respiratory diseases. The normal mean pulmonary artery pressure (mPAP) at rest is 14 ± 3.3 mm Hg. Since the 1st World Symposium on Pulmonary Hypertension (WSPH) in 1973, PH has been defined as mean mPAP 25 mmHg at rest, measured by right heart catheterisation (RHC) (Simonneau, Montani et al. 2019). However, the 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) PH Guidelines, modified the haemodynamic PH profile from mPAP ≥25 mmHg and pulmonary vascular resistance (PVR) >3 wood units (WU) to mPAP >20 mmHg and PVR >2 WU at rest in agreement with the 6th World Symposium (Thomas, Anderson et al. 2020, Humbert, Kovacs et al. 2022). Patients with PH present with symptoms of dyspnoea on exertion, fatigue, chest pain, syncope, palpitations, and lower extremity oedema(McLaughlin, Archer et al. 2009). Pulmonary hypertension can also be classified as pre- or postcapillary PH. Precapillary PH is due to a primary elevation of pressure in the pulmonary arterial (PA) system alone (e.g., pulmonary arterial hypertension [PAH]), while postcapillary PH is due to elevations of pressure in the pulmonary venous and pulmonary capillary systems (pulmonary venous hypertension, e.g., Group 2). For pre-capillary PH pulmonary artery wedge pressure (PAWP) ≤15 mmHg is recommended as the threshold (Humbert, Kovacs et al. 2022). Post-capillary PH is haemodynamically defined as mPAP >20 mmHg and PAWP >15 mmHg (Humbert, Kovacs et al. 2022).

1.1.2 Diagnosis

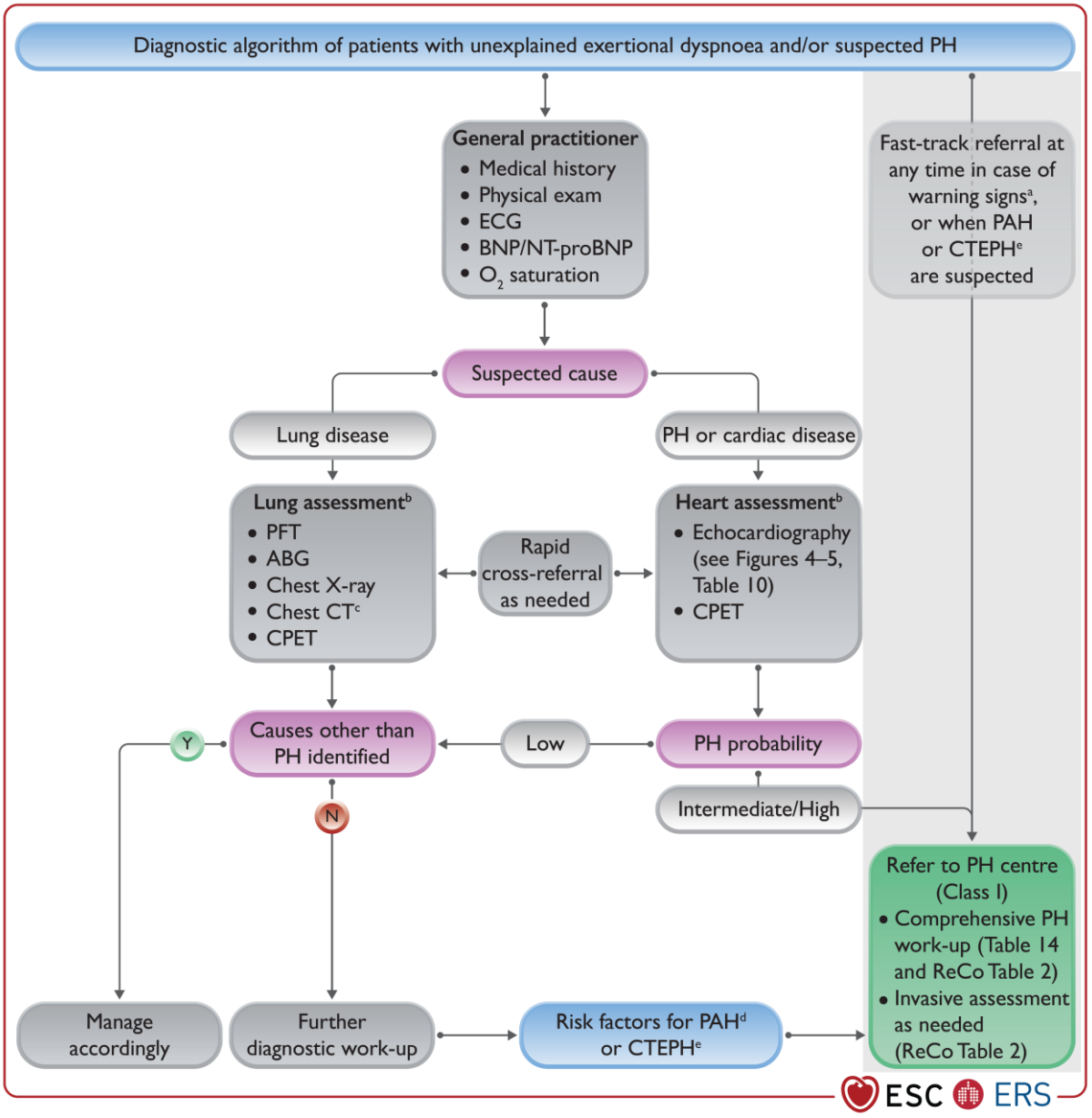
The diagnosis approach to PH has two main objectives:

1. To raise early suspicion of PH ensuring swift referral of medium-to-high risk patients to PH specialized centres,

2. To identify the underlying cause of PH, especially left heart disease (Group 2 PH), lung disease (LD) (Group 3 PH), as well as comorbidities to inform risk assessment and adequate treatment.

A multistep approach to diagnosis should be considered in patients with unexplained dyspnoea or symptoms/signs raising suspicion of PH, which was published in the 2022 ESC/ERS PH Guidelines and is presented in **Figure 1** (Humbert, Kovacs et al. 2022).

Figure 1: Diagnostic Algorithm of patients with suspected PH and/or exertional dyspnoea



Legend: Diagnostic algorithm of patients with unexplained dyspnoea and/or suspected pulmonary hypertension. ABG, arterial blood gas analysis; BNP, brain natriuretic peptide; CPET, cardiopulmonary exercise testing; CT, computed tomography; CTEPH, chronic thrombo-embolic pulmonary hypertension; ECG, electrocardiogram; HIV, human immunodeficiency virus; N, no; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PE, pulmonary embolism; PFT, pulmonary function tests; PH, pulmonary hypertension; ReCo, recommendation; Y, yes. [a]Warning signs include rapid progression of symptoms, severely reduced exercise capacity, pre-syncope or syncope on mild exertion, signs of right heart failure. [b]Lung and heart assessment by specialist as per local practice. cAs indicated; CT pulmonary angiography recommended if PH suspected. [d]Includes connective tissue disease (especially systemic sclerosis), portal hypertension, HIV infection, and family history of PAH. [e]History of PE, permanent intravascular devices, inflammatory bowel diseases, essential thrombocythaemia, splenectomy, high-dose thyroid hormone replacement, and malignancy.

1.1.3 Risk factors

Potentially life-threatening PH arises from a wide variety of pathophysiologic mechanisms and can be associated with several conditions, which could carry out risk factors suspected to play a predisposing or facilitating role in disease development: liver diseases, rheumatic disorders,

lung conditions, heart diseases, obesity, sleep apnoea (Blankfield, Hudgel et al. 2000, Nasser, Larrieu et al. 2021). In these conditions, a common denominator potentially triggering PH is hypoxia, which stimulates pulmonary vascular vasoconstriction, increasing pressure and consequently inducing pathological structural changes and injuries in the pulmonary vasculature. As a result, pulmonary vascular lumen occlusion occurs, leading to increased PVR and mPAP (Nathan, Barbera et al. 2019).

1.1.4 Classification

Pulmonary hypertension can be classified into five different clinical groups according to the underlying pathophysiology, clinical presentation, pathological findings, haemodynamic characteristics and treatment strategy(Galiè, Humbert et al. 2015). A comprehensive version of the clinical classification is presented in **Table 1.** Out of the five PH Groups this study focuses on Group 1 (PAH), Group 3 and PH with interstitial lung disease (ILD), Group 3.2, (Ryan, Thenappan et al. 2012).

Table 1: Clinical classification of pulmonary hypertension groups

1. Pulmonary Arterial Hypertension
1.1 Idiopathic 1.1.1 Non-responders at vasoreactivity testing 1.1.2 Acute responders at vasoreactivity testing 1.2 Heritable 1.3 Associated with drugs and toxins 1.4 Associated with: 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement 1.6 Persistent PH of the newborn
2. Pulmonary hypertension due to left heart disease
2.1 Heart failure: 2.1.1 with preserved ejection fraction 2.1.2 with reduced or mildly reduced ejection fraction 2.2 Valvular heart disease 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH
3. Pulmonary hypertension due to lung disease and/or hypoxia
3.1 Obstructive lung disease or emphysema 3.2 Restrictive lung disease 3.3 Lung disease with mixed restrictive/obstructive pattern 3.4 Hypoventilation syndromes 3.5 Hypoxia without lung disease (e.g. high altitude)

3.6 Developmental lung disorders
4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
4.1 Chronic thrombo-embolic PH 4.2 Other pulmonary artery obstructions
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1 Haematological disorders 5.2 Systemic disorders 5.3 Metabolic disorders 5.4 Chronic renal failure with or without haemodialysis 5.5 Pulmonary tumour thrombotic microangiopathy 5.6 Fibrosing mediastinitis

Source: (Humbert, Kovacs et al. 2022)

Legend: HF, heart failure; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary haemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease. aPatients with heritable PAH or PAH associated with drugs and toxins might be acute responders. bLeft ventricular ejection fraction for HF with reduced ejection fraction: ≤40%; for HF with mildly reduced ejection fraction: 41–49%. cOther causes of pulmonary artery obstructions include: sarcomas (high or intermediate grade or angiosarcoma), other malignant tumours (e.g. renal carcinoma, uterine carcinoma, germ-cell tumours of the testis), non-malignant tumours (e.g. uterine leiomyoma), arteritis without connective tissue disease, congenital pulmonary arterial stenoses, and hydatidosis. dIncluding inherited and acquired chronic haemolytic anaemia and chronic myeloproliferative disorders. eIncluding sarcoidosis, pulmonary Langerhans's cell histiocytosis, and neurofibromatosis type 1. fIncluding glycogen storage diseases and Gaucher disease

1.2 Group 1 Pulmonary Arterial Hypertension

1.2.1 Epidemiology

Pulmonary hypertension epidemiology at the global level is poor. Present estimates suggest a PH prevalence of approximately 1% of the global population, which increases up to 10% in individuals aged more than 65 years (Hoeper, Humbert et al. 2016). A population-based cohort study in Ontario, Canada, evaluating incidence and prevalence of groups 1 to 4 PH patients from 1993 to 2012, identified an emerging epidemic of PH , giving the increasing incidence and prevalence of adult (Wijeratne, Lajkosz et al. 2018). Based on a recent systematic review of literature, mostly based on European studies, the range of adult estimates per million was approximately 20-fold for pulmonary arterial hypertension incidence (1.5-32) and prevalence (12.4-268) (Leber, Beaudet et al. 2021). Recent (≤5 years) national systematic registry data from centralised healthcare systems provided the following ranges in adult estimates per million: approximately 5.8 for pulmonary arterial hypertension incidence, 47.6-54.7 for pulmonary arterial hypertension prevalence (Leber, Beaudet et al. 2021). A systematic review of studies with population-level data for PAH between 1980 and 2021 reported that the prevalence ranged from 0.4 to 1.4 per 100,000 persons, with sex-specific estimates of prevalence or incidence reported higher levels in females than males (Emmons-Bell, Johnson et al. 2022). Due to the presence of cardiac and pulmonary causes of PH, prevalence is higher in individuals aged 65 years or higher. Globally, left heart disease is the leading cause of PH. Lung disease, especially chronic obstructive pulmonary disease (COPD), is the second most common cause (Humbert, Kovacs et al. 2022).

1.2.2 Clinical definition

The symptoms of PAH are non-specific and mainly related to progressive right ventricular dysfunction consequent to progressive pulmonary vasculopathy. Patients often present with exertional dyspnoea, fatigue, weakness, chest pain, light-headedness/syncope and, less frequently, cough, which frequently overlap with several other conditions. The presentation of PAH may be modified by diseases that are associated with PAH, as well as comorbidities. Pulmonary arterial hypertension describes a group of PH characterized haemodynamically by parameters described in **Table 2** (Humbert, Kovacs et al. 2022). Of note, these specific haemodynamic parameters used to define PAH were different in the 2015 ESC/ERS Guidelines (Galiè, Humbert et al. 2015). Pulmonary arterial hypertension is characterized haemodynamically by the presence of pre-capillary PH, defined by a PAWP ⩽15 mmHg and a PVR >2 WU in the absence of other causes of pre-capillary PH such as PH due to LDs, chronic thromboembolic pulmonary hypertension (CTPH) or other rare diseases (Hoeper, Bogaard et al. 2013, Galiè, Humbert et al. 2015). Furthermore, patients presenting a mPAP between 21 and 24 mmHg were carefully followed only when at risk of developing PAH (e.g., patients with connective tissue disease [CTD] or family members of patients with heritable pulmonary arterial hypertension [HPAH]), as the clinical significance of this range of values was unclear (Galiè, Humbert et al. 2015).

Table 2: Haemodynamic definitions of pulmonary hypertension

Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVR >2 WU
IpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR ≤2 WU
CpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

CO, cardiac output; CpcPH, combined post- and pre-capillary pulmonary hypertension; IpcPH, isolated post-capillary pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood units.

Some patients present with elevated mPAP (.20 mmHg) but low PVR (≤2 WU) and low PAWP (≤15 mmHg); this haemodynamic condition may be described by the term 'unclassified PH' (see text for further details).

The prognosis and 1-year mortality of patients with PAH is influenced by several factors, including the haemodynamic variables, the World Health Organization-functional classification (WHO-FC), and the 6-minute walking distance test (6MWD), among others. The WHO-FC is a tool used to measure disease severity in patients with PAH based on patient reports of

symptom experience and activity limitations. Patients assessed by the WHO-FC are allocated into class I, II, III, or IV; a higher class is indicative of more severe disease (i.e., greater functional impairment) (Highland, Crawford et al. 2021). In the 2015 ESC/ERS Guidelines for the diagnosis and treatment of PH, risk assessment was based on a multiparametric approach using a three-strata model to classify patients at low, intermediate, or high risk of death. Originally, these strata were based on estimated 1-year mortality rates of <5%, 5% to 10%, and >10%, respectively. Since then, registry data has demonstrated that the 1-year mortality rates of the intermediate and high-risk groups were higher than predicted. Thus, the risk assessment of PAH patients was updated accordingly and are presented in **Table 3 (**Humbert, Kovacs et al. 2022**)**.

