PHederation – the Federated Network of Pulmonary Hypertension Registries

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Background

Pulmonary Hypertension [PH] is a progressive pathophysiological disorder that may be associated with cardiovascular and respiratory diseases. Managing PH requires a holistic and multidisciplinary approach, as it is etiologically diverse and complex *(1)*. Pulmonary Arterial Hypertension [PAH] is one of the rare subgroups of PH. In contrast to most other forms of PH, disease progression of PAH can be delayed with the help of well-targeted approved PAH therapies.

Due to the non-specific symptoms of P(A)H, mis-diagnosis rates are high, screening pathways are burdensome, and time to treatment initiation is long *(2)*. Advancing real-world evidence [RWE] generation can help improve diagnosis and disease management of P(A)H and thus ultimately improve patients' lives. However, in complex and rare diseases such as PAH, RWE generation is usually restricted due to small patient numbers, global geographic distribution of specialty care centers, and limited data accessibility.

Disease-specific federated data networks [FDNs], such as, e.g., LupusNet *(3)*, the Federated Tumor Segmentation Initiative FeTS *(4)*, the European Hematology Outcomes Network HONEUR *(5)*, or the Virus Outbreak Data Network VODAN *(6)*, allow the collation of multiple clinically detailed data sources and initiation of collaborative studies across regions and healthcare systems. Such FDNs are gaining increasing popularity, as they are offering data access for different stakeholder groups interested in a specific therapeutic area, including, e.g., (specialized) healthcare professionals, researchers, and institutions, that otherwise might need to collect their own patient data *(7)*.

The PH federated data network *PHederation* aims to improve the care of patients with PH through the power of disease-specific registry data and scientific collaboration. In the following, we will describe the network in more detail.

Methods

Multiple stakeholder scientific collaborations through FDNs require a strong governance model, resulting in clear transparency and reproducibility achieved through data curation, data harmonization, and distributed analytics methodology.

PHederation is a public-private partnership governed by the Board of data representatives including academic and industry stakeholders. Each database owner is in full control of their patient-level data and responsible for data privacy, ethical and legal compliance, and data curation.

To date, all technical operations have been performed, supported, or sponsored by Johnson & Johnson. This includes the connection of data partners and assets through the PHederation Portal

(Figure 1) based on Feder8 *(8)*, local installations of Feder8 at the participating center, the listing of high-level database information (size, start and end dates, etc.) in the Data Catalog, the mapping of source data to the OMOP Common Data Model [CDM], the distribution of programming code for quality checks [QCs], and PHederation Dashboard creation (Figure 2).

When an FDN member proposes a new study, each data center may choose to participate, and involve at minimum a clinician, an epidemiologist, and a statistician to build a study team. The study team aligns on details of the research question and feasibility assessment. Both require precise pre-specified protocols and analysis plans to be in place and the study team's statisticians to translate these into analysis scripts. ATLAS *(9)* and other OHDSI software tools *(10)* may be used as appropriate. To keep patient-level data firewall-protected, each participating data partner runs the analysis scripts on their data and only returns aggregate results to the study team for interpretation or further processing.

The feasibility assessment typically investigates patient or event counts. It helps determine whether the planned study can be conducted, and which centers would qualify to contribute aggregate study results. After a successful feasibility assessment and study execution, all or some of the aggregate study results might be included in a meta-analysis *(11,12)*.

