**NRS Roadmap Pulmonary Hypertension report**

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## 1. Inventory of Dutch research efforts in this field over the past five years (2008-2013) by ISI web of knowledge

Search terms: Pulmonary Hypertension OR Pulmonary arterial hypertension; address = Netherlands

***Clinical research***

| | **Article type** | | | |
|---|---|---|---|---|
| Institute | Original article | Review | Guidelines | Total |
| AMC | 58 | 8 | 0 | 66 |
| Erasmus MC | 39 | 11 | 0 | 50 |
| LUMC | 42 | 4 | 0 | 46 |
| Maastricht MC | 14 | 7 | 0 | 21 |
| Radboud | 48 | 2 | 0 | 50 |
| St. Antonius | 8 | 1 | 0 | 9 |
| UMC Groningen | 42 | 7 | 0 | 49 |
| UMC Utrecht | 44 | 5 | 0 | 49 |
| VUmc | 86 | 10 | 2 | 98 |
| **Total** | **381** | **55** | **2** | **438** |

***Basic research***

| | **Article type** | | |
|---|---|---|---|
| **Institute** | **Original article** | **Review** | **Total** |
| AMC | 2 | 0 | 2 |
| Erasmus MC | 10 | 1 | 11 |
| LUMC | 19 | 4 | 23 |
| Maastricht MC | 11 | 0 | 11 |
| Radboud | 1 | 0 | 1 |
| St. Antonius | 0 | 0 | 0 |
| UMC Groningen | 9 | 2 | 11 |
| UMC Utrecht | 8 | 0 | 8 |
| VUmc | 19 | 2 | 21 |
| **Total** | **79** | **9** | **88** |

## 2. Visibility Dutch research as judged by international experts (see also appendix )

| Areas with good visibility | Less visible |
|---|---|
| Phenotyping and Severity | Enviroment and lifestyle |
| Biological mechanisms | Development and ageing |
| Diagnosis monitoring | Prevention |
| Therapy medical | Biobanking |
| Genetics | Endothelium and epithelium |
| Exercise limitation | |

## 3. Research needs

*Facts and figures*
Pulmonary hypertension is a hemodynamic condition (mean pulmonary artery pressure 25mmHg) which is encountered in more than 40 different clinical conditions. The current WHO classification subdivides all causes of pulmonary hypertension into five subgroups:

- Pulmonary arterial hypertension (e.g. idiopathic, familial, associated with connective tissue disease, associated with congential systemic-to-pulmonary shunts etc)
- Pulmonary hypertension associated with left heart disease (systolic, diastolic, valvular)
- Pulmonary hypertension associated with chronic lung disease and/or hypoxemia (e.g. COPD and idiopathic pulmonary fibrosis)
- Chronic Thrombo-embolic pulmonary hypertension
- Other causes (e.g. sarcoidosis, tumor microangiopathy etc).

Left heart disease (group 2) and chronic lung disease (group 3) are responsible for the vast majority (88%) of all cases of pulmonary hypertension. An estimated 30-70% of all patients with severe COPD suffer from pulmonary hypertension. Although the presence of pulmonary hypertension is a bad prognostic sign in these patients, hemodynamic abnormalities in these patients are usually mild and progression slow. Based on the above data, the total number of Dutch patients with pulmonary hypertension can be estimated at several thousands, perhaps as much as 15.000. Pulmonary hypertension is the registered primary cause of death in about 200 Dutch patients every year, two thirds of whom are female.

Dutch prevalence and incidence estimates are only available for WHO groups 1 and 4 patients. In 2012, the prevalence of PAH in the Netherlands was 500, i.e. 29 per 1 million inhabitants. The incidence of PAH in the Netherlands is about 36 per year, or 2.2 per 1 million inhabitants, and is slightly increasing due to increased recognition and improved survival. Out of 268 registered PAH patients in 2009, 209 were females and 59 males. 41% of patients was aged 41-60 and 36% was aged 61-80 years. In 2009, 114 patients with CTEPH were registered in the Dutch referral centers. The prevalence of CTEPH in the Netherlands is 6.9 per 1 million, representing 0.5 to 8,8% of all patients with acute pulmonary embolism and equal

numbers of patients with no prior history of venous thrombo-embolic disease. 50% of CTEPH patients is aged 61-80 and 30% is aged 41-60 years. Every year, 40 patients are newly diagnosed with CTEPH in the Netherlands, more than half of these patients can be surgically treated. Epidemiological data is available for children with PH thanks to a national pediatric PAH registry, with a recent study showing 1-, 3-, and 5-year transplantation-free survival rates of 84%, 71% and 62%, respectively[4].