Table 3: Comprehensive risk assessment in pulmonary arterial hypertension (three-strata model)

Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Clinical observations and modifiable variables			
Signs of right HF	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope[a]	Repeated syncope[b]
WHO-FC	I, II	III	IV
6MWD[c]	>440 m	165–440 m	<165 m
CPET	Peak VO_2 >15 mL/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 mL/min/kg (35–65% pred.) VE/VCO_2 slope 36–44	Peak VO_2 <11 mL/min/kg (<35% pred.) VE/VCO_2 slope >44
Biomarkers: BNP or NT-proBNP[d]	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–800 ng/L NT-proBNP 300–1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
Echocardiography	RA area <18 cm^2 TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion	RA area 18–26 cm^2 TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion	RA area >26 cm^2 TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion
cMRI[e]	RVEF >54% SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37–54% SVI 26–40 mL/m^2 RVESVI 42–54 mL/m^2	RVEF <37% SVI <26 mL/m^2 RVESVI >54 mL/m^2
Haemodynamics	RAP <8 mmHg CI ≥2.5 $L/min/m^2$ SVI >38 mL/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 $L/min/m^2$ SVI 31–38 mL/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 $L/min/m^2$ SVI <31 mL/m^2 SvO_2 <60%

Legend : 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; cMRI, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; pred., predicted; RA, right atrium; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; SvO_2, mixed venous oxygen saturation; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; VE/VCO_2, ventilatory equivalents for carbon dioxide; VO_2, oxygen uptake; WHO-FC, World Health Organization functional class. [a]Occasional syncope during heavy exercise or occasional orthostatic syncope in a stable patient. [b]Repeated episodes of syncope even with little or regular physical activity. [c]Observe that 6MWD is dependent upon age, height, and burden of comorbidities.

The main limitation of the 2015 ESC/ERS there-strata model is that most patients (60% to 70%) are classified as intermediate risk. Thus, based on new survival and biomarker data, a four-strata risk prediction model was built (see **Table 4**). The main advantage of the four-strata model over the three-strata model is better discrimination within the intermediate-risk group, which helps guide therapeutic decision-making. Thus, the updated four-strata model for risk prediction is part of the updated treatment algorithm. However, the three-strata model is maintained for initial assessment, and the four-strata abbreviated model should be applied at follow-up (Humbert, Kovacs et al. 2022).

Table 4: Variables used to calculate the simplified four-strata risk-assessment tool

Determinants of prognosis	Low risk	Intermediate–low risk	Intermediate–high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II[a]	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP,[a] ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

Legend: 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; WHO-FC, World Health Organization functional class. Risk is calculated by dividing the sum of all grades by the number of variables and rounding to

the next integer. aWHO-FC I and II are assigned 1 point as both are associated with good long-term survival (Humbert, Kovacs et al. 2022).

1.2.3 Disease Management and Therapies

The time from symptom onset to PH diagnosis remains at >2 years (Strange, Gabbay et al. 2013, Armstrong, Billings et al. 2019). Decreasing the time to diagnosis may reduce emotional uncertainty in patients, reducing the use of healthcare resources, and enabling treatment at an earlier stage when therapies may be more effective (Kiely, Lawrie et al. 2019).

Once a diagnosis of PAH is confirmed, the condition is classified according to how the symptoms affect a patient's daily life. Regular assessment of patients with PAH in expert PH centres is strongly recommended by the recent ESC/ERS Guidelines. Strategies of follow-up vary between centres and there are uncertainties around the optimal timing of follow-up RHC. However, there is consensus among experts that RHC should be performed whenever therapeutic decisions can be expected from the results, which may include changes in medications and/or decisions regarding listing for transplantation.

Managing patients with PAH requires a comprehensive treatment strategy and multidisciplinary care. In addition to applying PAH drugs, general measures and care in special situations represent integral components of optimized patient care.

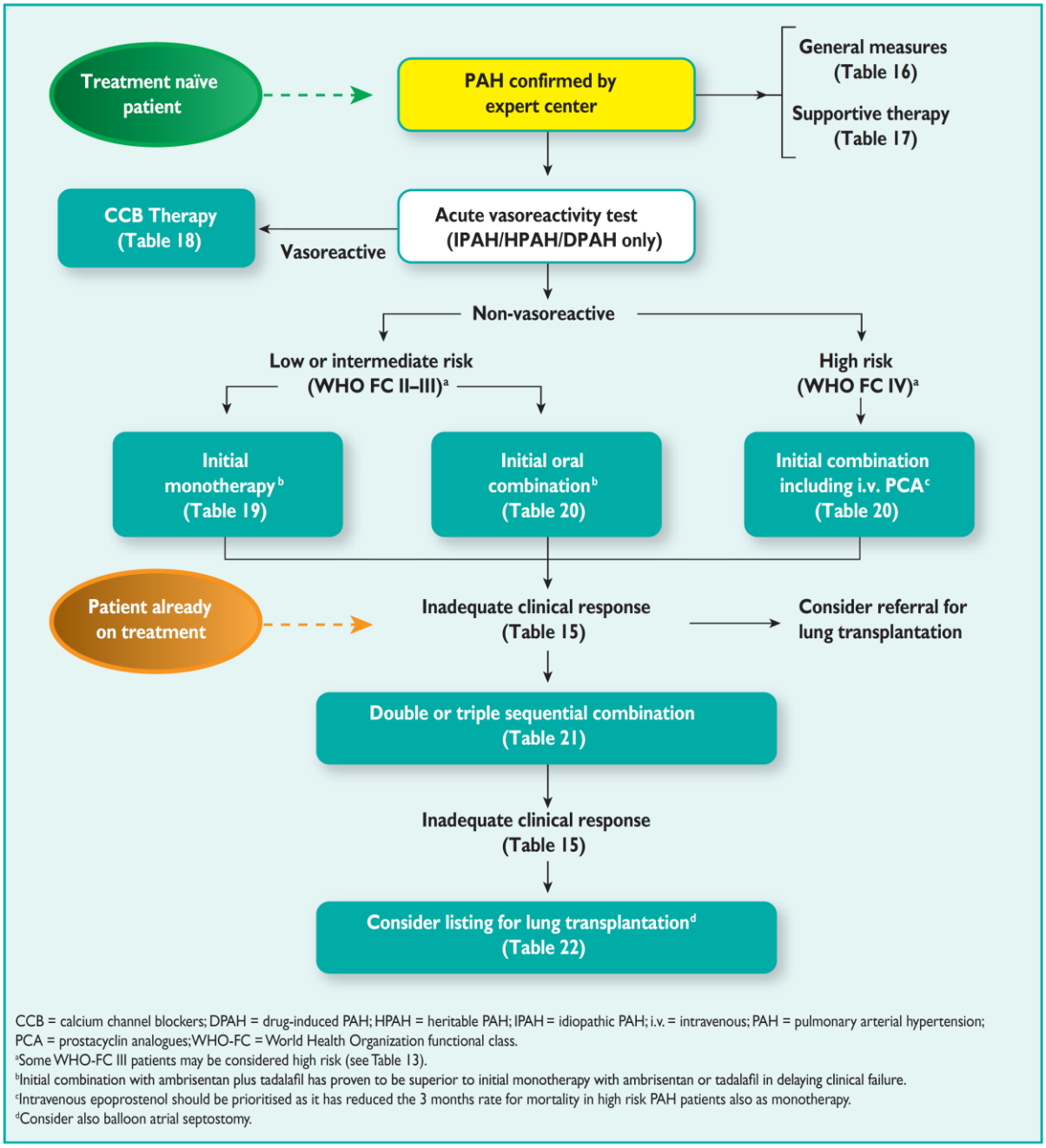
Therapies used to treat PAH patients are of particular relevance to this study, as this information will be leveraged to inform the algorithm to identify PAH patients from claims and electronic medical record (EMR) data sources, as well as to inform the characterization of treatment patterns.

The 2022 ESC/ERS Guidelines make different disease management recommendations based on patients having cardiopulmonary comorbidities, which include conditions associated with an increased risk of left ventricular diastolic dysfunction, and include obesity, hypertension, diabetes mellitus, and coronary heart disease; pulmonary comorbidities may include signs of mild parenchymal LD and are often associated with a low diffusing capacity of the lungs for carbon monoxide (DL_{CO}) (45% of the predicted value) (Humbert, Kovacs et al. 2022).

Patients without cardiopulmonary comorbidities, with low or intermediate risk, should initiate a combination treatment with endothelin receptor antagonists (ERAs) and phosphodiesterase-5 inhibitors (PDE5is), whereas patients with high risk should initiate treatment with an ERA, PDE5i and intravenous/subcutaneous (IV/SC) prostacyclin analogues (PCA). On the other hand, patients with cardiopulmonary comorbidities should initiate monotherapy with a PDE5i or ERA. As the disease progresses, adding a prostanoid analogues and prostacyclin receptor agonists (PRA) or switching from PDE5is to a soluble guanylate cyclase stimulator (sGCs) should be considered for intermediate-low risk patients. For intermediate-high or high-risk patients, addition of an IV or SC PCA and/or lung transplantation should be considered (Humbert, Kovacs et al. 2022).

Given that the nature of the current study is retrospective, the application of the 2022 ESC/ERS Guidelines will not be reflected in the data collected and analysed. Thus, the treatment algorithm recommended in the 2015 ESC/ERS Guidelines are more relevant and is summarized in **Figure 2**. A list of therapies is reported in **Table 21** and **Table 23**.

Figure 2: Evidence based treatment algorithm for pulmonary arterial hypertension patients, Group 1, from the 2015 ESC/ERS PH Guidelines



CCB = calcium channel blockers; DPAH = drug-induced PAH; HPAH = heritable PAH; IPAH = idiopathic PAH; i.v. = intravenous; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogues; WHO-FC = World Health Organization functional class.
[a]Some WHO-FC III patients may be considered high risk (see Table 13).
[b]Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure.
[c]Intravenous epoprostenol should be prioritised as it has reduced the 3 months rate for mortality in high risk PAH patients also as monotherapy.
[d]Consider also balloon atrial septostomy.

1.2.4 Epidemiology of PAH

The global epidemiology of PAH is largely unknown. Recent data from economically developed countries suggest a PAH incidence and prevalence of ~6 and 48 to 55 cases/million adults, respectively (Leber, Beaudet et al. 2021). The HPAH Group 1.2 affects younger individuals and twice as many females as males. Overall, PAH is also frequently diagnosed in older patients (≥65 years) who often present with cardiovascular comorbidities, with a similar incidence in

males and females. Among the different PAH subtypes, idiopathic pulmonary arterial hypertension (IPAH) is the most common, accounting for 50% to 60% of all cases, followed by PAH, associated with CTD, congenital heart disease (CHD) and portal hypertension (Humbert, Kovacs et al. 2022). In the United Kingdom (UK), a prevalence of 97 cases per million with a female: male ratio of 1.8 has been reported (Galiè, Humbert et al. 2015). In the United States (US), approximately 500 to 1,000 new cases are diagnosed each year, confirming the rarity of this disorder, and approximately 15% to 20% of patients with PAH have inherited the condition. The French PAH registry estimates a survival rate of 58% at 3 years (Humbert, Sitbon et al. 2010).

1.2.5 Burden of disease

Pulmonary arterial hypertension is a debilitating disease that pervades all aspects of a patient's daily life, from physical activity, general health, and vitality to emotional and social functioning (Delcroix and Howard 2015). Besides the impact on the quality of life, PAH places a considerable economic burden on patients and their families, the healthcare system, and society, also impacting labour productivity (Zhai, Zhou et al. 2017, Bergot, De Leotoing et al. 2019, Zozaya, Abdalla et al. 2022).

The causes and circumstances surrounding death are understudied in patients with PAH. According to the Centres for Disease Control and Prevention–Pulmonary Hypertension Surveillance, 1980–2002, PH has increased as a contributor to death. A study performed in the US in 2013 demonstrates that the main cause of death in patients with PAH is PAH, followed by right ventricular failure or sudden death in less than half of the patients (Tonelli, Arelli et al. 2013). A systematic review of 65 studies with population-level data, between 1980 and 2021, reported 1-year survival ranged from 67% to 99% for clinically diagnosed PAH(Emmons-Bell, Johnson et al. 2022). In the United States the REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) enrolled patients with PAH from 55 centres between 2006 and 2009 (Badesch, Raskob et al. 2010, Benza, Miller et al. 2012, Farber, Miller et al. 2015). The 1-, 2-, and 3-year mortality rate for patients with PAH in the REVEAL was 10%, 19%, and 25%, respectively. Similar results were reported by large single-center US registries (Thenappan, Shah et al. 2010, Kane, Maradit-Kremers et al. 2011).

A recent investigation showed that the best absolute-threshold values for 1 year mortality and 1 year survival, respectively, were 165 m and 440 m, respectively, for PAH patients (Zelniker, Huscher et al. 2018).

The 2015 European pulmonary hypertension (PH) guidelines proposed a risk stratification strategy for patients with PAH. Low-, intermediate- and high-risk strata are defined by estimated 1-year mortality risks of <5%, 5–10% and >10%, respectively (Hoeper, Kramer et al. 2017). Since then, registry data have shown that observed 1 year mortality rates in the intermediate- and high-risk groups were sometimes higher than predicted (i.e. up to 20% in the intermediate-risk group and 20% in the high-risk group). These numbers have been updated accordingly in the revised three-strata risk model (**Table 18**, in the 2022 ESC/ERS Guidelines)(Humbert, Kovacs et al. 2022).

1.3 Group 3 Pulmonary Hypertension Associated with LD and/or Hypoxia

1.3.1 Clinical definition

Group 3 includes PH due to chronic lung disease (CLD) and/or hypoxia (low oxygen levels) and is associated with reduced functional ability, impaired quality of life, greater oxygen requirements and mortality (Blankfield, Hudgel et al. 2000, Nathan, Barbera et al. 2019, Harder and Waxman 2020). The most common LDs associated with PH are COPD, ILD and combined pulmonary fibrosis and emphysema (CPFE). In any LD, the development of PH is accompanied by a deterioration of exercise capacity, worsening of hypoxaemia and shorter survival (Galiè, Humbert et al. 2015). The aetiology of CLD-PH is complex and multifactorial, with differences in the pathogenic sequelae between the diverse forms of CLD (Nathan, Barbera et al. 2019). Chronic lung disease-pulmonary hypertension is characterized by an increase of blood pressure in the pulmonary artery, pulmonary vein, or pulmonary capillaries, together known as the lung vasculature, leading to shortness of breath, dizziness, fainting, and other symptoms (McLaughlin, Archer et al. 2009). There are six types of Group 3 associated with LD and /or hypoxia (**Table 1**) (Humbert, Kovacs et al. 2022).
Chronic obstructive pulmonary disease (COPD, PH 3.1) and ILD are two large subgroups of CLD patients who often develop PH. Emphysema and chronic bronchitis are the two most common conditions that contribute to COPD, often occurring together and can vary in severity among COPD patients (McLaughlin, Archer et al. 2009). In the Group 3.2, ILDs are composed by a heterogeneous group of disorders, which encompass a wide range of diffuse parenchymal lung conditions. Development of PH is a common complication in patients with ILD. Pulmonary hypertension due to ILD (PH-ILD) can complicate a multitude of ILDs, including idiopathic pulmonary fibrosis, chronic hypersensitivity pneumonitis, and non-specific interstitial pneumonia (Forey, Thornton et al. 2011). Development of PH-ILD is associated with an increased need for supplemental oxygen, reduced mobility, and decreased survival (Nasser, Larrieu et al. 2021).