Results are interpreted and published in line with ICMJE guidelines. All ongoing and completed studies are listed in the PHederation Portal's Study Catalog (Figure 1). Feder8 includes a transparent audit trail; i.e., all study-related artefacts are "frozen" at partner sites so that the study and its respective data remains available for inspection and execution for reproducible results.
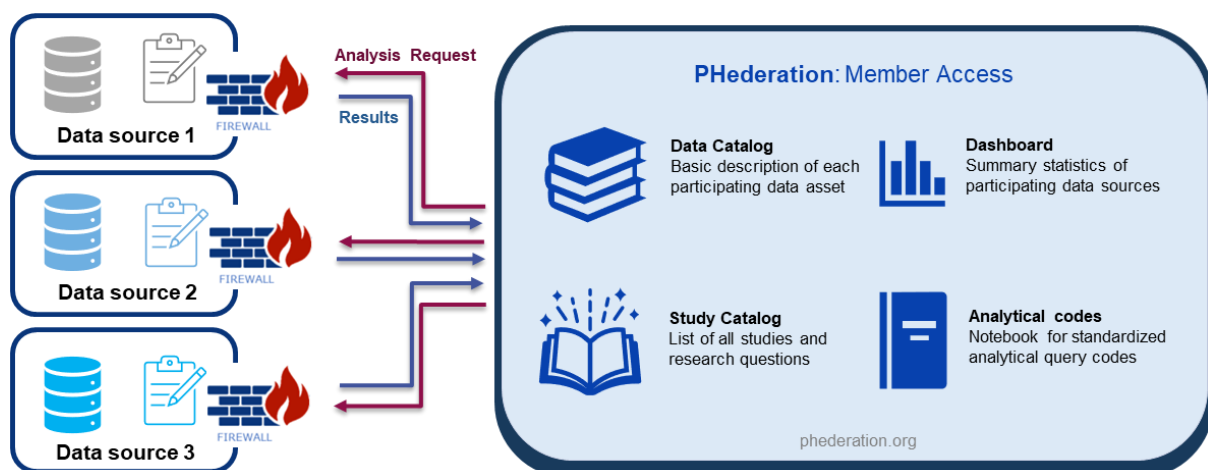
Figure 1. PHederation Portal and mechanisms for transparent scientific collaboration.

Results

PHederation was launched in 2020 and currently comprises six PH databases of diverse origins and geography, contributing data from >12'000 patients (Table 1, Figure 2 top). Onboarding discussions for additional data sources are ongoing, including an imaging database.

Title of the database	Data description	Observation period	Number of PH and PAH patients	Geographic coverage	Source data format/ collection
Canadian PH Registry (CPHR)	Prospective PH patient registry	2017 - ongoing	PH – 1´995 PAH – 1´076	Canada	PAHTool
EXPOSURE (EUPAS19085)	Registry of PAH patients newly treated with either Uptravi or any other PAH-specific therapy	2017 - ongoing	PAH – 2'354	Europe, Canada	CDISC SDTM
OPUS (NCT02126943)	Opsumit drug registry	2014 - 2018	PH – 2'674 PAH – 2'208	USA	CDISC SDTM
ORPHEUS (NCT03197688)	Opsumit user medical chart review to supplement OPUS	2013 - 2017	PH – 3'031 PAH – 2'410	USA	CDISC SDTM
Porto center of Portuguese PH network	Northern Region Portuguese PH registry	2001 - ongoing	PH – 578 PAH – 216	Portugal – Northern Region	PAHTool
SPHERE NCT03278002)	Selexipag drug registry	2016 - 2020	PH – 829 PAH – 759	USA	registry-specific
Stanford University clinical PH database	PH Registry	2004 - ongoing	PH – 1´189 PAH – 987	USA – Western Region	registry-specific

Table 1. PHederation Data Catalog.

Most data points could be harmonized to the OMOP CDM using standard mappings. Custom mappings were introduced to preserve the diverse provenance and depth of the clinical data, including detailed information on differential diagnoses, novel treatments, specific clinical assessments, and fact-relationships (e.g., reason for treatment discontinuation) *(13)*. Over time, some custom mappings have become standard, such as, e.g., the concept for drug- and toxin-induced PAH. The *Handbook for PAH registry conversion to the OMOP CDM (14)* is a living guidance document fostering consistency of mapping logics across databases.