*Euro costs[2]*
No data on DALY's or health care costs and usage are available.

*Unmet needs (extracted from: LAN verkenning 2010[3])*
In conclusion, the different types of pulmonary hypertension together are associated with a considerable disease burden, in terms of morbidity, mortality and loss of quality of life. Effective treatment is still lacking, in part because the origins of this group of conditions are still poorly understood. Right heart failure is the leading cause of death in patients with pulmonary hypertension, but little is known about the exact mechanisms determining success or failure of right heart adaptation to an increased load. Therefore, research is needed to elucidate the underlying mechanisms of pulmonary vascular disease and associated right heart failure. Development of new therapeutic strategies in this rare group of diseases requires bundling of expertise and research (translational and clinical) in centers of excellence. Specific research needs can be identified pertaining to the diagnosis and treatment of children with PH: phenotyping of different subtypes of paediatric PH, development of less invasive diagnostic modalities, development of appropriate surrogate end-points for clinical trials and pharmacological research specific for paediatric patients with PH.

*References*


[1] Feiten en cijfers 2013 Chronische Longziekten, LAN 2013
[2] Maatschappelijke kosten voor astma, COPD en respiratoire allergie. RIVM Rapport 260544001/2012
[3] Feiten en cijfers chronische Longziekten, LAN 2010
[4] Zijlstra WM, Douwes JM, Rosenzweig et al. Survival differences in pediatric pulmonary arterial hypertension: clues to a better understanding of outcome and optimal treatment strategies. J Am Coll Cardiol. 2014;63:2159-69

## 4. Summary of a SWOT analysis

Results of the web-based SWOT

| Strengths | Weaknesses |
|---|---|
| 1. Phenotyping and severity group 1 PH and paediatric PH<br>2. Biological mechanisms group 1 PH<br>3. Diagnosis and monitoring group 1 PH | 1. Phenotyping groups 2,3 PH<br>2. Biological mechanisms groups 2,3 PH<br>*3.* Participation in large treatment trials (medical and non-medical), both for adult and paediatric patients |
| **Opportunities** | **Threats** |
| 1. Phenotyping and severity<br>2. Therapy (medical and non-medical)<br>3. Biobanking | 1. National competition vs. collaboration<br>2. International competition<br>3. Limited Funding |

*Relevance of research judged by international experts (order of importance):*
*See Table Relevance of research judged by international experts in appendix*

| | **Mean** |
|---|---|
| Phenotyping and Severity | 4.50 |
| Biological mechanisms | 4.00 |
| Environment and lifestyle | 1.00 |
| Development and ageing | 1.00 |
| Prevention | 1.00 |
| Diagnosis monitoring | 4.50 |
| Therapy medical | 4.00 |
| Therapy non-medical | 4.00 |
| Biobanking | 3.00 |
| Data management clinical studies | 3.00 |
| Implementation and care | 3.00 |

## 5. Description of the Interface of Pulmonary Hypertension with other Roadmap areas

There are a number of possibilities for synergy between team PH and other Roadmap areas. Several other teams deal with disease states which are known risk factors for the development of pulmonary hypertension (WHO group 3), in particular BPD, CF, COPD and ILD. Although PH is a well-established prognostic factor in these conditions, little is known about the mechanisms of development of PH in chronic lung disease. Many patients with BPD, CF, COPD and ILD who ultimately require lung transplantation will have concomitant pulmonary hypertension, which is a determinant of risk and survival on the transplant waiting list. Lung transplantation

is the last resort treatment for patients with all forms of pulmonary hypertension and intensified collaboration with the Lung transplantation team could lead to improved biobanking and phenotyping of post-transplant patients. Specific synergy is anticipated in the following areas:

- Phenotyping and severity: BPD, CF, COPD, ILD, LTx (risk factors for PH development in chronic respiratory conditions; right heart adaptation in chronic respiratory conditions)
- Biological mechanisms: BPD, COPD, ILD (vascular biology; immunology) and cancer (apoptosis resistance, proliferation, angiogenesis)
- Environmental and lifestyle: All (exercise and rehabilitation)
- Development and aging: BPD (lung vascular development and regeneration)
- Therapy, medical: BPD, CF, COPD, ILD (pulmonary vasodilator treatment in WHO group 3 PH) and ICU (management of acute and chronic right heart failure with inotropes and vasopressors)
- Therapy, non-medical: LTX (prevalence of PH on LTX waiting list; dealing with right heart failure around the transplant procedure; tissue banking)
- Biobanking: LTX
- Data management clinical studies: All
- Implementation and Care: All

## 6. Priorities for Dutch research in the area of Pulmonary Hypertension for 2014-2019

- Participation in international randomized clinical trials of novel drugs in PAH and other forms of pulmonary hypertension, in particular paediatric PAH, PH associated to left heart disease and PH associated to chronic lung disease
- Translational studies exploring the pathobiological mechanisms of all forms of PH
- Translational studies exploring the determinants of right heart adaptation to increased load
- Phenotypic characterization of non WHO-group 1 PH patients

## 7. What is needed to let the research priorities listed be successful?

- A national PH research network uniting dedicated scientists and providers in expert centres and satellite centres. This will allow maximal patient participation in clinical trials and will ensure access to novel drugs for all patients
- Develop and support a national blood and tissue bank for storage of blood samples and lung and heart tissue from patients with all groups of PH
- Consortia of PH scientists organized by WHO PH groups
- Exploration of patient expectations and research priorities and active participation from patient groups for research prioritization
- Intensified collaboration with other Roadmap teams and between adult and paediatric PH

## 8. What do patients want?

Insufficient data is available to justify a general statement pertaining to patients' preferences. On July 15th 2013, a focus group discussion was held at the VU University Medical Center. Present at this meeting were the chair of the PH patient association, three PH patients and two representatives from the PH knowledge center (physician assistant and HJB). In general terms, the SWOT analysis was recognized as valid and accurate. Patients stressed the importance of collaboration between all Dutch providers and scientists. Patients favored a model of research centralization, with one (in case of idiopathic or heritable PAH) or only few national research centers extensively collaborating with a number of regional PH centers. This would lead to a more efficient development of, and easy access to newer and experimental treatments for all Dutch patients, while at the same time allowing routine care and follow-up in a patient's local region. Patients had the impression that collaboration with scientists/providers from other medical fields (within the respiratory realm but also cardiology, rheumatology, etc.) needs to be improved as well. Specific research topics that were considered underdeveloped from a patient's perspective were:

- Development of models to increase PH awareness among general practitioners, pulmonologists, cardiologists
- development of methods to assess and monitor different aspects of quality of life, specific to the condition of PH
- identification and validation of self-help strategies and life-style interventions, e.g. exercise training, diets, specific to PH patients. The meeting was concluded with the intent to hold regular (e.g. once every 6 months) focus group meetings (varying composition) in the future, both to improve care and research.