1.3.2 Disease Management and Therapies

The accepted diagnostic paradigm for PH-ILD follows a suspect, support, confirm, and stratify approach(Nathan, Barbera et al. 2019).
For a diagnosis, non-invasive tests, such as an electrocardiogram (ECG), showing right axis deviation or right ventricle (RV) strain, elevated levels of brain natriuretic peptide/n-terminal pro B-type natriuretic peptide (BNP/NT-proBNP), cardiopulmonary exercise testing (CPET), or features on cross-sectional imaging, may suggest the diagnosis of PH in patients with LD(Kovacs, Avian et al. 2016, Torres-Castro, Gimeno-Santos et al. 2021). Echocardiography remains the most widely used non-invasive diagnostic tool for assessing PH; however, the accuracy of echocardiography in patients with advanced respiratory diseases is low, with a tendency to overestimate pulmonary artery pressure (PAP) and misclassify patients with PH (Humbert, Kovacs et al. 2022). Indications for RHC in LD is recommended favouring

phenotyping of disease and consideration of therapeutic interventions. Such testing should ideally be conducted in PH centres when patients are clinically stable and treatment of underlying LD has been optimized (Humbert, Kovacs et al. 2022).
Clinical, functional, or imaging results, may suggest the presence of PH in a patient with ILD. Useful data based on clinical history, symptoms, signs, an ECG, chest radiograph, (pulmonary function tests [PFTs], including DL_{CO}, arterial blood gas analysis and nocturnal oximetry, if required) and high-resolution computed tomography (CT) of the chest are initially requested, as presented above (**Figure 1**)
Since concomitant left heart disease (LHD) is frequently found in patients with CLD, patients presenting respiratory disorders with symptoms that are more severe than expected, based on their pulmonary function, should be further evaluated by thoracic echocardiography to search for concomitant LHD or PH. A follow-up echocardiogram will support the suspected diagnosis if there is evidence of elevated systolic pulmonary artery pressure (sPAP) (>45 to 50 mmHg) and/or signs of right ventricular dysfunction (Nathan, Barbera et al. 2019, King and Shlobin 2020, Behr and Nathan 2021). For PH-ILD, although traditional transthoracic echocardiography is the most used screening test, it lacks sensitivity and specificity. Newer echocardiographic tools involving a 3-dimensional assessment of the right ventricle may have a role in both prognosis and the monitoring of patients with PH-ILD.
Right heart catheterization with direct measure of PAP and pulmonary capillary wedge pressure (PCWP) remains the gold standard for confirming a diagnosis of PH-ILD (Forey, Thornton et al. 2011, Shlobin and Nathan 2011). After confirmation, PH-ILD was stratified into either mild to moderate PH or severe PH, depending on haemodynamic finding (Nathan, Barbera et al. 2019), considering that in the 2015 ESC/ERS Guidelines, severe PH was defined by mPAP >35 mmHg or mPAP ≥25 mmHg with CI <2.5 L/min/m^2 (Galiè, Humbert et al. 2015). However, according to the 2022 ESC/ERS Guidelines, in patients with LD disease, PH is categorized as non-severe or severe, depending on haemodynamic finding for PVR (Humbert, Kovacs et al. 2022). Two recent studies have demonstrated that a PVR >5 WU is a better threshold for predicting worse prognosis in patients with PH associated with both COPD and ILD (Olsson, Hoeper et al. 2021, Zeder, Avian et al. 2021).

The 2022 ESC/ERS PH Guidelines recommend that patients with Group 3 PH should be referred to PH centres for individualized treatment decision-making. The therapeutic approach to Group 3 PH starts with optimizing the treatment of the underlying CLD, including supplementary oxygen and non-invasive ventilation, where indicated, as well as enrolment into pulmonary rehabilitation programmes. Drugs approved for PAH have been investigated in several randomised controlled trials in PH-ILD patients, leading to discouraging results (Waxman, Elia et al. 2022) until the recent INCREASE study. In this trial and in the following post hoc analyses, inhaled Treprostinil (Tyvaso, United Therapeutics) improved exercise capacity in patients with PH due to interstitial lung disease, preventing clinical worsening (15% decrease in 6-min walk distance, cardiopulmonary hospitalization, lung transplantation, or death) and achieving clinical improvement (15% increase in the six-minute walk distance with 30% reduction NT-proBNP and clinical worsening events) (Waxman, Restrepo-Jaramillo et al. 2021, Humbert, Kovacs et al. 2022).

The 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension, for the first time include a recommendation of pharmacological treatment for patients with PH-ILD: inhaled treprostinil may be considered for PH-ILD patients, irrespective of the severity of

PH (Humbert et al., 2022) based on the clinical evidence of the INCREASE trial. There's also a conditional consideration for PDE5 inhibitors in patients with severe PH associated with ILD, very low quality of evidence based on a PICO question as there are no direct data from RCTs on the safety, tolerability, and efficacy of PDE5is in these patients. Given the lack of robust evidence, the Task Force members recommend that these patients are referred to a PH centre for individualized decision-making. The remaining PAH drugs are not recommended for WHO Group 3 PH, with ambrisentan and riociguat being contraindicated for PH-IPF and PH-IIP patients, respectively (Humbert, Kovacs et al. 2022).

Remarkably the significant effects of inhaled Treprostinil were observed even in non-severe PH patients with lung disease. Of note, the routine use of other medication approved for PAH is not recommended in patients with ILD and non-severe PH (Humbert, Kovacs et al. 2022). The treatment patterns of Group 3 may vary between countries and even within countries between centres. Treatment of Group 3 PH patients can be challenging since particularly bothersome symptoms, such as dyspnea, are often multifactorial and may not consistently improve with disease-specific therapies (DuBrock, Nathan et al. 2021). The use of combination therapy for treatment has increased since 2015, but since there was limited evidence of overall survival rate improvement, no clear recommendations have been made by the 2022 ESC/ERS Guidelines (Humbert, Kovacs et al. 2022).

1.3.3 Risk factors

Some risk factors have been found to be associated with the development of Group 3 PH (Raghu, Amatto et al. 2015). Strong risk factors include a family history of PH, blood clotting disorders or family history of blot clots in the lung, whereas other non-respiratory risk factors include being overweight, ischaemic heart disease (IHD) and gastro-oesophageal reflux, exposure to asbestos, use of certain drugs, including some weight-loss medicines and illegal drugs such as cocaine (Friedman and Andrus 2012, Raghu, Amatto et al. 2015, Alzghoul, Abualsuod et al. 2020). In developed countries, the main cause of PH-COPD is tobacco smoking. Besides tobacco exposure, or in combination, people with a family history of asthma and respiratory infections in childhood, or with long-term exposure to chemical fumes, vapours and dusts in the workplace, or genetic predisposition (e.g., the uncommon genetic disorder, alpha-1-antitrypsin deficiency) may present a higher risk of developing COPD, even when young (Galiè, McLaughlin et al. 2019). Whereas, in the developing world, COPD often occurs in people exposed to fumes from burning fuel for cooking and heating in poorly ventilated homes (de Marco, Accordini et al. 2011).
In patients with Group 3 PH, the disease severity is categorized based on the haemodynamic profile: non-severe PH is characterized by a PVR ≤ 5 WU and severe PH as PVR >5 WU. It is estimated that approximately 20% of patients with advanced COPD, CPFE or ILD have non-severe PH and 5% to 10% have severe PH (Humbert, Kovacs et al. 2022).

1.3.4 Epidemiology

The prevalence of Group 3 PH in Europe remains largely unknown. Most studies report the prevalence of PH associated with specific LDs. The prevalence of Group 3 is estimated to range between 0.49 and 6.9 per 10,000 people (Ferrer Data on File 2022). Among patients with COPD, the estimated prevalence of PH ranges between 28 and 224 per 10,000 people and

among ILD, ranges between 0.8 and 1 per 10,000 (Ferrer Data on File 2022). The prevalence of PH associated with sleep disorders such as apnoea, is largely unknown. Wide ranges in prevalence can be due to heterogeneity in PH definitions, diagnostic modalities, differences in patient populations, physiologic characteristics, and severity of underlying LD (Han, McLaughlin et al. 2007).

The 3-year survival rate in Group 3 varies by subgroup with 90% for sleep-disordered breathing, 41% for PH-COPD, and 16% for PH-ILD (Heresi, Platt et al. 2017). In COPD, PH has been reported as predicting worse survival, as the 5-year survival rate was 37% in COPD patients with PH versus 63% in patients without PH (Andersen, Iversen et al. 2012, Hurdman, Condliffe et al. 2012). Survival in ILD patients with PH has been reported to be worse than in patients without PH at any PH level, even in borderline PH (defined as mPAP 21 to 24 mm Hg and PVR ≥3 WU), with a 3-year overall survival of 32% in the latter (Piccari, Wort et al. 2022).

One of the main objectives of this study is to determine the epidemiology of Group 3 PH and Group 3.2 PH in Germany, France, and the UK.

1.3.5 Burden of disease

Pulmonary hypertension (PH) due to chronic lung disease, classified as Group 3 PH, is the second most common cause of PH after left-heart disease (Strange, Playford et al. 2012). Describing the burden of disease for Group 3 PH patients is challenging due to the limited amount of literature.

Group 3 patients have a lower quality of life, increased morbidity, and mortality due to worsened functional status, and higher medical costs as compared with patients with chronic lung disease without PH (Barberà and Blanco 2015). Shortness of breath, fatigue, cough, and swelling were the most frequently reported symptoms of PH due to chronic obstructive pulmonary disease or interstitial lung disease (DuBrock, Nathan et al. 2021). This observation on higher medical costs is consistent with what reported by a retrospective observational study on Group 3 PH patients compared to LD controls in US (Heresi, Platt et al. 2017). The study showed that the higher economic burden was driven by inpatient admissions, prescriptions, and outpatient care (Heresi, Platt et al. 2017). A subsequent Real-Word analysis using US claims data performed by the same team showed that patients with PH-ILD had significantly increased utilization of healthcare resources, including inpatient admissions, and costs, following an initial diagnosis of PH (Heresi, Castillo et al. 2021). The analysis showed that hospitalizations appeared to be more severe for PH-ILD patients, with significant increases in the length of stay per hospitalization and in the percent of patients requiring intensive care (Heresi, Castillo et al. 2021).

According to a population-based cohort study in Ontario, Canada, from 1993 to 2012, Groups 2 and 3 are the most common and lethal forms of PH. In this cohort of 50 529 patients with PH, mortality in adults was 13.0%, 36.4%, and 62.4%, at 30 days, 1 year, and 5 years, respectively (Wijeratne, Lajkosz et al. 2018). PH was reported to be associated with worse survival in in patients with end-stage COPD and in idiopathic pulmonary fibrosis (IPF) patients who were referred for transplantation (Andersen, Iversen et al. 2012, Kimura, Taniguchi et al. 2013).

Exacerbations

A COPD exacerbation is defined as an acute worsening of respiratory symptoms that results in additional therapy (**GOLD 2020**). Mild and moderate exacerbations require treatment

intensification, whereas severe exacerbations require hospitalizations or emergency room visits. Severe exacerbations may also be associated with acute respiratory failure (**GOLD 2020)**. Establishing the diagnosis of acute exacerbations in ILD often comprises a challenge. Adverse event (AE) is better described in idiopathic pulmonary fibrosis (IPF) but also reported in ILD secondary to connective tissue diseases (CTD) and vasculitis. In order to get to this diagnosis, various diagnostic tests should be performed and differential diagnosis like myocardial infarction, pulmonary embolism, or fluid overload need to be excluded. The clinical presentation of acute exacerbation in ILD is usually a rapid worsening of respiratory symptoms with increased dyspnea within less than 1 month. Additional findings can be cough, increased sputum production, fever, and flu-like symptoms. Since many patients present with a severe hypoxemia in the arterial blood gas analysis and respiratory failure, admission to the intensive care unit and assisted ventilation is often required. For this reason, in this study, exacerbations in ILD will not be captured due to the absence of necessary data to capture a exacerbation in ILD (Leuschner and Behr 2017, Manfredi, Sebastiani et al. 2019).

1.4 Study Rationale

Overall, there are few studies on PAH treatment patterns and no studies reporting the incidence or prevalence of Group 3 PH patients. Existent studies focus on two subclasses of Group 3 PH, namely PH associated with COPD and PH associated with ILD, in specific data sources. In this study, we will leverage large national data sources in Germany, France and the UK, representative of the overall country population, to estimate the incidence and prevalence of Group 3 PH. Additionally, we will characterize the treatment patterns of patients with Group 1, Group 3 and Group 3.2 PH. Finally, we will describe the real-world outcomes of Group 3 and Group 3.2 PH.

2. STUDY OBJECTIVES

Primary objectives

1. Estimate the prevalence and incidence of Group 3 PH and Group 3.2 PH-ILD in Germany, France, and the UK
2. Characterize the treatment patterns of patients with Group 3 PH, Group 3.2 PH-ILD, and Group 1 PAH on the incident population

Secondary objectives

1. Estimate the burden of disease of patients with Group 3 PH and Group 3.2 PH-ILD in terms of:
    a. Resource use (inpatient and outpatient resource use)
    b. Costs for Group 3 PH and Group 3.2 PH-ILD patients, including evaluating expenditure on tests, procedures, diagnostics, and medications
2. Characterize the patient profile and real-world outcomes of patients with Group 3 PH and Group 3.2 PH-ILD in terms of:
    a. Demographic and clinical characteristics of the patients
    b. Comorbidity burden
    c. Survival rate
    d. Yearly hospitalization rate

3. METHODOLOGY

3.1 Study Design

This is a retrospective longitudinal cohort study, based on claims databases in France and Germany, and electronic medical records (EMRs) in the UK. The study design period was adapted considering the potential impact that the COVID-19 pandemic had on an overall reduction in diagnosis of diseases in 2020.

3.1.1 Study Cohorts

This study will be focused on two main cohorts and a subgroup:

1. Group 1 PAH Cohort: Patients with Group 1 PAH
2. Group 3 PH-LD Cohort: Patients with Group 3 PH associated with LD and/or hypoxia
    a. PH-ILD Sub-group: Patients with Group 3.2 PH associated with ILD

3.1.2 Study period

The study design includes the three following periods (**Figure 3, Figure 4**):

- **Inclusion period** between Jan 2017 and Dec 2019 (except in Germany where it will be 2018-2019 to allow a minimum of 24-month lookback). The inclusion period was defined to allow a minimum of 24-month look back to accurately identify incident (newly diagnosed) patients.
    - **Index date:**
        - For the Group 1 PAH cohort, the earliest of the following (both primary and secondary diagnosis are considered):
            - the first recorded PH diagnosis during the inclusion period (**Table 5**);
            - the first recorded event within a specialist PH referral centre during the inclusion period (not considered in Germany as centre location is not available).
        - For the Group 3 PH-LD cohort: the first recorded PH diagnosis during the inclusion period (**Table 5**) (for the PH diagnosis to be considered index date, a recorded LD diagnosis must have occurred up to 24 months prior or 60 days after the PH diagnosis).
- **Lookback period**: minimum of 24 months before the index date
- **Follow-up period**: Patients will be followed from index date until:
    - date of death or (describe reason for death)
    - exit from the data source (with a reason – when available) or
    - end of study on 31 December 2021 (if the last date recorded in the data source occurred within 6 months of end of study) or
    - date of last observation (if last observation recorded occurred ⩾6 months (180 days) before end of study).