After data conversion and QC, programming code was shared to create PHederation Dashboards for initial fit-for-purpose database evaluations (Figure 2). PHederation Dashboards are interactive visualizations of high-level summary statistics and include overall number and geographic distribution of patients, demographic, diagnostic and clinical characteristics, and treatment distributions.
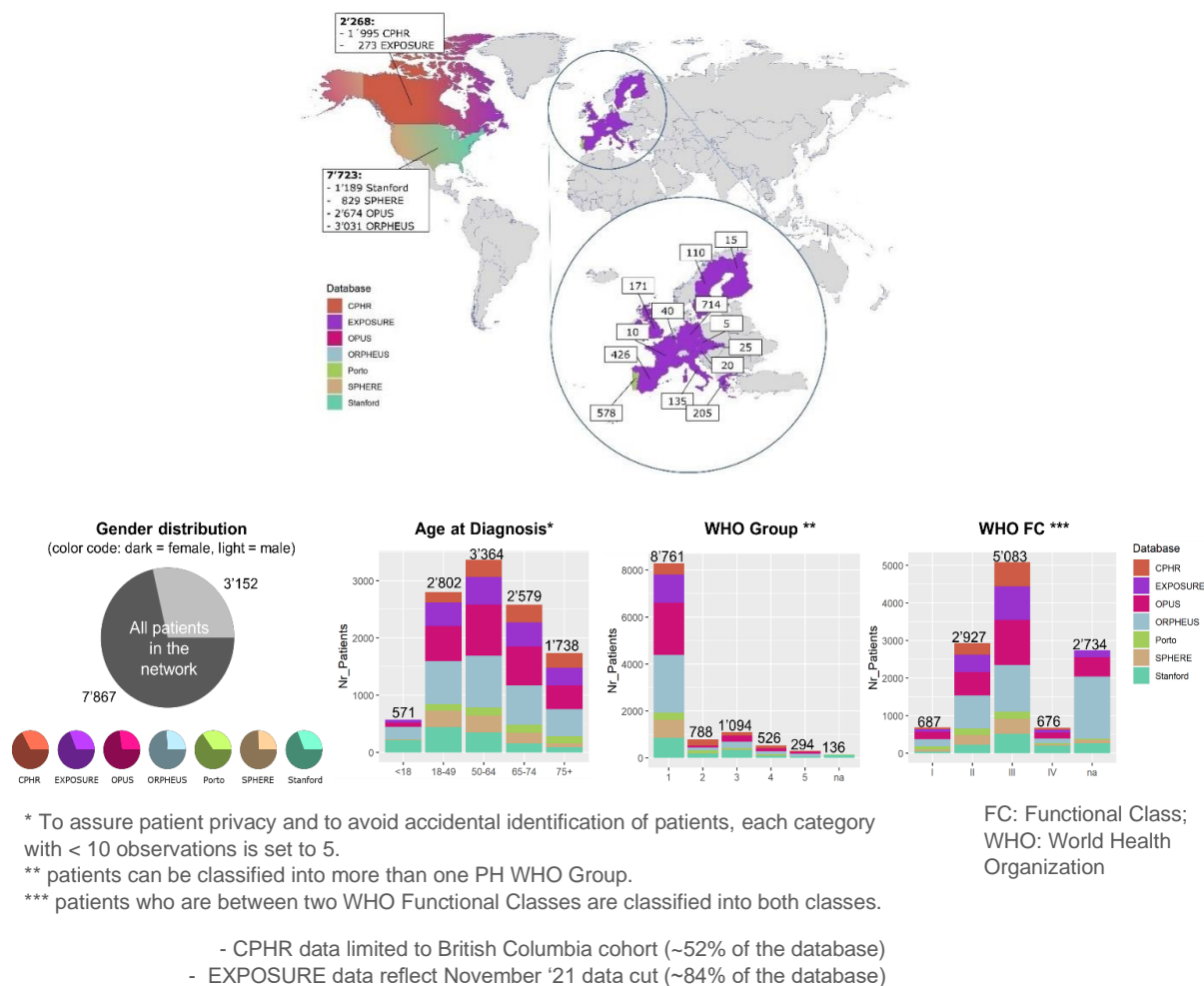
Figure 2. PHederation Dashboard: Geographic distribution of databases, and patient demographics and disease characteristics at enrolment.

The PHederation Board is about to kick off the first PHederation Network Study. The study will likely address a similar research question as Darwin EU's EUPAS106052 *(15)* on *co-prescribing of endothelin receptor antagonists and phosphodiesterate-5 inhibitors in PAH*. The Board aims to complement Darwin EU's findings in a federated network of disease-agnostic databases with findings from a disease-specific FDN.

Conclusion

PHederation established a network of databases of diverse purpose and origin with the common goal of advancing scientific knowledge in PH through distributed data sources and analytics, harmonization, and automation. It looks to expand the breadth and depth of individual PH databases, to increase diversity and geographic coverage, and to accelerate and enhance RWE generation. The PHederation Portal connects all data assets, centers and study collaborators, gives insights into ongoing and completed studies, allows fit-for-purpose assessments, and helps to select the largest possible patient cohorts for new studies. PHederation sets a template and model for future disease-specific FDNs. Visit us at PHederation.org! *(16)*

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