**Table 1. Top 10 most cited basic research initiated by a Dutch group:**

| Theme | Article | Citations | |
|---|---|---|---|
| | | Total | Corrected |
| Right heart failure | Bogaard et al. Chronic pulmonary artery pressure elevation is insufficient to explain right heart failure. Circulation 2009; 120:1951. | 91 | 7.9 |
| PH and exercise | Handoko et al. Opposite Effects of Training in Rats With Stable and Progressive Pulmonary Hypertension. Circulation 2009; 120:42-49 | 41 | 3.6 |
| PH Treatment | De Visser et al. Sildenafil attenuates pulmonary inflammation and fibrin deposition, mortality and right ventricular hypertrophy in neonatal hyperoxic lung injury. Resp Res 2009; 10:30 | 32 | 2.8 |
| PH Treatment | Redout et al. Antioxidant treatment attenuates pulmonary arterial hypertension-induced heart failure. Am J Physiol Heart Circ Physiol 2010; 298:H1038-H1047 | 28 | 3.3 |
| Cardiovascular Modeling | Lumens et al. Three-Wall Segment (TriSeg) Model Describing Mechanics and Hemodynamics of Ventricular Interaction. Ann Biomed Eng. 2009:37:2234-55 | 26 | 1.1 |
| PH Treatment | Mouchaers et al. Fasudil reduces monocrotaline-induced pulmonary arterial hypertension: comparison with bosentan and sildenafil. Eur Resp J 2010; 36:800-807 | 25 | 3.0 |
| PH Treatment | Bogaard et al. Suppression of Histone Deacetylases Worsens Right Ventricular Dysfunction after Pulmonary Artery Banding in Rats. Am J Resp Crit Care Med 2011; 183:1402-1410. | 23 | 4.3 |
| PH Treatment | Handoko et al. Right ventricular pacing improves right heart function in experimental pulmonary arterial hypertension: a study in the isolated heart. Am J Physiol Heart Circ Physiol 2009; 297:H1752-H1759 | 23 | 2.0 |
| Animal Models | Gomez-Arroyo et al. The monocrotaline model of pulmonary hypertension in perspective. Am J Physiol 2012;302:L363-9 | 22 | 9.1 |
| PH Treatment | de Man et al. Bisoprolol Delays Progression Towards Right Heart Failure in Experimental Pulmonary Hypertension. Circ Heart Fail 2012; 5:97-105 | 19 | 7.8 |

**Table 2. Top 10 most cited clinical research initiated by a Dutch group:**

| Theme | Article | Citations | |
|---|---|---|---|
| | | Total | Corrected |
| PAH | Marcus et al. Interventricular mechanical asynchrony in pulmonary arterial hypertension. J Am Coll Cardiol 2008; 51:750-757. | 70 | 4.9 |
| Congenital Heart Disease | Verheugt et al. Mortality in adult congenital heart disease. Eur Heart J 2010;31:1220-9 | 58 | 6.9 |
| COPD associated PH | Rietema et al. Sildenafil treatment in COPD does not affect stroke volume or exercise capacity. Eur Resp J 2008;31:759-64. | 55 | 3.9 |
| PAH | Van de Veerdonk et al. Progressive Right Ventricular Dysfunction in Patients With Pulmonary Arterial Hypertension Responding to Therapy. J Am Coll Cardiol 2012; 58:2511-2519. | 53 | 9.9 |
| PAH | Lankhaar et al. Pulmonary vascular resistance and compliance stay inversely related during treatment of pulmonary hypertension. Eur Heart J 2008; 29:1688-1695. | 46 | 3.2 |
| CDH | Reiss et al. Standardized Postnatal Management of Infants with Congenital Diaphragmatic Hernia in Europe: The CDH EURO Consortium Consensus. Neonatology 2010;98:354-64 | 41 | 4.9 |
| Paediatric PH | Berger et al. Clinical features of paediatric pulmonary hypertension: a registry study. Lancet 2012;379:537-46 | 38 | 15.6 |
| SSc | Overbeek et al. Pulmonary arterial hypertension in limited cutaneous systemic sclerosis: a distinctive vasculopathy. Eur Resp J 2009; 34:371-379. | 38 | 3.3 |
| PAH | Groepenhoff et al. Exercise Testing to Estimate Survival in Pulmonary Hypertension. Med Science Sports Exercise 2008; 40:1725-1732 | 37 | 5.5 |
| CDH | Keijzer et al. Congenital Diaphragmatic Hernia. Sem Ped Surg 2010;19:180-5. | 37 | 4.4 |