- **Study period**

- Jan 2016 until Dec 2021

Figure 3: Study period for Group 1 PAH cohort in the UK and France

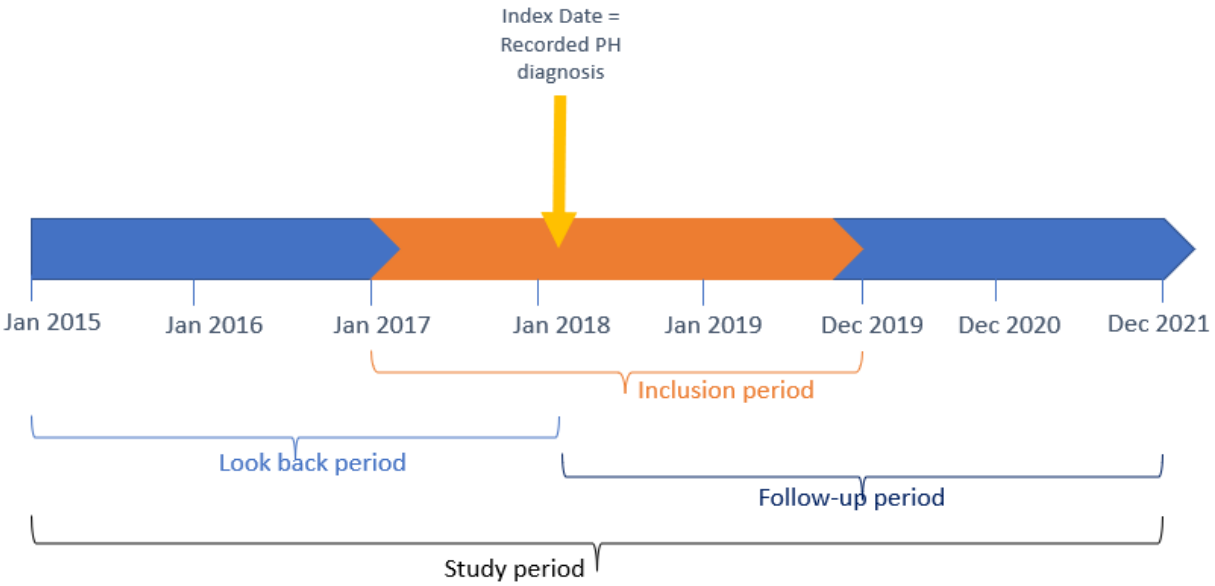
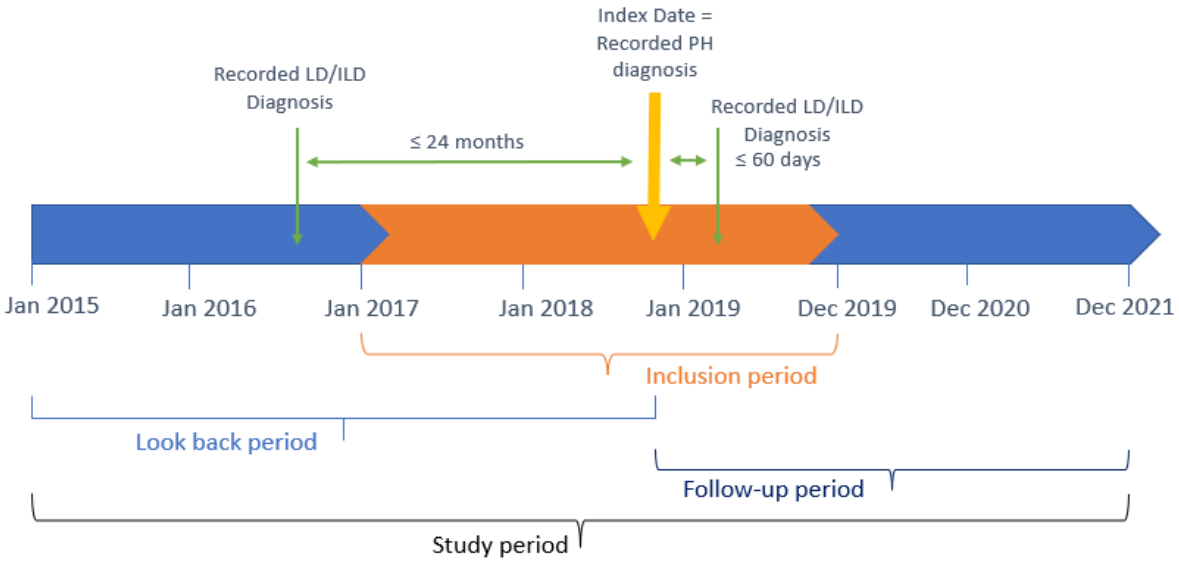


Figure 4: Study period for Group 3 PH-LD/ILD cohort in the UK and France



Note: the index date can occur anytime within the inclusion period.

3.1.3 Group 1 PAH Cohort

Currently, PAH patients are not directly identifiable in claims nor in EMR databases as no specific ICD-10 code is available for PAH at a four-character level. The ICD-10 code I27.0 for

primary and heritable PH correspond to idiopathic PAH in the current PAH classification, but there are no ICD-10 codes that differentiate the other PH classes. Therefore, patients with PAH were identified using an algorithm, integrating PH diagnosis codes, procedures associated with PAH, PAH-specific therapies, and visits to PH specialist centres (applicable in the CPRD/HES, PMSI and SNDS, information about the centres is not available in the German claims data source). This algorithm is based on previous studies that used validated methods with claims and EMR data sources, and is represented in **Figure 5** (Exposto, Petrică et al. 2020, Exposto, Hermans et al. 2021).

Inclusion criteria:

- Patients aged ≥ 18 years at index date.

AND

- Patients with a recorded PH diagnosis (I27.0 or I27.2) whether primary or secondary (**Table 5** or **Table 6**) during the inclusion period
  OR Patients with a visit to a PH specialist centre during the inclusion period (**Table 13** or **Table 14**) (parameter not considered in Germany due to the absence of centre location in the data source)

Eligibility was further defined by different combinations of criteria as shown in **Figure 5**. The algorithm did not require an ICD-10 code for PH if a patient had other strong indicators of PAH, namely a combination of a visit to a PH specialist centre (identified by trust codes in France and UK, not available in Germany), RHC (identified by procedure codes), and the dispensation of PAH-specific drugs (identified by drug codes) (**Table 30**). The following information will be screened and combined in different ways:

  - Having a visit in a PH reference centre during the study period (see **Table 13** or **Table 14**)
  - Having a RHC procedure during the study period (see **Table 16, Table 17** or **Table 18**).
  - Having been dispensed at least one specific PAH drug during the study period (**Table 24** , **Table 25** or **Table 26**)

Exclusion criteria

- Any record indicative of a PH diagnosis other than Group 1 PAH during the lookback period based on a list of diseases typically associated with other PH Groups (see **Table 22**).
- Patients without a minimum of 24-month lookback period.
- For the treatment patterns, resource use and outcome analyses, patients without a minimum of 12-months follow up data.

Sub-cohorts

The proportion of patients with the following comorbidities will be presented:

- Group 1 PAH with cardiopulmonary comorbidities (COPD [ICD-10 J44] or cardiovascular disease [**Table 27**])
- Group 1 PAH without cardiopulmonary comorbidities (COPD [ICD-10 J44] or cardiovascular disease [**Table 27**])

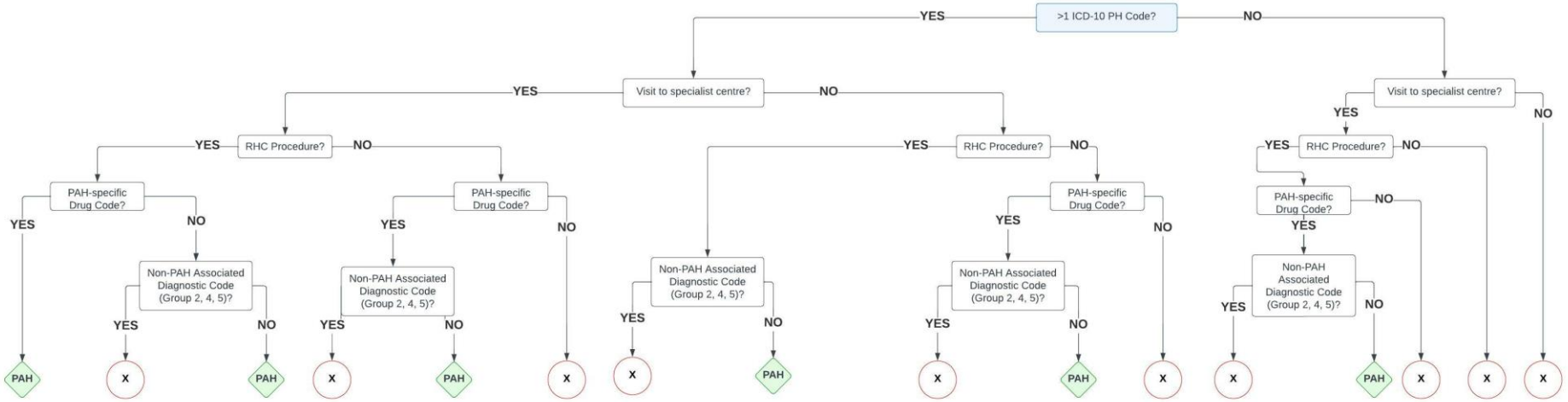
Description of the decision-tree:

1. Patients with an ICD-10 code for PAH, and with a visit to a specialist center, and with an RHC procedure and receiving PAH-specific drugs
2. Patients with an ICD-10 code for PAH, and with a visit to a specialist center, and with an RHC procedure, without PAH-specific drugs, and without Group 2, Group 4 or Group 5 associated codes
3. Patients with an ICD-10 code for PAH, and with a visit to a specialist center, and without an RHC procedure, and receiving PAH-specific drugs and without Group 2, Group 4 or Group 5 associated codes
4. Patients with an ICD-10 code for PAH, and without a visit to a specialist center, with an RHC procedure, and without Group 2, Group 4 or Group 5 associated codes
5. Patients with an ICD-10 code for PHA, and without a visit to a specialist center, without an RCH procedure, without PAH-specific drugs, and without Group 2, Group 4 or Group 5 associated codes
6. Patients without ICD-10 code for PH but with a visit to a PH specialist center, and a RHC procedure, and receiving PAH-specific drugs, and without Group 2, Group 4 or Group 5 associated codes

Adaption of the decision-tree in Germany where visit to PH specialist center is not available

1. Patients with an ICD-10 code for PAH and with an RHC procedure, without PAH-specific drugs, and without Group 2, Group 4 or Group 5 associated codes
2. Patients with an ICD-10 code for PAH, and without an RHC procedure, and receiving PAH-specific drugs and without Group 2, Group 4 or Group 5 associated codes
3. Patients with an ICD-10 code for PAH, with an RHC procedure, and without Group 2, Group 4 or Group 5 associated codes
4. Patients with an ICD-10 code for PAH, and with an RHC procedure, and with PAH-specific drugs
5. Patients without an ICD-10 code for PAH, and with an RCHC procedure, and receiving PAH-specific drugs, and without Group 2, Group 4 or Group 5-associated codes

Figure 5: Decision Tree algorithm used to identify a cohort of PAH patients based on published administrative data



Adapted from: (Exposto, Petrică et al. 2020, Exposto, Hermans et al. 2021)

3.1.4 Group 3 PH cohort

Currently, PH-LD patients are not directly identifiable in claims or EMR databases as no specific ICD-10 code is available. Thus, an algorithm has been developed to identify these patients (**Figure 6**) (Heresi, Dean et al. 2022).

Inclusion criteria (see Figure 6 for the flow chart):

- Patients aged ≥ 18 years
  AND
- Patients with a recorded inpatient PH diagnosis or two outpatient visits (primary or secondary) (see **Table 5** and **Table 6**) during the inclusion period. If a single recorded PH outpatient visit is identified in the inclusion period, the search will be expanded to the full study period to identify a second outpatient or inpatient PH visit occurring any time after the first LD diagnosis identified in the study period. This PH diagnosis is set as the index date.
  AND
- Patients with a LD diagnosis (see **Table 19**), primary or secondary, inpatient occurring up to 24 months lookback period prior to or 60 days after the index date
  OR
  Patients with 2 LD outpatient visits recorded up to 24 months prior to or 60 days after the index date. The 60 days after Index date was included based on PH expert feedback, to capture those patients whose Index date triggers further testing and an underlying lung disease is detected at the same time as PH.

Note: Diagnosis will be searched during an inpatient or outpatient hospitalization and/or outpatient visit (visit to general practitioner or specialist).

Exclusion criteria:

- Patients with a recorded diagnosis typically associated with PH Group 2, PH Group 4 [Chronic Pulmonary thromboembolism I27.24; I27.82] or PH Group 5 recorded prior to the PH index date (see **Table 22**).
- Patients with a recorded diagnosis for PH Group 4 [Acute Pulmonary thromboembolism I26] recorded more than 60 days before or 60 days after the PH index date (see **Table 22**).
- Patients without a minimum of 24-month lookback period are excluded. For the treatment patterns, resource use and outcome analyses, patients without a minimum of 12-months follow up data will be excluded.

In the descriptive analysis, the fraction of patients corresponding to each of the Group 2, 4 or 5 groups will be reported (as for **Table 22**), based on the ICD-10 codes associated with each PH Group as reported in **Table 5**.

Table 5: ICD-10 codes PH inclusion criteria

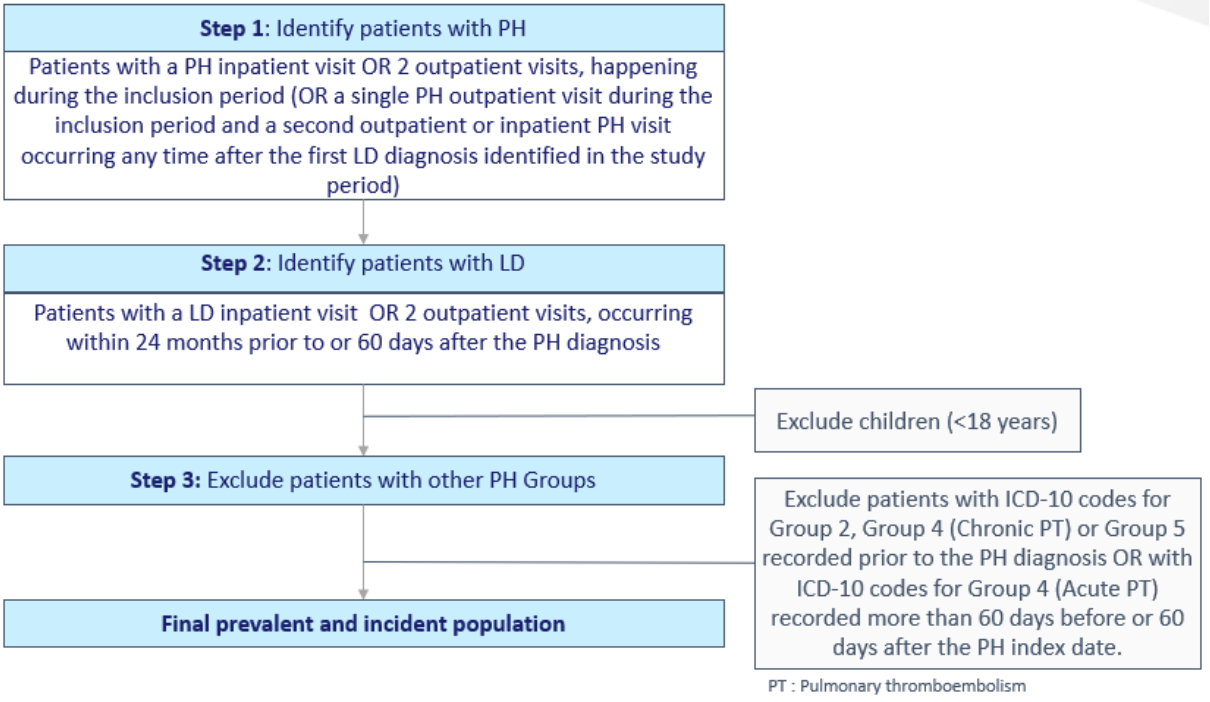
ICD-10 codes (four-character level and all the associated sub-codes)	Label
I27.0	Primary pulmonary hypertension

I27.2	Other: secondary pulmonary hypertension

Table 6: "Read codes" PH inclusion criteria,

Read codes	Label
G42.11	Pulmonary vessel disease
G41z.00	Chronic pulmonary heart disease NOS
G41.00	Chronic pulmonary heart disease
G410.00	Primary pulmonary hypertension
G41y000	Secondary pulmonary hypertension

Figure 6: Algorithm to identify PH-LD Group 3 patients



The final population identified with the algorithm (Figure 6) constitutes the "Baseline Group 3". Two additional populations will be considered in the prevalence and incident estimations. Considering that it might be difficult to distinguish PH-LD patients with comorbid left heart disease (Group 2), versus Group 2 PH patients with comorbid LD a broad case definition was considered. The broad Group 3 PH corresponds to patients with a recorded PH diagnosis and having both an LD and left heart disease diagnosis prior to the index date.

On the other side of the spectrum, PH-LD can only be accurately diagnosed if an RHC is performed. Hence, we define a narrow case definition with confirmed PH corresponding to the subgroup of patients from the baseline population that have an RHC procedure recorded before the index date.
The analyses associated with the secondary objectives will be applied to the baseline population only.

3.1.4.1 Group 3.2 PH-ILD Subgroup

Currently, PH-ILD patients are not directly identifiable in claims or EMR databases as no specific ICD-10 code is available. The Group 3.2 PH-ILD sub-group corresponds to the patients that had a recorded ILD diagnosis up to 24 months before or 60 days after PH index date, identified in Step 2 in the Group 3 algorithm (section 3.1.4) (see **Table 19** ILD section). Descriptive analysis of different ILD diseases will be reported.

3.1.4.2 Sensitivity analyses applicable to Group 3 PH and Group 3.2 PH-ILD

- Assess the impact of considering a single PH recorded outpatient visit (instead of two) in the algorithm
- Assess the impact of considering a single LD recorded outpatient visit (instead of two) in the Group 3 algorithm
- Report the number of patients identified with recorded LD more than 12 months and less than 24 months from index date
- Assess the impact of the exclusion criteria of requiring a minimum of 24-month look-back period instead of 12 months
- When conducting the sensitivity analyses, we will present:
    - The impact of the analysis in the step where it applies (e.g., number of patients with a single record of PH hospital visit instead of two)
    - The impact of the analysis on the final count of prevalence and incidence
- Describe the number of patients that enter the study cohort with an LD diagnosed withing 60 days after the PH diagnosis
    - A descriptive analysis will be performed to do a naïve comparison of PH-LD patients who enter the cohort having LD diagnosed prior to PH vs LD diagnosed up to 60 days after PH index date. Descriptive analysis will include mean age, gender and comorbidities (identified by comorbidities codes, see **Table 27** and **Table 28**, and including Group 2, 4 and 5 comorbidities). Should the two patient subgroups appear different, a decision will be made, together with the medical experts as to how to proceed (e.g., exclude patients with LD diagnosis after PH or perform separate analyses for each subgroup)
- Additional analysis may be conducted for the following sub-groups of interest including but not limited to:
    - Patients with ILD diagnosis prior to PH diagnosis, Patients with PH diagnosis prior to ILD diagnosis
    - Patients with PAH with and without cardio-pulmonary comorbidities

3.2 Data analysis

3.2.1 Estimate the prevalence and incidence of Group 3 PH and Group 3.2 PH-ILD

Definition of prevalent patients

Group 3 PH-LD Cohort

- All patients having a Group 3 PH diagnosis based on the validated algorithm during the inclusion period

Group 3.2 PH-ILD Cohort

- All patients having a Group 3 PH-ILD diagnosis based on the validated algorithm during the inclusion period
- Present the number of patients split for the following ILDs:
    - IPF
        - Other interstitial pulmonary diseases with fibrosis (J84.1, including the associated sub-codes, see **Table 19**)
    - Hypersensitivigy pneumonitis
        - Hypersensitivity pneumonitis due to organic dust (J67)
    - Connective Tissue Disease-ILD (CTD-ILD) including the following ICD-10 codes:
        - Rheumatoid arthritis (M05-M06)
        - Systemic sclerosis (M34.0–M34.9)
        - Mixed connective tissue disease (M35.1)
        - Polymyositis/dermatomyositis (M33.0–M33.9)
        - Systemic lupus erythematosus (M32.0–M32.9)
        - Sjögren's disease (and M35.0)

Definition of incident patients

Group 3 PH-LD Cohort

- Number of patients with a new diagnosis of Group 3 PH diagnosis during the inclusion period defined as not having any prior records of PH diagnosis prior to the index hospitalization

Group 3.2 PH-ILD Cohort

- Number of patients with a new diagnosis of Group 3 PH-ILD diagnosis during the inclusion period defined as not having any prior records of PH diagnosis records prior to the index hospitalization

Prevalence

The period prevalence will be reported as the number of cases identified within the inclusion period (between Jan 2017 until December 2019), divided by the total number of people at risk, which corresponds to the number of adults (≥18 years) recorded during the inclusion period in a specific country population (France, UK, and Germany). The prevalence rate represents the number of new and pre-existing cases within a given period in relation to the total population at risk within which these cases have arisen (in the same period) (CDC 2012).

The prevalence will be expressed in number of cases per 10,000.

Incidence rate

The incidence rate represents the number of newly diagnosed patients within the inclusion period in relation to the total population at risk within which these cases have arisen (in the same period) (INSEE 2016).

The incidence will be expressed in "number of persons affected per 100,000 of the population", per person years.

The denominators for the rates will be the number of adults (≥18 years) recorded during the years of inclusion in a specific country population (France, UK, Germany).

3.2.2 Characterize the treatment patterns of patients with Group 3 PH, Group 3.2 PH-ILD and Group 1 PAH

A treatment pathway analysis will be used to describe the therapeutic management of incident patients (PH-LD, PH-ILD and PAH) over the study period for each of the populations for patients newly treated with PH drugs, as listed in **Table 7**.

For prevalent PAH patients, the analysis will be restricted to baseline description of treating medications. Percentage of patients treated with each therapy class and combination therapy based on **Table 8** will be presented.

Including percentage of patients on monotherapy, double therapy and triple therapy. For interclass analyses the considered PAH therapy classes are: ERAs, Pas, PDE5 inhibitors or CCBs. Patients were defined as monotherapy users if they were treated with only one class of PAH medication during the first 90 days of the follow-up period. Patients who were treated with more than one class of PAH medication during the first 90 days of the follow-up period were defined as combination therapy users.

The treatments will be analysed by chronological order, by year of follow-up from index. The use of the treatment sequence analysis will enable the identification of each treatment, over time for each patient.
The description of the therapeutic sequence will end at the death of the patient, last treatment claim observed, or study end on 31 December 2021. In addition, a treatment pathway visualization of the treatments will be performed, e.g., through a Sankey diagram.

The following indicators will be analysed in each population:

- Frequency of treatment switch between treatment classes

- Description of the most common treatment sequence observed during the follow-up period after treatment initiation
- The treatments used during the follow-up period, if available, by main pharmacologic classes and/or by specific drugs:
    - The distribution of the number of hospitalizations/claims for specific treatments will be presented.

Treatment patterns for Group 1 PAH cohort

Patients included in this analysis were required to have at least one pharmacy claim for a PAH-specific medication as listed in **Table 7**.

3.2.3 Treatment Patterns Analysis Definitions

The date of start of treatment will be defined as the first date of prescription of any treatment of the drug class, which is provided in **Table 7**, within the inclusion period. Drug treatment will be assessed at the Class level.

New Prescription (therapy) If at the index date no prior treatment within the same class of drug is found within 90-day look-back period, the treatment will be classed as new (at index date or post-index). Treatment duration analysis will be starting at the date of the new prescription. The patient who does not receive a new prescription at index is classified as "no therapy" based on **Table 8**.

Therapy discontinuation is defined by a gap in therapy of ≥ 90 days between the end of a prescription (taking into account its duration from the prescription date) and the next prescription of any PAH treatment of the same class.

Treatment Switch If there is a change in treatment from one class to another, this will be noted as a switch. The second treatment line starts when the member receives a new fill for a PAH medication after treatment interruption or at the time of switch.

Treatment intensification if there is a change in treatment from one class to another, this will be noted as treatment intensification or add-on if the prior therapy is continued. In the switch analysis, this will appear as a switch from monotherapy or double therapy to double therapy or triple therapy, respectively.

Outputs: Treatment patterns will be assessed for up to four lines of treatment. A Sankey diagram showing the treatment lines by class of medications for up to four lines of treatment will be created.

Repeat Prescription If there is no change in treatment, it will be classed as a repeat.

Table 7: PAH Treatment Classes that will be considered for the treatment pattern analysis and treatment switches

Therapeutic Class	Drug	
ERA: Endothelin receptor antagonists	Bosentan	
	Ambrisentan	
	Macitentan	
PDE5i: Phosphodiesterase type 5 inhibitors	Sildenafil citrate	
	Tadalafil	
sGCs: soluble guanylate cyclase stimulator	Riociguat	
	Vericiguat – **not approved in Europe**	
PCA: prostacyclin analogues	PCA oral or inhaled	Selexipag
		Iloprost inhaled
		Treprostinil oral or Inhaled
		Beraprost
	Parenteral PCA SC or IV	Epoprostenol
		Iloprost intravenous
		Treprostinil intravenous/subcutaneous
CCB: calcium channel blocker	Amlodipine	
	Diltiazem	
	Felodipine	
	Nifedipine	
Other	Anticoagulants (warfarin)	
	Diuretics (furosemide, bumetanide, torsemide, Hydrochlorothiazide, Chlorothiazide, Chlorthalidone, Metolazone) (Hansen, Burks et al. 2018)	
	Digoxin	
	Oxygen therapy	

Class definition based on the sources: (Ogbomo, Tsang et al. 2021, Hoeper, Pausch et al. 2022)

Table 8: Therapy definitions that will be used for the descriptive analysis

Therapy Type	Definition	
No therapy		
Monotherapy	Any of the classes alone	
Combination Therapy	Double therapy	ERA+PDE5i, with ≥ 1 overlapping days of supply

		Other tan ERA + PDE5i, with ≥ 1 overlapping days of supply
	Triple therapy	ERA+PDE5i+PCA, with ≥ 1 overlapping days of supply
		Triple combination therapy including i.v. or s.c. PCA, with ≥ 1 overlapping days of supply

Definitions based on: (Hoeper, Pausch et al. 2022)

3.2.4 Estimate the burden of disease of PH-LD and PH-ILD patients

Descriptive analyses will be presented separately for the following groups:

- Group 3 PH
- Group 3 PH-ILD

3.2.4.1 Resource use

A longitudinal analysis of the care management will be run from the index date to the end of the follow-up period through the following indicators:

- Hospital care– Inpatient and outpatient. Inpatient is defined as spending at least one night at the hospital, whereas an outpatient is defined as a hospital visit without spending the night.
    - Presence and number of hospitalizations of interest, documented by an ICD-10 code diagnosis,
        - Type of hospitalization (inpatient or outpatient, i.e., length of stay = 0)
        - Length of hospitalisation (days) for inpatient hospitalization
            - Length of hospitalisation for inpatient admissions was calculated as the number of days between a patient's admission and discharge dates for the same visit.
    - Presence and number of technical and surgical procedures of interest carried out in the hospital, by type of procedure
    - Presence and number of public hospital external visits, mainly visits to a specialist
    - Presence and number of emergency room visits not followed by hospitalisation (spending the night).

- Primary care, non-hospital care, if available

- Distribution of the number and frequency of office-based practice consults of:
    - General practitioner
    - Pulmonologist
    - Cardiologist
    - Rheumatologist
    - Other specialties
- Distribution of the number of drugs and amount prescribed or dispensed per patient (depending on the database) and the number of times (frequency per month) a drug is prescribed or dispensed
- Distribution of the number of drugs in term of number of prescriptions, physical quantity of drugs prescribed and/or distributed, and cost, per patient
- Receiving oxygen therapy, if available

The analyses will be performed on patient-level-basis (distribution of the number and frequency of patients having at least a resource consumption of interest and mean number of a resource consumption of interest by patient.

3.2.4.2 Economic Burden

The methods of cost estimation will vary according to each healthcare system and data source used, and range from gathering costs directly from the data source to referring to national tariffs.

Economic outcome measures derived from claims and EMR data may include drug or medical devices claims, outpatient physician office visits claims (referred to as "physician office"), all other specialist outpatient visits claims (referred to as "outpatient"), laboratory test or biological analysis claims (outpatient analysis), outpatient technical procedures claims, inpatient/outpatient hospital admissions (diagnosis-related group [DRG] tariff), expensive inpatient drug or medical claims, and emergency department (ED) visits claims.
Costs will be presented as annual direct medical costs by patient, paid by the payer, and were adjusted to 2022 EUR using the Consumer Price Index.

3.2.4.3 Methods of cost estimation for censored data

Based on the study design, the claims and EMR database includes censored cost data. For the economic evaluation, four estimation methods will be implemented to deal with the issue of censored costs data (Gray, Clarke et al. 2011)(Gray, Clarke et al. 2011) (**Table 9**).

Table 9: Advantages and limitations of the four methods for cost estimation

Economic evaluation methods	Advantages	Limitations
AS estimator: Naïve mean (classic method)	Easy to implement. Applicable on the overall population	

CC estimator: Complete case mean	Easy to implement. Applicable on complete cases (death patients and fully observed patients over studied period)	Incomplete observed expenditure is not considered: we analyse only the hospital health care claims. Full follow-up information it is not available because death or other reasons (patients alive and having no hospital health care claim): Censored data is not considered: the portion of health care cost that is unobserved in this setting may be especially important. Death drives up costs in the period before death. Underestimate the mean cost
BT estimator: Weighted Complete Case mean cost (Bang & Tsiatis)	Recommended for health economic evaluation Consider censored data. Applicable on complete patient cases (death patients and fully observed patients over studied period)	Use only the total cost information from uncensored subjects; excludes potentially informative data, and that it could be biased if the complete cases differ systematically from the original sample
ZT estimator: Weighted Available Case mean cost (Zhao & Tian)	Recommended for health economic evaluation Consider censored data. Applicable on the overall population	Assumes that no further costs were incurred by the patient after he/she was censored

3.2.5 Characterize the patient profile and real-world outcomes of Group 3 PH-LD and PH-ILD

3.2.5.1 Characterize the patient profile

An analysis of the population will be carried out at index date and during the lookback period concerning:

- Distribution of sociodemographic and characteristics of the patients at index date:
  - Number of patients,
  - Age distribution (mean, median, etc.) and age group (N, %),
    - The adopted age groups are by 10 years interval. If a small number of patients is identified per group, a 15 years interval or "<50, 51-64, ≥ 65 years" should be used.
  - Gender (N, %),
  - Region of residence location, if available,
  - Complementary universal health coverage (CMU-C) (N, %), if available.

- Disease severity level for PH and LD will be defined based on the events during the lookback period:
    - Number of hospitalizations (e.g. emergency room)
    - Number of specific treatments (e.g. long-term oxygen therapy, LTOT) and drugs (e.g. PH drugs, when not Group 1 patients, and/or anti-fibrotic drugs, commonly used for IPF, progressive or non-progressive fibrosis)
    - Number of comorbidities of interest (e.g. cardiopulmonary comorbidities), identified during the study period before the index date
    - Number of pulmonary rehabilitations, if available
- Descriptive analysis of the medical care identified during the lookback period

A patient-level analyses will be performed throughout the lookback period.

3.2.5.2 Real-world outcomes

The following outcomes will be measured for the study cohorts:

- Overall survival, all-cause, if available
- Survival rate at 1-year, 2-years and 3-years
- Overall survival at the hospital
- Hospitalization
    - PH-associated
    - Lung-disease associated (specify which lung disease)
    - Cardiopulmonary hospitalization (associated with COPD or cardiovascular disease) (**Table 27**)
- Organ transplant procedure
- Mortality
    - All-cause
    - PH-associated, if available
    - Right-ventricular failure (right heart failure), if available
- Lung disease exacerbations

- COPD severe exacerbation defined as all hospitalizations for COPD in emergency department or with at least 1 night (inpatient) of hospitalization (excluding maternity). If two exacerbations are identified within a 14-day window, they are considered as a single event.