**Table 3. Top 10 most cited collaborative international basic research (excl. reviews, guidelines):**

| Theme | Article | Citations | |
|---|---|---|---|
| | | Total | Corrected |
| Hemolysis | Donadee et al. Nitric Oxide Scavenging by Red Blood Cell Microparticles and Cell-Free Hemoglobin as a Mechanism for the Red Cell Storage Lesion. Circulation 2011;124:465-76 | 77 | 14.4 |
| PH pathophysiology | Umar et al. Estrogen Rescues Preexisting Severe Pulmonary Hypertension in Rats 2011;184:715-23. | 18 | 3.4 |
| Development pulmonary circulation | Roubliova et al. Effect of maternal administration of betamethasone on peripheral arterial development in fetal rabbit lungs. Neonatology 2008;93:64-72. | 15 | 1.1 |
| PH pathophysiology | Tu et al. A Critical Role for p130(Cas) in the Progression of Pulmonary Hypertension in Humans and Rodents. Am J Resp Crit Care Med 2012;186:666-76. | 9 | 3.7 |
| PH pathophysiology | Dahal et al. Involvement of mast cells in monocrotaline-induced pulmonary hypertension in rats. Resp Res 2011;12:60. | 9 | 1.7 |
| PH pathophysiology | Belik et al. Pulmonary vascular and cardiac effects of peroxynitrite decomposition in newborn rats. Free Rad Biol Med 2010;49:1306-14. | 8 | 0.7 |
| PH pathophysiology | Kwapiszewska et al. PAR-2 Inhibition Reverses Experimental Pulmonary Hypertension. Circ Res 2012;110:1179-91 | 7 | 2.9 |
| PH pathophysiology | Herrera et al. Carbon monoxide: a novel pulmonary artery vasodilator in neonatal llamas of the Andean altiplano. Cardiovasc Res. 2008;77:197-201 | 7 | 0.5 |
| PH pathophysiology | Zemse et al. Restoration of endothelin-1-induced impairment in endothelium-dependent relaxation by interleukin-10 in murine aortic rings. Can J Physiol Pharmacol 2008;86:557-65 | 7 | 0.5 |
| Serotonin metabolism | Durk et al. Production of Serotonin by Tryptophan Hydroxylase 1 and Release via Platelets Contribute to Allergic Airway Inflammation. Am J Resp Crit Care Med 2013;187:476-85 | 6 | 14.6 |

**Table 4. Top 10 Most cited collaborative international clinical research (excl. reviews, guidelines):**

| Theme | Article | Citations | |
|---|---|---|---|
| | | Total | Mean/yr |
| SSc | Tyndall et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis 2010;69:1809-15 | 98 | 11.6 |
| Congential Heart disease | Gatzoulis et al. Longer-term bosentan therapy improves functional capacity in Eisenmenger syndrome: Results of the BREATHE-5 open-label extension study. Int J Cardiol 2008;127:27-32 | 67 | 4.7 |
| BMP signaling | Kodach et al. The bone morphogenetic protein pathway is inactivated in the majority of sporadic colorectal cancers. Gastroenterology 2008;134:1332-41. | 52 | 3.7 |
| CTEPH | Mayer E et al. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: Results from an international prospective registry. J Thorac Cardiovasc Surgery 2011; 141:702-710. | 49 | 9.2 |
| SSC | Denton et al. Long-term effects of bosentan on quality of life, survival, safety and tolerability in pulmonary arterial hypertension related to connective tissue diseases. Ann Rheu Disease 2008; 67:1222-1228. | 48 | 3.4 |
| CTEPH | Pepke-Zaba J et al. Chronic Thromboembolic Pulmonary Hypertension (CTEPH) Results From an International Prospective Registry. Circulation 2011; 124:1973-1981. | 46 | 8.6 |
| High Altitude | Qiu et al. The yak genome and adaptation to life at high altitude. Nature Genetics 2012;44:946-9 | 30 | 6.4 |
| CTEPH | Suntharalingam J et al. Fibrinogen A alpha Thr312Ala polymorphism is associated with chronic thromboembolic pulmonary hypertension. Eur Resp J 2008; 31:736-741. | 26 | 1.8 |
| Hypoxia | Faoro et al. Bosentan Decreases Pulmonary Vascular Resistance and Improves Exercise Capacity in Acute Hypoxia. Chest 2009;135:1215-22. | 19 | 1.7 |
| Scimitar syndrome | Vida et al. Scimitar Syndrome A European Congenital Heart Surgeons Association (ECHSA) Multicentric Study. Circulation 2010;122:1159-66 | 17 | 2.0 |