3.3 List of Variables

3.3.1 Demographics and clinical characteristics

- At index date:
  - Age
  - Gender
  - Ethnicity (if available)
  - Socio-economic index (if available)
  - Smoking status (if available)
  - Body Mass Index (if available)

3.3.2 Comorbid conditions at index and during follow-up

Table 10: Comorbidities

Neurological diseases
Parkinson's disease
Epilepsy
Multiple sclerosis
Psychiatric disorders and related drug therapies
Substance abuse disorders (drugs, alcohol, cannabis)
Schizophrenia and psychotic disorders
Cardiovascular, cerebrovascular and metabolic diseases, and drug related therapy
Morbid obesity
Diabetes
Acute cerebrovascular disease (excluding transient attacks)
Sequelae of cerebrovascular disease of history of acute cerebrovascular disease
Chronic ischemic heart disease or history of acute ischemic heart disease
Acute ischemic heart disease
Cardiac arrhythmias and conduction disorders
Antihypertensive drug therapy
Traumatic brain injury
Cardiopulmonary diseases

3.3.3 Tests and Procedures

Diagnostic procedures

- Echocardiography
- RHC
- High-resolution CT of the chest
- Stress echocardiography
- Chest radiograph
- Other radiography
- Electrocardiography
- CT
- Angiography
- Magnetic resonance imaging (MRI)
- Transthoracic echocardiogram (TTE)
- PFTs
    - DL_{CO}
    - PFTs

3.3.4 Treatments

- Organ Transplant
- Vena cava procedure
- Ventilation perfusion
- Oxygen therapy

3.3.5 Pharmacotherapy (based on the 2015 ESC/ERS Guidelines)

See **Table 18** in the Appendix.

3.4 Data source description

All data are subject to strict statistical disclosure control, to ensure maintenance of patient confidentiality. The databases are compliant with the European Union General Data Protection Regulation (GDPR). All data used in the present study are anonymised.
In this study, four main data sources will be leveraged to meet the study objectives. In France, the main data source will be the national claims data source, the French Healthcare Database (SNDS). Considering that patients with PH are treated in the hospital, most of these patients' care can be captured by a hospital data source thus, a first analysis on the French Hospital Discharge Data Source (the PMSI) will be performed.
In the UK, the CPRD, including the Hospital Episode Statistics (HES) and the Office for National Statistics (ONS) mortality data will be used.
In Germany, a representative sample of five million patients from the claims statutory health insurance (SHI) funds database will be used.

Table 11: Summary of the data sources

Data source	Availability	Sample
PMSI	2015-2021	All French hospitalized population
SNDS	2010-2023	All French hospitalized population
CPRD/HES	2014-2021	Representative sample of 16 million patients
Germain SHI Funds	2016-2021	Representative sample of 5 million patients

3.4.1 PMSI

The PMSI records all overnight or day hospitalizations in France, in all public and private healthcare centres. This database includes four types of hospitalizations: MSO, home care (HAD), follow-up and rehabilitation care (FRC), external technical procedures and visits (ACE). Each patient in the database is attributed a unique anonymous patient identifier. This identifier can be used to track individual patients across multiple hospitalizations.
At the time of final discharge, a standardised discharge summary (SDS) is issued which lists all hospital procedures undergone by the patient during their stay, identified through standardised procedure codes.
The reason for hospitalisation is identified by a diagnosis, based on the ICD-10. Three different types of diagnoses may be attributed to an individual stay. The principal diagnosis corresponds to the condition for which the patient was hospitalised (for example, myocardial infarction); the related diagnosis (RD) corresponds to any underlying condition which may have been related to the principal diagnosis (for example, coronary artery disease); the significantly associated diagnosis (SAD) corresponds to comorbidities or complications which may affect the course of hospitalisation (for example, chronic kidney failure). All medical procedures are listed, including surgery, and the specific medical units in which the patient was hospitalised during the stay are documented (specific list is provided by the PMSI).
Most medications and non-pharmacological treatments cannot be specifically identified in the PMSI since they are integrated into the DRG cost or delivered to the community or hospital pharmacy. However, delivery of certain expensive drugs administered during the hospitalization can be identified.
Socio-demographic information is limited to gender, age, and postcode of residence.
No information is available on the outcome of any procedure or the results of any test.
Sociodemographic data: Patients' age, sex, region of residence, death.

Medical data included for MSO:

- PD, RD, and relevant-associated diagnosis, related to hospital admission (i.e., diseases, symptoms or complications of the main morbidity or treatment of such morbidity, comorbidities)

- Medical procedures performed, including surgery (coded according to the common classification of medical procedures (CCAM))
- Duration of hospital stay, month and year of hospital discharge,
- Healthcare provider information (private/public practice, office location); the prescriber specialty is not available in hospital settings
- On top of the DRG (costly, innovative) drugs (drugs from the “liste en sus”) administered during the hospital stay are captured. Drugs dispensed by the hospital pharmacy to outpatients and drugs dispensed out of the hospital (community pharmacy) are not captured in the PMSI
- Expensive medical devices (coded according to the list of products and services qualifying for reimbursement [LPP]) implanted during hospital stays (medical device from the “liste en sus”)
- DRG information and associated costs (homogeneous groups of patients, (GHM); Homogeneous Group of Stay, (GHS)
- Cost of expensive drugs and medical devices

3.4.2 SNDS

The SNDS is the largest and most comprehensive healthcare dataset available in Europe, with a 10-year longitudinal follow-up for more than 50 million patients.
The SNDS includes anonymized administrative and healthcare claims data from the French national health care insurance system databases. The data recorded include hospital-discharge summaries (PMSI), all outpatients reimbursed health expenditures (Données de Consommation Inter-Régime, [DCIR]) and national death registry, including cause of death (Centre d'Epidémiologie sur les Causes médicales de Décès [CépiDC]).
The SNDS data consist of anonymized data of reimbursed claims for all patients affiliated with of compulsory health insurance providers (the general scheme covers approximately 86% of French residents, and 14 other schemes cover the rest) which cover approximately 99% of French residents.
Data from the DCIR and data from the PMSI have been linked for each patient to allow for follow-up across different settings of care, including outpatient practice and hospital admissions related to MSO. Currently, the date of death from the national death registry is linked to the other data for the periods. Causes of death are progressively integrated (only available for 2013, 2014, and 2015). Healthcare use of the patient can then be tracked since birth / first residence in France for 10 years even if a subject is not working, changes occupation or retires and irrespective of socioeconomic status. There is no loss to follow-up except for emigration.
The SNDS contains information on beneficiaries’ age, sex, region of residence, death date, complementary universal health coverage status, and all outpatient healthcare consumption, including all reimbursed prescription drugs identified by their Anatomical Therapeutic Chemical (ATC) code, the date of delivery, quantity, and brand name. Medical procedures performed on an outpatient basis or in a healthcare institution are identified by the CCAM, laboratory procedures are identified by the “Nomenclature des Actes de Biologie Médicale”

(NABM) and paramedical or medical visits are identified by the "Nomenclature Générale des Actes Professionnels" (NGAP).
The SNDS provides information if the patient is enrolled in the long-term disease (LTD) program. In France, patients enrolled in LTD program are eligible for 100% reimbursement of all healthcare expenditure. In the SNDS, information regarding the date of the LTD diagnosis; and its nature, coded according to the ICD-10 is also available. Registration for LTD is requested by the patient's general practitioner, and diagnoses are approved by the health insurance medical consultant. Registration is not mandatory. It may be missing, for instance, if the medical expenses are already covered by another chronic disease or the treatment is not expensive.
Information on occupational diseases, sick leaves is also available.
All information presented for the PMSI database (see 3.4.1) are also available in the SNDS database. A section describing data protection for the health databases in France is reported in **Section 5.8**.

3.4.3 CPRD /HES

The UK provides public healthcare to all permanent residents, approximately 58 million people. Healthcare is free at the point of need. In the UK, General Practitioners (GPs) are considered gatekeepers since patients must see a primary care provider who decides whether specialist care is necessary. Such referral regulates the access to specialty care, hospital care, or diagnostic tests. Thus, in the UK, a significant proportion of healthcare data is available within the GP network.

The CPRD is a UK government, not-for-profit research service that has been supplying anonymized primary care data for public health research for more than 30 years. The CPRD collects anonymised patient data from a network of GP practices across the UK. CPRD Aurum is based on EMIS Web software, and it has 41 million registered patients with 13 million active patients (representing 20% of the UK population). The CPRD Aurum covers 1,492 GP practices (Wolf, Dedman et al. 2019). The primary care data, including the Hospital Episode Statistics (HES), mental health service providers, the national cancer registry, death registry and deprivation measures to provide a longitudinal and representative UK population health dataset. The HES database includes details of all inpatient admissions, outpatient visits and Accident and Emergency (A&E) attendances (equivalent to emergency department visits in other countries) at all NHS hospital trusts in England.

Patients are affiliated with a practice, which centralizes the medical information from the GPs, specialist referrals and hospitalizations. The data recorded include demographic information, prescriptions, clinical events, preventive care, specialist referrals, hospital admissions and their major outcomes. Clinical observations from the CPRD Aurum are recorded using a mixture of Read 2 or SNOMED-CT codes, and drug and appliance prescriptions are coded using the Dictionary of Medicines and Devices (DM+D).

The national HES data contain details of all admissions to National Health Service (NHS) hospitals in England. If available, for each hospitalized patient, the hospital charts are reviewed, dates of admission and discharge and main diagnoses are extracted, coded by the coding staff and collated nationally into HES. Diagnostic data recorded in HES are coded using the ICD-10 coding frame and procedure information is coded using the UK Office of Population, Census and Surveys (OPCS) classification 4.6. Further details on HES data can be found in the online supplement material. Data is available since April 1997 (CPRD 2021, CPRD 2021, CPRD 2022).
The ONS mortality data contain the date and cause of death from the official death certificate recorded in the ICD-10, for the population of England and Wales from January 1998 (CPRD 2022).
HES and ONS data are linked to Aurum data via the unique identifier NHS number.

3.4.4 German SHI Funds

The SHI database is an anonymized database, including five million insured subjects covered by approximately 60 German statutory health insurance companies. The number of covered subjects corresponds to a 6% nationwide sample, and the data are adjusted to Germany's age and sex distribution, to insure the representativeness of the German population in terms of morbidity, mortality, and drug (Andersohn and Walker 2016, Häuser, Schubert et al. 2020). The longitudinal follow-up corresponds to a 6-year period with data that are considered stable. For these characteristics, the SHI database is suitable for longitudinal epidemiological analyses.
Claims data are transferred directly from the healthcare providers to a specialized data centre owned by the health insurance companies. These claims data are regularly audited by the insurance companies for reimbursement purposes and are prepared in accordance with German Social Law (paragraphs 287 SGB V and 75 SGB X). In the data centre, data are anonymized before entering the SHI database.
The SHI database contains information on:

- Demography (subjects' age, sex, death date, insured status);
- Outpatient and inpatient healthcare consumption and costs (ICD-10 diagnosis and comorbidities, OPS-2022 operations, procedures, and general medical measures, admitting and discharging department, the type of inpatient treatment (partial/full, before/after hospitalization, emergency), DRG billed flat rate per case and Dwell time;
- Medications (prescription date, quantity and costs, prescriber, ATC coding of active substance, pharma central number (PZN) official pharmaceutical central number,
- Incapacity for work /sickness benefit (number of days depends on the certificate of incapacity for work, so called Arbeitsunfähigkeitsbescheinigung, AU), ICD-10-GM diagnosis (ICD-10-GM, an adaptation of ICD -10- WHO translated in German), benefit claimants, costs and physician group);
- Therapeutics and aids (quantity and type, doctor/practitioner number, costs).

The database is fully compliant with all data protection regulations in Germany and has been certified as such (Häuser, Schubert et al. 2020).

3.5 Data Management

Before proceeding with the analyses of pseudo-anonymised data, work will be done on data preparation and quality control. Data preparation prior to the analysis steps consists of the selection of relevant data, the management of outliers and the creation of derived variables. Assessment of the availability and completeness of variables, including missing data, will be carried out.

3.6 Statistical Analyses

The queries, management and statistical analysis of the data used will be developed by Alira Health using R and RStudio software or Python for France and UK databases, whereas for the German claims data, SAS and Excel will be used.
Descriptive statistics will be presented for all evaluation criteria for each population, as follows:

- Quantitative variables
    a. Quantitative variables will be described with standard statistics including, the mean, standard deviation (SD), median, quartiles, and minimum and maximum. The number of patients with missing data will be reported for each variable and will be described accordingly. Quantitative variables may be categorized into quantiles as required.
- Categorical variables
    a. Counts and percentages will be computed for categorical variables.
- If relevant, all statistical tests will be two-sided and considered significant at the 5% level.

3.7 Study Limitations

For this study, large, population-based data sources were selected to ensure that the results were representative of the respective country. The major limitation of using such data sources is in the data coverage. Although the national data sources are extremely rich of relevant information about inpatient care as well as outpatient medical procedures prescribed, test results are generally not available. Missing information, relevant for identifying PH patients include clinical characteristics (6MWD functional classification [FC]), lab test results, RHC test, and 5-character ICD-10 codes or identifying Group 3 PH-ILD patients such as specific 5-character ICD-10 codes. Thus, an algorithm was developed, based on previous publications and validated with two medical experts from each of the countries in scope to identify the target patients as accurately as possible. Contrary to PAH, there are no specifically indicted therapies for PH-LD or PH-ILD in Europe thus, prescription of disease-specific therapies could not be used to build the algorithm to identify this patient population.
The characterization of the patient burden was also limited by the lack of data about the patient's e.g., quality of life, 6MWD, FC.
Additional limitation is related to the differences of clinical opinions about a particular patient's profile and choices of care depending on the country policy, centre policy, or physician's speciality and experience. Non-differential misclassification of confounding factors, which can

be caused by under-coding of an existing condition that leads to its non-existence in the research database, will lead to incomplete control of such confounders and ultimately to residual confounding bias.

3.8 Publication of Results and Value

The results will be analysed and interpreted with the help of medical experts with the final aim of scientific publication, i.e., an abstract for an international conference (poster or oral communication) and/or manuscript for a peer-reviewed journal. Our findings will provide real-world insight into patient characteristics, treatment patterns and clinical outcomes. The analysis will help understanding the potential challenges in effectively treating Group 1 and Group 3 and 3.2 patients. Improving patient management to ameliorate the life quality and to reduce the economic burden associated with different treatment patterns is of public interest.

4. MILESTONES

Table 12: Study Milestones*

Milestone	Planned Periods
Study protocol endorsement	18 Nov 2022
Data extraction/access PMSI SNDS SHI CPRD/HES	 13 July 2022 Q1 2024 (TBC) Dec 2022 (TBC) Mid-Feb 2022
Statistical analysis PMSI SNDS SHI CPRD/HES	 25 Nov 2022 TBD Mid-March 2023 (TBC) Mid-April 2023 (Study 1- PH Group 3) End-June (Study 2 – PH Group 1)
Final report of study results PMSI SNDS SHI CPRD/HES	Aug 2023 21 Dec 2022 TBD Mid-April 2023 (TBC) End-July 2023

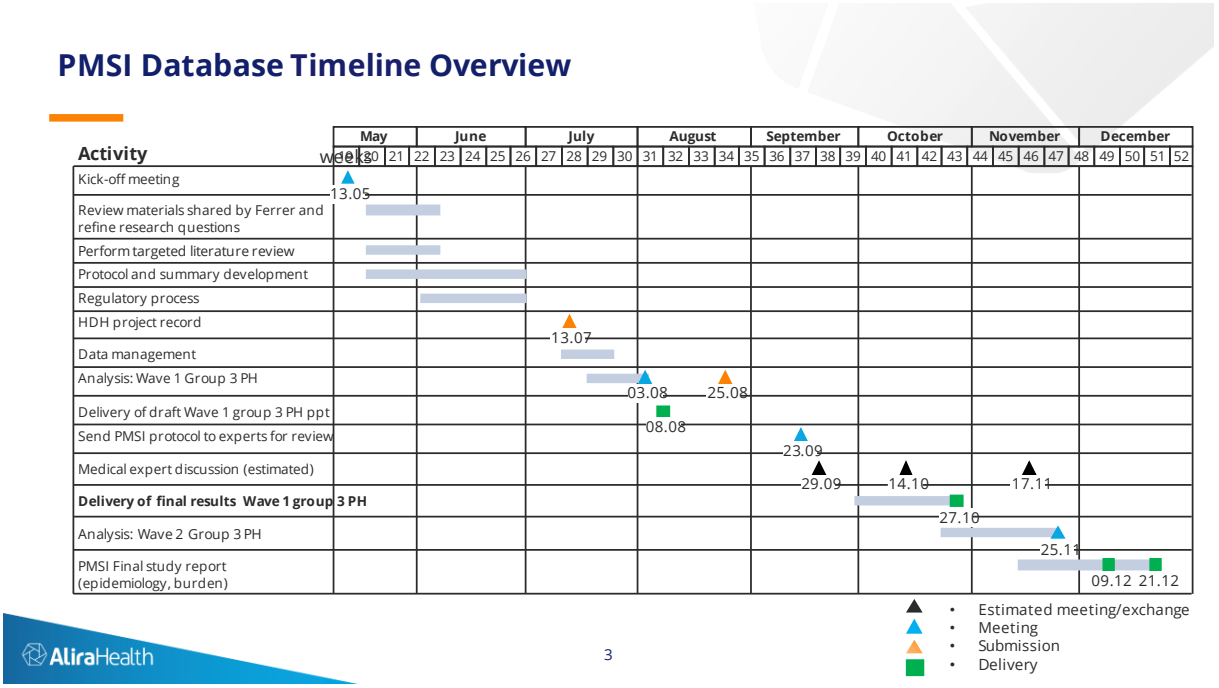
*Timelines are subjected to all parties meeting review time timelines. Regarding data source access, we are provided approximate range timelines, which are set by the data source itself and are out of control of Alira Health.

Justification of the feasibility of the project

Responsibility for the implementation of the study, the Alira Health Paris office, has already been responsible for the implementation of 20 studies using the SNDS and PMSI data sources and the UK Biobank cohort. The project team is skilled in processing the data that will be analysed in this project. Two experienced data scientists will perform the data analyses. They have both completed the SNDS and PMSI training courses and have recognized experience in the analysis of medico-administrative data as well as in pharmaco- epidemiology.
The project is 100% financed by Ferrer International S.A.
The deadlines for the completion of this project are compatible with the study progress.

4.1 France

Kick-off of the PMSI study protocol: May 13, 2022.
Kick-off of the PMSI regulatory process: June 2, 2022.
Completing the HDH access: July 13, 2022, subject to signature and approval of the Ferrer AIHC declaration.
Expected data access: July 15, 2022, subject to signature and approval of the Ferrer AIHC declaration.
Analysis of the data and validation of the results by the study scientific committee: between July 15, 2022 and November 25, 2022.
Writing and validation of the study report by the end of December, 2022.
Optional: publication results in 2023.

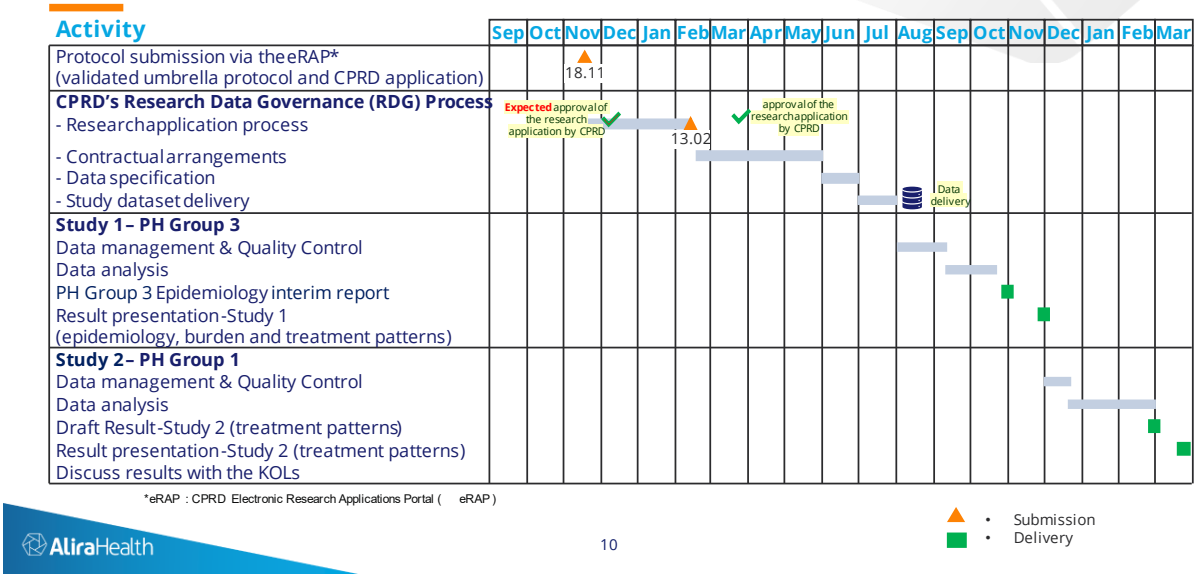


Additional statistical analyses will be performed on the French PMSI data study: between June and July 2023.

4.2 UK

Expected data access: mid-February 2023, subject to research application approval by CPRD.
Analysis of the data and validation of the results for Study 1 by the study scientific committee and report: mid-April, 2023.
Analysis of the data and validation of the results for Study 2 by the study scientific committee and report: end of June, 2023.
Writing and validation of the study report by end of July, 2023.
Optional: publication results in 2023.

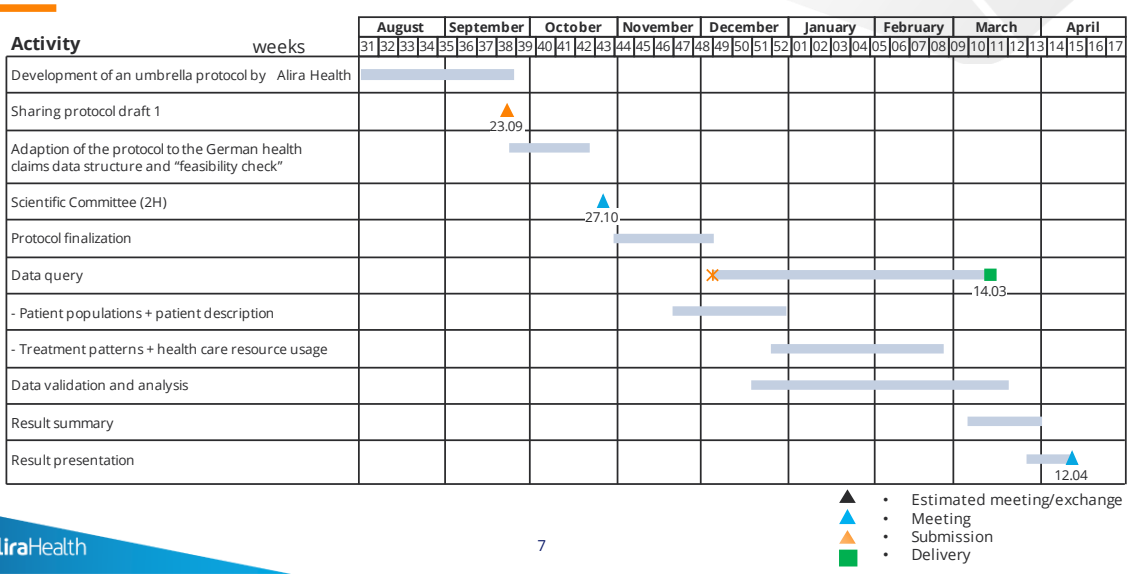
CPRD Database Timeline Overview – (depending on data delivery)



4.3 Germany

Expected data access: December, 2022, subject to protocol approval by the Ferrer.
Analysis of the data and validation of the results by the study scientific committee: between mid-January, 2023, and mid-March, 2023.
Writing and validation of the study report by mid-April, 2023.
Optional: publication results in 2023.

German claims Timeline Overview



5. APPENDICES

5.1 PAH Reference Centres

Table 13: French PAH Reference Centres

Type	Hospital	JURIDIQUE FINESS Code
Reference Centre	Hôpital Bicêtre	940140015
	Hôpital Marie Lannelongue	750150120 /920000684
Centres of Competence	CHRU Lille	590780193
	CHU Rouen	760780239
	CHU Caen	140000100
	CHU Brest	290000017
	CHU Rennes	350005179
	CHU Nantes	440000289
	CHU Reims	510000029
	CHU Nancy	540023264
	CHRU Strasbourg	670780055
	CHU Dijon	210780581
	CHU Tours	370000481
	CHU Poitiers	860014208
	CHU Limoges	870000015
	CHU Clermont Ferrand	340780543
	CHU St Etienne	420784878
	CHU Lyon	690781810
	CHU Grenoble	380780080
	CHU Bordeaux	330781196
	CHU Toulouse	310781406
	CHU Montpellier	340780477
	Hôpitaux de Marseille	130786049
	CHU Nice	060785011
	CHR Reunion	970408589

	CHU Fort de France	970211207

Source: (Ministry of Solidarity and Health 2022)

Table 14: PAH Reference Centres in England

Specialist referral centres for PAH in England	Trust code
Great Ormond Street Hospital for Children part of Great Ormond Street Hospital for Children NHS Foundation Trust	RP4
Hammersmith Hospital part of Imperial College Healthcare NHS Trust	RYJ
Royal Brompton Hospital part of Royal Brompton and Harefield NHS Foundation Trust	RT3
Royal Free Hospital part of Royal Free London NHS Foundation Trust	RAL
Papworth Hospital part of Papworth Hospital NHS Foundation Trust	RGM
Royal Hallamshire Hospital part of Sheffield Teaching Hospitals NHS Foundation Trust	RHQ
Freeman Hospital part of The Newcastle Upon Tyne Hospitals NHS Foundation Trust	RTD

Table 15: French nomenclature CCAM codes for identification of progressive fibrosing ILD
(UK and German codes will be included in the individual country protocol)

Code	Imaging and respiratory function tests
EQQP002	Measurement of walking distance on level ground in 6 minutes, with monitoring of oxygen saturation by transcutaneous measurement and measurement of useful oxygen flow
EQQP003	Measurement of walking distance on level ground in 6 minutes, with monitoring of oxygen saturation by transcutaneous measurement
GLHF001	Arterial blood sampling with blood gas and pH measurement, without hyperoxia test
GLHF002	Arterial blood sample with blood gas and pH measurement, with hyperoxia test
GLQD001	Measurement of the pulmonary transfer capacity of carbon monoxide (TLCO) or another gas in apnoea or in stable state, during a functional respiratory test
GLQP012	Measurement of slow vital capacity and forced expiration, with recording [Standard spirometry]
GLQP002	Measurement of slow vital capacity and forced expiration, with measurement of lung volumes that can/cannot be mobilised by plethysmography
GLQP008	Measurement of slow vital capacity and forced expiration, with arterial blood gasometry (standard spirometry with blood gas)

GLQP009	Measurement of vital capacity and tidal volume by inductance plethysmography
GLQP003	Forced expiration measurement (flow-volume curve) with recording
ZBQK001	Computed tomography scan of the chest, without intravenous injection of contrast product
ZBQH001	Computed tomography scan of the chest, with intravenous injection of contrast product

5.2 Right Heart Catheterisation identification

Table 16: French nomenclature CCAM Right Heart Catheterisation procedure codes for reference

Code	Description
EQQF001	Measurement and recording of the pressures of the right-side heart, the pulmonary artery and the left side heart, without injection of contrast product, by transcutaneous venous route and by transcutaneous arterial route or catheterization of the oval foramen « Mesure et enregistrement des pressions du cœur droit, de l'artère pulmonaire et du coeur gauche, sans injection de produit de contraste, par voie veineuse transcutanée et par voie artérielle transcutanée ou cathétérisme du foramen ovale »
EQQF004	Measurement and recording of the pressures of the right-side heart, the pulmonary artery, and the left side heart, without injection of contrast product, by transcutaneous venous route with perforation of the interatrial septum « Mesure et enregistrement des pressions du coeur droit, de l'artère pulmonaire et du cœur gauche, sans injection de produit de contraste, par voie veineuse transcutanée avec perforation du septum interatrial »
EQQF006	Measurement and recording of the pressures of the right-side heart and the pulmonary artery, without injection of contrast medium, by the transcutaneous venous route « Mesure et enregistrement des pressions du coeur droit et de l'artère pulmonaire, sans injection de produit de contraste, par voie veineuse transcutanée »

EQQH001	Measurement and recording of the pressures of the right-side heart and the pulmonary artery, with injection of contrast product, by the transcutaneous venous route « Mesure et enregistrement des pressions du coeur droit et de l'artère pulmonaire, avec injection de produit de contraste, par voie veineuse transcutanée »
EQQH004	Measurement and recording of the pressures of the right-side heart, the pulmonary artery and the left side heart, with injection of contrast product, by the transcutaneous venous route with perforation of the interatrial septum « Mesure et enregistrement des pressions du coeur droit, de l'artère pulmonaire et du cœur gauche, avec injection de produit de contraste, par voie veineuse transcutanée avec perforation du septum interatrial »
EQQH006	Measurement and recording of right-side heart, pulmonary artery, and left heart pressures, with injection of contrast material, transcutaneously in a vein, and transcutaneously by arterial or foramen ovale catheterization, at age 24 months or older « Mesure et enregistrement des pressions du cœur droit, de l'artère pulmonaire et du cœur gauche, avec injection de produit de contraste, par voie veineuse transcutanée et par voie artérielle transcutanée ou cathétérisme du foramen ovale, à l'âge de 24 mois ou plus »

Source: (Exposto, Petrică et al. 2020)

Table 17: OPCS-4 Right Heart Catheterisation procedure codes

OPCS-4 Code	Description
K65.2	Catheterisation of right side of heart NEC
K65.8	Other specified catheterisation of heart
K65.9	Unspecified catheterisation of heart

Table 18: OPS-2022 Right Heart Catheterisation procedure codes

OPS-2022	Description
1-273	Catheterisation of right side of heart NEC

5.3 Identification of Lung diseases

For all 3-character ICD10 code included in the table below, all subcategories will be considered for the analysis.

Table 19: ICD-10 codes for lung diseases, Group 3 (Nasser, Larrieu et al. 2021**,** Heresi, Dean et al. 2022**)**

*For all 3 digits codes, all the sub-codes (4th and 5th digit) will be considered in the analysis.