**Table 5. Top 10 best cited review and guideline papers with Dutch collaborators:**

| Theme | Article | Citations | |
|---|---|---|---|
| | | Total | Corrected |
| PH | Galie et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2009; 30:2493-2537. | 158 | |
| Right heart failure | Bogaard et al. The Right Ventricle Under Pressure Cellular and Molecular Mechanisms of Right-Heart Failure in Pulmonary Hypertension. Chest 2009; 135:794-804. | 122 | 10.6 |
| TGFbeta signaling | Goumans et al. TGF-beta signaling in vascular biology and dysfunction. Cell Res 2009;19:116-27 | 107 | 4.6 |
| HFpEF | Borlaug et al. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J 2011;32:670-9 | 92 | 17 |
| PH | Galie et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Resp J 2009; 34:1219-1263 | 67 | |
| Gaucher disease | Cox et al. Management of non-neuronopathic Gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring. J Inherit Metab Dis 2008;31:319-36 | 52 | 2.9 |
| LVAD | Klotza et al. Impact of left ventricular assist device (LVAD) support on the cardiac reverse remodeling process. Prog Biophys Mol Biol 2008;97:479-96 | 50 | 2.8 |
| CDH | Peetsold et al. The long-term follow-up of patients with a congenital diaphragmatic hernia: a broad spectrum of morbidity. Pediatr Surg Int 2009;25:1-17 | 45 | 3.9 |
| Congenital heart disease | Van der Bom et al. The changing epidemiology of congenital heart disease. Nat Rev Cardiol 2011;8:50-60 | 44 | 8.2 |
| Arginase | Maarsingh et al. Arginase and pulmonary diseases. Naunyn Schmiedebergs Arch Pharmacol 2008;378:171-84 | 37 | 2.6 |

**APPENDIX**

**Opinions of international key opinion leaders**

**Question 1**
**Which research topics and groups in Pulmonary Hypertension research are visible and have impact on pulmonary physicians and researchers outside the Netherland?**

**Expert 1**

The most important and visible groups are in the VU Medical Centre Amsterdam, especially that of Dr Vonk-Noordegraaf. Most (but not all) other excellent PAH researchers in the Netherlands have either worked or published with this group, and there have been many joint publications with the key international researchers in the US and UK, amongst others. The group at the University Medical Center Groningen-GUIDE (Dr Berger) also has a high international visibility and impact. Other groups in the Netherlands also have significant international impact, but much less so than these two.

Key topics where there is significant strength in the Netherlands include treatment of PAH, right ventricular function in PAH, associated genetic abnormalities, and sequelae of PH in terms of limitations to exercise.

**Expert 2**

In the field of Pulmonary Hypertension, the most prominent and visible group is the VUMC group led by Dr Anton Vonk-Noordegraaf. In the field of CTEPH, Dr Paul Bresser has an excellent profile. In basic science very basic mechanisms are covered by the talented group of Dr Peter ten Dijke

- Phenotyping and severity are very visible, especially in the field of right heart function and failure (5/5)
- Biological mechanisms are visible in the fields of pulmonary vascular physiology (5/5) and pathobiological mechanisms (4/5)
- Diagnosis and monitoring is visible (5/5)
- Therapy medical and non-medical are visible (4/5)

**Expert 3**

**Question 2**
**Which research topics in Pulmonary Hypertension research are less visible to physicians and researchers outside the Netherland?**

**Expert 1**

**Expert 2**

Average research is observed in the fields of
- Biobanking (3/5)
- Data management clinical studies (3/5)
- Implementation and care (3/5)

Less visible topics include
- Environment and lifestyle (1/5)
- Development and ageing (1/5)
- Prevention (1/5)

**Expert 3**

Even the link between endothelium and epithelium seems not to be one of the main topics in the Netherlands.