Codes *	**Description – Official label (paper label)**
3.1 COPD	
J44	Other chronic obstructive pulmonary disease
J43	Emphysema
3.2 ILD	
C96.6	Unifocal Langerhans-cell histiocytosis
J84.81	Lymphangioleiomyomatosis
J60	Coal worker's pneumoconiosis
J61	Asbestosis
J62.8	Pneumoconiosis due to other dust containing silica
J63	Pneumoconiosis due to other inorganic dusts
J64	Unspecified pneumoconiosis
J66	Airway disease due to specific organic dust
J67	Hypersensitivity pneumonitis due to organic dust
J680	Bronchitis and pneumonitis due to chemicals, gases, fumes and vapours
J68.4	Chronic respiratory conditions due to fumes or vapours
J70.	Respiratory conditions due to other external agents
J84	Other interstitial pulmonary diseases
M05	Seropositive rheumatoid arthritis
M06	Other rheumatoid arthritis
M120	Chronic postrheumatic arthropathy
M130	Polyarthritis, unspecified
M31.0	Goodpasture syndrome
M31.3	Wegener granulomatosis

M32	Systemic lupus erythematosus
M33	Dermatopolymyositis
M34	Systemic sclerosis
M35	Other systemic involvement of connective tissue
J178	Pneumonia in other diseases classified elsewhere
J990	Rheumatoid lung disease
M05.1 + J99.0	Rheumatoid lung
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern (CPFE)	
J84.10	Combined pulmonary fibrosis and emphysema (CPFE)
J84.11	Idiopathic interstitial pneumonia
J84.111	Idiopathic interstitial pneumonia, not otherwise specified
J84.112	Idiopathic pulmonary fibrosis
J84.113	Idiopathic non-specific interstitial pneumonitis
J84-114	Acute interstitial pneumonitis
J84-115	Respiratory bronchiolitis interstitial lung disease
J84-116	Cryptogenic organizing pneumonia
J84-117	Desquamative interstitial pneumonia
J84.17	Other interstitial pulmonary diseases with fibrosis in diseases classified elsewhere
3.4 Hypoventilation syndromes (sleep apnea)	
G47.34	Idiopathic sleep related nonobstructive alveolar hypoventilation
G47.35	Congenital central alveolar hypoventilation syndrome
G47.3 (if 5 digits not available)	Sleep apnea
3.5 Chronic exposure to high altitude (Hypoxia)	
T70.2	Other and unspecified effects of high altitude
W94	Exposure to high and low air pressure and changes in air pressure
3.7 Developmental Lung Diseases	
J98.1	Pulmonary collapse (Atelectasis)
J80	Adult respiratory distress syndrome
J96.0	Acute respiratory failure

J98.5	Mediastinitis
Q79.0	Congenital diaphragmatic hernia
J84.8	Other specified interstitial pulmonary diseases (Alveolar capillary dysplasia/ with vein misalignment OR Surfactant mutations of the lung OR Pulmonary interstitial glycogenosis OR Other interstitial lung diseases of childhood)
Q33.2	Sequestration of lung (Agenesis, hypoplasia, and dysplasia of lung)
Q33.3	Agenesis of lung (Agenesis, hypoplasia, and dysplasia of lung)
Q33.6	Hypoplasia and dysplasia of lung (Agenesis, hypoplasia, and dysplasia of lung)

Table 20: French nomenclature CCAM for technical procedure - Lung or Heart lung transplantation

Code	Description
GFEA001	Transplantation séquentielle des 2 poumons, par thoracotomie avec CEC
GFEA002	Transplantation de lobe pulmonaire, par thoracotomie avec CEC
GFEA003	Transplantation d'un poumon, par thoracotomie sans CEC
GFEA004	Transplantation séquentielle des 2 poumons, par thoracotomie sans CEC
GFEA005	Transplantation de lobe pulmonaire, par thoracotomie sans CEC
GFEA006	Transplantation bipulmonaire, par thoracotomie avec CEC

Table 21: Lung disease and associated treatments

Lung disease	Drug Class	Recommended Therapies
Idiopathic pulmonary fibrosis (IPF) (not identifiable by a single ICD-10, under J84)	Anti-fibrotics	• Pirfenidone • Nintedanib
Nonspecific interstitial pneumonia	Immunomodulatory agents	• Prednisone (main) • Mycophenolate • Azathioprine

		• cyclophosphamide
Hypersensitivity Pneumonitis	Immunomodulatory agents	• Prednisone (main) • Mycophenolate • Azathioprine • Cyclophosphamide
Connective Tissue Disease - ILD	Immunomodulatory agents	• Prednisone • mycophenolate • Azathioprine • cyclophosphamide • rituximab • tocilizumab

Source: (Wells and Hirani 2008, Raghu, Remy-Jardin et al. 2018, Corral, DeYoung et al. 2020, van den Bosch, Luppi et al. 2022)

5.4 Identification of other PH groups

Table 22: Other WHO PH groups and associated ICD-10 codes

PH Group	ICD-10 code/ CCAM code	ICD description/ CCAM labels	Source
Group 2 (left heart disease)	I34	Non-rheumatic mitral valve disorders	Exposto, Petrică et al. 2020
	I35	Non-rheumatic aortic valve disorders	Exposto, Petrică et al. 2020
	I20	Angina pectoris	Exposto, Petrică et al. 2020
	I21	ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	Exposto, Petrică et al. 2020
	I22	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	Exposto, Petrică et al. 2020
	I23	Certain current complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (within the 28-day period)	Exposto, Petrică et al. 2020
	I24	Other acute ischemic heart diseases	Exposto, Petrică et al. 2020
	I25	Chronic ischemic heart disease	Exposto, Petrică et al. 2020Heresi, Dean et al. 2022
	I27.22	Pulmonary hypertension due to left heart disease	Heresi, Dean et al. 2022
	I42.4	Endocardial fibroelastosis	Heresi, Dean et al. 2022
	I50.1	Left ventricular failure	Exposto, Petrică et al. 2020, Heresi, Dean et al. 2022
	I50.22	Chronic systolic heart failure	Heresi, Dean et al. 2022
	I50.3	Diastolic heart failure	Heresi, Dean et al. 2022

	I34.0, I34.8	Non-rheumatic mitral valve insufficiency/disorder	Heresi, Dean et al. 2022
	I35.x	Disease/disorders of aortic valve	Heresi, Dean et al. 2022
	I08	Disease of mitral and aortic valve	Heresi, Dean et al. 2022
	I42.1	Hypertrophic obstructive cardiomyopathy	Heresi, Dean et al. 2022
	I43	Cardiomyopathy in other diseases classified else- where	Heresi, Dean et al. 2022
	I11.0	Hypertensive heart disease with heart failure	Heresi, Dean et al. 2022
	I13.0, I13.2	Hypertensive heart and chronic kidney disease with heart failure and stage 1–4 chronic kidney disease or unspecified	Heresi, Dean et al. 2022
	Q23	Congenital malformations of aortic and mitral valves	Exposto, Petrică et al. 2020 Heresi, Dean et al. 2022)
	Q24	Other congenital malformations of heart	Exposto, Petrică et al. 2020 Heresi, Dean et al. 2022
Group 4 (CTEPH)	I26	Pulmonary thromboembolism	Exposto, Petrică et al. 2020 Heresi, Dean et al. 2022
	I27.24	Chronic thromboembolic pulmonary hypertension	Heresi, Dean et al. 2022
	I27.82	Chronic pulmonary embolism	Heresi, Dean et al. 2022
Group 5	D86	Sarcoidosis	Agreed by Ferrer and SC (27Oct2022)
	D55	Anemia due to enzyme disorders	Heresi, Dean et al. 2022
	D56	Thalassemia	Heresi, Dean et al. 2022
	D57	Sickle cell disorders	Heresi, Dean et al. 2022
	D58	Other hereditary haemolytic anaemias	Heresi, Dean et al. 2022
	D59	Acquired hemolytic anemias	
	D45	Polycythemia vera	

	C96.0	Multifocal and multisystemic (disseminated) Langerhans cell histiocytosis	Heresi, Dean et al. 2022
	E88.89	Other specified metabolic disorders	Heresi, Dean et al. 2022
	D18.1	Lymphangioma any site	Heresi, Dean et al. 2022
	E74	Other disorders of carbohydrate metabolism	Heresi, Dean et al. 2022)
	E75.2	Other sphingolipidosis: Gaucher	Heresi, Dean et al. 2022
	E00-E07	Disorders of thyroid gland	
	J98.5	Diseases of mediastinum, not elsewhere classified	Heresi, Dean et al. 2022
	N17	Acute kidney failure	
	N18	Chronic kidney disease (CKD)	
	N19	Unspecified kidney failure	
	Q22	Congenital malformations of pulmonary and tricuspid valves	Heresi, Dean et al. 2022
Others	J961	Chronic respiratory failure	(Bergot, De Leotoing et al. 2019)
	Z95.4	Left valvular surgery	(Bergot, De Leotoing et al. 2019)

5.5 PAH treatment identification

Table 23: Oral Treatment Options in PH

Calcium channel blockers
- Amlodipine
- Diltiazem
- Felodipine
- Nifedipine
Endothelin Receptor Antagonists (ERAs)
- Ambrisentan (Letairis®)
- Bosentan (Tracleer®)
- Bosentan (Tracleer®) for Pediatric Use
- Macitentan (Opsumit®)
Phosphodiesterase Inhibitors (PDE-5 Inhibitors)
- Sildenafil (Revatio™)
- Sildenafil (Revatio™) for Pediatric Use
- Tadalafil (Adcirca®)
Prostacyclin Analogue (oral administration)
- Oral Treprostinil (Orenitram®)
- Beraprost sodium
- Beraprost extended release
Prostacyclin receptor agonist (oral administration)
- Selexipag (Uptravi®)
Soluble guanylate cyclase stimulator (oral administration)
- Riociguat (Adempas®)
Prostacyclin analogues (inhaled administration)
- Iloprost (Ventavis®)
- Inhaled Treprostinil (Tyvaso®)
Intravenous Treatment Options
Prostacyclin analogues (i.v. or s.c. administration)
- Treprostinil s.c. or i.v.
- Epoprostenol (Flolan®)

- Room Temperature Stable Epoprostenol (Veletri®)

Source: (Galiè, Humbert et al. 2015, PHA 2022)

Table 24: French nomenclature - PAH specific drugs available on top of DRG ("liste en sus")

Category	Label	DCI	On top of DRG in 2021	On top of DRG before 2021	Date
Endothelin receptor antagonists (ERA)	Tracleer	(bosentan)	No	Yes	2005-2006
	Volibris	(ambrisentan)	No		
	Letairis (US)	(ambrisentan)	No		
	Opsumit	(macitentan)	No		
Phosphodiesterase type 5 inhibitors and guanylate cyclase stimulators (PDE5)	Revatio	(sildenafil citrate)	No		
	Adcirca	(tadalafil)	No		
	Adempas	(riociguat)	No		
Prostacyclin Derivates	Veletri	(epoprostenol)	No	Yes	2015-2016
	Flolan	(epoprostenol sodium)	No	Yes	2005-2016
	EPOPROSTENOL	(epoprostenol)	No	Yes	2011-2016
	Remodulin	(treprostinil)	No		2006 - 2016
	Ventavis	(iloprost)	Yes	Yes	2005 - Present
Prostacyclin Receptor Agonist	Uptravi	(selexipag)	No	Temporary use utilisation	
	Ralinepag	Treprostinil technosphere	No		
Calcium channel blockers			No		

Ambrisentan, sildenafil and tadalafil are also approved and commonly used for the treatment of PAH in France, but not part of the "on top of DRG" list

Table 25: OPCS-4 codes - PAH-specific drugs

PAH-specific drugs considered indicative of PAH reserved for treating PAH according to coding standards and only in the absence of ICD-10 codes indicative of a diagnosis of digital ulcers, erectile dysfunction or renal failure (Exposto, Hermans et al. 2021).

Codes	Label
X82.1	Pulmonary arterial hypertension drugs Band 1
X82.2	Pulmonary arterial hypertension drugs Band 2
X82.3	Pulmonary arterial hypertension drugs Band 3
X82.4	Pulmonary arterial hypertension drugs Band 4

Table 26: "Read codes" - PAH-specific drugs

Codes	Label
7Q01000	Primary pulmonary hypertension drugs band 1
7Q01100	Primary pulmonary hypertension drugs band 2
7Q01200	Primary pulmonary hypertension drugs band 3
7Q01300	Primary pulmonary hypertension drugs band 4

5.6 Comorbidities

Table 27: ICD-10 codes for diseases considered under the label cardiovascular diseases

Comorbidities	ICD-10 codes
Coronary heart disease	I20, I20.0, I20.1, I20.8, I20.9 I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9 I22, I22.0, I22.1, I22.8, I22.9 I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8 I24, I24.0, I24.1, I24.8, I24.9
Chronic ischemic heart disease or history of acute ischemic heart disease	I25
Ischemic stroke	I63, I63.0, I63.2, I63.3, I63.5, I63.6, I63.8, I63.9 , I64, I65, I65.0, I65.1, I65.2, I65.3, I65.8, I65.9
Peripheral artery disease	I70, I70.2, I70.8, I70.9 I73, I73.8, I73.9 I74.3

Source: (Oger, Kerbrat et al. 2022)

Table 28: ICD-10 codes for other diseases

Comorbidities[1]	ICD-10 codes
Neurological diseases	G00-G99
Parkinson's disease	G20
Epilepsy	G40
Multiple sclerosis	G35, G36, G37
Psychiatric disorders and related drug therapies	F02, F03, F04
Substance abuse disorders (drugs, alcohol, cannabis)	F10-F19
Schizophrenia and psychotic disorders	F20-F29
Morbid obesity	E66.01, E66.2, Z68.4
Diabetes	E10, E11
Sequelae of cerebrovascular disease of history of acute cerebrovascular disease	I60-I69
Cardiac arrhythmias and conduction disorders	I48
Traumatic brain injury[2]	S02.0, S02.1, S02.8, S02.91, S04.02, S04.03, S04.04, S06, S07.1

Source: 1. (Song, Lee et al. 2018); 2. (Wisconsin Dept. of Health Services 2021)

5.7 Other

Table 29: ICD-10 codes related to PAH management

Codes	Description
M34.0	Progressive systemic sclerosis
R06.0	Dyspnoea

Table 30: ICD-10 codes related to renal failure, digital ulcers or erectile dysfunction

Diagnosis	Codes	Description
Renal failure	N17	Acute kidney failure
	N18	Chronic kidney disease (CKD)
	N19	Unspecified kidney failure
Digital ulcers	L97	Non-pressure chronic ulcer of lower limb, not elsewhere classified
	L98	Other disorders of skin and subcutaneous tissue, not

		elsewhere classified
Erectile dysfunction	F52.2	Failure of genital response
	N48.4	Impotence of organic origin

Table 31: **OPCS-4 codes related to tests and procedures**

Tests and procedures	OPCS-4
Carbon monoxide transfer factor test	E92.1
Blood gas analysis	E92.4
Complex lung function exercise test	E92.5
Simple lung function exercise test	E92.6
Measurement of peak expiratory flow rate	E93.1
Spirometry	E93.2
Measurement of static lung volume	E93.5
Angiocardiography of combination of right and left side of heart	K63.1
Catheterisation of right side of heart NEC	K65.2
Arteriography of pulmonary artery	L13.3
Computed tomography of chest	U07.1
Cardiac magnetic resonance imaging	U10.3
Myocardial perfusion scan	U10.6
Doppler ultrasound of vessels of extremities	U11.2
Lung perfusion scanning NEC	U15.1
24 hour ambulatory electrocardiography	U19.2
Exercise electrocardiography	U19.4
Other specified diagnostic electrocardiography	U19.8
Unspecified diagnostic electrocardiography	U19.9
Transthoracic echocardiography	U20.1
Transoesophageal echocardiography	U20.2
Stress echocardiography	U20.5
Other specified diagnostic echocardiography	U20.8
Unspecified diagnostic echocardiography	U20.9
Computed tomography of pulmonary arteries	U35.4

5.8 Data protection for PMSI and SNDS databases

As of March 4, 2021, Alira Health is a certified contract research organization that has an established commitment to comply with the French data protection authority (CNIL), which determines the criteria for confidentiality, expertise and independence for research laboratories and design offices.
Section 193 of Act No. 2016-41 of January 26, 2016 (Article L.1461-1 of the Public Health Code) establishes two prohibited purposes:

"Data from the national health data system cannot be processed for one of these goals:

- the promotion of the products mentioned in Article L. 5311-1 to health professionals or healthcare facilities,
- excluding guarantees from insurance contracts and changing premiums or insurance premiums for an individual or group of individuals with the same risk."

In terms of risk, data available within the PMSI does not contain competitive information that can be used for marketing purposes. The Alira Health Team will only have access to pseudo-anonymized data; no prohibited purpose can be implemented from these elements. In addition, no detailed data will be available to Ferrer, who contracted Alira Health for data analysis. Ferrer will have restricted access to annualized aggregated study results of healthcare claims data, and by therapeutic area or product class. This study does not; therefore, fall within the framework of a prohibited use.

The study will also be conducted in strict compliance with the reference methodology, MR-006, published by the CNIL, for which Ferrer made a compliance commitment dated March 6, 2022. Alira Health is contractually committed to Ferrer to adhere to this methodology as part of its operations.

The study will be published on the Health Data Hub website, as required.

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