Relevance of research judged by international experts (order of importance)

Research performed in the Netherlands in the field of **Pulmonary Hypertension**

0= no relevant research
5= excellent research international top level

| | A | B | C* | Mean |
|---|---|---|---|---|
| **Phenotyping and Severity** | 4 | 5 | | 4.50 |
| **Biological mechanisms** | 4 | 4 | | 4.00 |
| **Environment and lifestyle** | | 1 | | 1.00 |
| **Development and ageing** | | 1 | | 1.00 |
| **Prevention** | | 1 | | 1.00 |
| **Diagnosis monitoring** | 4 | 5 | | 4.50 |
| **Therapy medical** | 4 | 4 | | 4.00 |
| **Therapy non-medical** | | 4 | | 4.00 |
| **Biobanking** | | 3 | | 3.00 |
| **Data management clinical studies** | | 3 | | 3.00 |
| **Implementation and care** | | 3 | | 3.00 |

* Relevance not given

**SWOT analysis (appendix 2)**

| | ***Strength*** | ***Weakness*** | ***Opportunities*** | ***Threats*** |
|---|---|---|---|---|
| *Domains* | | | | |
| Health and Disease | | | | |
| Phenotyping & Severity | • Use of novel imaging techniques (MRI, PET) and invasive hemodynamics<br>• Focus on WHO Groups 1 and 4 | • Not all Group 1 patients are evaluated in expert centers<br>• Fragmented care for patients in WHO Groups 2 (PH associated with left heart disease) and 3 (PH associated with hypoxia and/or chronic lung disease) | • Evaluate all Group 1 patients in expert centers<br>• Develop a network of PH providers outside but linked to the expert centers<br>• Clinical phenotyping of WHO groups 2, 3, 5 | • Competition within the Netherlands for market share, where collaboration and shared responsibility would be preferable |
| Biological mechanisms | • Availability of several animal models to predict treatment responses in WHO group I PH<br>• Studies on cells and tissue derived from WHO group I patients | • Minor research effort to understand cellular and molecular mechanisms of other PH groups | • Financial stimulus via CVON for PH research<br>• Nationally, outstanding centers for cardiology are present to collaboratively study Group 2 PH<br>• Nationally, outstanding centers for chronic lung diseases are available to collaboratively study Group 3 PH | |
| Environment and lifestyle | | • Not a current research topic | | • Few opportunities in an orphan disease |
| Development and ageing | | • Not a current research topic | | • Few opportunities in an orphan disease |
| Prevention | | • Not a current research topic | | • Few opportunities in an orphan disease |

| | | | | |
|---|---|---|---|---|
| *Disease* | | | | |
| | • VUmc is world leading in novel (imaging) methods for PAH and CTEPH monitoring | • The same monitoring methods have not been used in other groups of PH | • Use the VUmc model for other groups of PH patients | • Not all group 1 patients are diagnosed and monitored in expert centers<br>• No expert centers exist for other groups of PH |
| Therapy medical | | • Few WHO group 1 patients participate in randomized clinical trials<br>• Hardly any clinical studies on other groups of PH patients | • Treat all adult and paediatric PH patients in expert centers with significant research focus<br>• Develop a network of PH scientists and providers to facilitate access to clinical trials | |
| Therapy non-medical | • Completed study on the use of rehabilitation in PAH | • No follow-up studies have been done or planned | • Rehab in other groups of PH could be studied<br>• Anxiety disorders and depression have been little studied in PH, but their prevalence and impact could be considerable | • Limited funding for this specific kind of research |
| Biobanking<br>Data management | • National Registry for Paediatric PH | • Limited availability of biological material from patients (blood, DNA samples, lung tissue) | • Expert centers collecting materials of patients from all PH groups | • International competition |
| Implementation and care | | | • Limited knowledge of patient needs for specific research topics | |