The Pulmonary Hypertension Association Registry: Rationale, Design, and Role in Quality Improvement

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The Pulmonary Hypertension Association (PHA) Scientific Leadership Council (SLC) prioritized the development of the PH Care Centers (PHCC) initiative in part to identify centers that adhere to expert consensus diagnostic and treatment guidelines in both community and academic practice settings, decreasing the chances of misdiagnosis and inappropriate medical management. The overall goal of the PHCC is to improve outcomes of patients with pulmonary hypertension (PH). It is generally accepted that measurement of processes and outcomes are required in order to improve quality of care: the degree to which health services increase the likelihood of desired health outcomes and are consistent with current professional knowledge. The PHA Registry (PHAR) was developed to collect data regarding key measures to facilitate the achievement of these goals of the PHCC.

The PHAR is a multisite, prospective patient registry based at the participating clinical sites accredited as PHCCs. Currently, 33 adult and pediatric sites are active in the study with several others in the startup process (see Online Supplement 1 for a site list at the time of publication, and www.PHAssociation.org/PHAR for a current list). The first patient entered PHAR in September 2015, and, to date, more than 500 patients have been enrolled (see Table 1). The PHAR is enrolling adult and pediatric patients with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) who can speak either English or Spanish. Patients are eligible for enrollment if they are newly seen by the PHCC (ie, within 6 months of the first visit). PAH and CTEPH patients are the initial focus of the PHAR due to the availability of expert consensus guidelines in terms of evaluation and treatment of these types of PH.[1] Patients incident to the center have been included in order to assess centers' adherence to diagnostic and treatment guidelines, avoid basing conclusions on patients evaluated in different diagnostic

Table 1.

Baseline Characteristic	All Patients N=539
Age – year	54.8 ± 17.7
Female sex – no. (%)	375 (69.7)
Race – no. (%)	
White	382 (71.4)
Black	62 (11.6)
Asian	32 (6.0)
Other	24 (4.5)
Unknown	35 (6.5)
Ethnicity – no. (%)	
Non-Hispanic or Latino	441 (85.8)
Hispanic or Latino	73 (14.2)
Classification of Pulmonary Hypertension – no. (%)	
PAH	477 (88.5)
CTEPH	62 (11.5)
Classification of Pulmonary Arterial Hypertension – no. (%)	
Idiopathic	195 (40.9)
Heritable	15 (3.1)
Drug and toxin induced	54 (11.3)
Associated with:	
Connective tissue disease	147 (30.8)
Human immunodeficiency virus infection	4 (0.8)
Portal hypertension	29 (6.1)
Congenital heart disease	30 (6.3)
Pulmonary veno-occlusive disease	1 (0.2)
Persistent PH of the newborn	2 (0.4)
WHO Functional Classification – no. (%)	
I	41 (8.4)
II	158 (32.4)
III	256 (52.5)
IV	33 (6.8)

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and treatment eras, and to minimize missing data and selection bias.[2,3]

Following informed consent and HIPAA authorization, electronic case report forms (eCRFs) are completed on a computer tablet. Two eCRFs are completed for each baseline and follow-up visit: one completed by the patient and one by the staff. The current PHAR eCRFs are included in paper form as Online Supplement 2. Follow-up questionnaires are collected during normally scheduled clinic visits thereafter, approximately every 6 months.

eCRFs have been programmed as proprietary software on Microsoft Surface Pro 3 tablets provided to sites specifically by the PHAR. This design takes advantage of preprogrammed range and logic tests, as well as form customization and skip patterns, ensuring that subjects see and complete only relevant and age-appropriate sections. This allows the same tablet and data collection procedures to be used for any age patient, from children and their parents to the elderly. Broadly, PHAR collects data on demographics, socioeconomic status, anthropometrics, medical history, social history, symptom burden, PH medications, health-related quality of life (HRQOL), and longitudinal outcomes (see Table 2). Where possible, the PHAR collects data for variables drawn from Common Data Elements (CDEs) from the National Institutes of Health (NIH) Office of Rare Diseases and the Phenotypes and eXposures (PhenX) Toolkit.[4,5] CDEs were developed to standardize data collection across studies in order to facilitate patient information integration and secondary analyses including more than one study.

Table 2. PHAR – Data Elements

Section	Data Element
Demographic	Sex/gender Race Ethnicity (including Hispanic/Latino subgroup)
Socioeconomic Status	Health insurance Education Income Employment status Marital status
Anthropometric	Height Weight
Medical History	PH diagnosis Guideline-recommended diagnostic tests completion status Diagnostic right heart catheterization results BNP/NT-proBNP Creatinine 6-minute walk distance
Social History	Alcohol use Cigarette use Methamphetamine use
Symptoms	WHO functional classification
PH Medication	Prior targeted therapies Current targeted therapies
Clinical Research	Current research participant Interest in future participation
Health-related Quality of Life	emPHasis-10 SF-12 PedsQL (children)
Outcomes	Death Transplantation Hospitalization

A unique and important component of the PHAR data collection plan is a longitudinal assessment of HRQOL across the lifespan utilizing 2 separate instruments. emPHasis-10 is a 10-question, PH-specific HRQOL instrument, which assesses breathlessness, fatigue/lack of energy, social restrictions, and self-reported concerns of burden on others on a 6-point scale, returning an overall score between 0 and 50.[6] emPHasis-10 has demonstrated the ability to discriminate between World Health Organization (WHO) functional classification in PAH, and moderately correlates with 6-minute walk distance (6MWD).[6,7] The Medical Outcome Study Short Form-12 (SF-12) is derived from the SF-36 and designed to assess quality of life in 8 domains: physical functioning, social functioning, role physical, role emotional, mental health, energy/vitality, pain, and general health perception.[8] A mental component score (MCS) is calculated utilizing the vitality, social functioning, role emotional, and mental health domains; a physical component score (PCS) is calculated utilizing the physical functioning, role physical, pain, and general health perception domains. Studies have demonstrated the SF-12 results to correlate well with the parent SF-36 (ICC 0.90 for MCS and 0.84 for PCS).[9] HRQOL is assessed in the pediatric population utilizing a PH adaptation of the Pediatric Quality of Life (PedsQL) Generic Core Scales and Cardiac Module. PedsQL can be completed either by child self-report, for those old enough to complete the surveys, and parental proxy report.

Many clinical research studies avoid collecting personally identifiable information (PII) to simplify research procedures and data storage security. However, with protections in place, the obligation of researchers to ensure "maximum possible benefit" of research by collecting PII may counterbalance the small risk of loss of confidentiality entailed.[10] Not collecting names, birthdates, and other PII can lead to duplicate enrollments (for example, if a patient moves between centers or changes her name) and/or inability to use administrative databases to facilitate follow-up; these issues have been encountered in other rare disease registries. To avoid these structural

limitations, the PHAR collects PII as part of the study protocol, including birth and current name, birthdate, sex, and location of birth. The PHAR holds an NIH Certificate of Confidentiality, which forbids disclosure of names or other sensitive information other than in specific situations, usually with the specific consent of the individual. The systems used to protect this information include robust encryption and data transfer from the local site to the data coordinating center and storage of encrypted data on a physically separate server, along with multiple physical security measures. The PHAR will not distribute PII and will de-identify personal health information using the "Safe Harbor" method before distribution and use in analyses. The PHAR has also planned for the sharing and harmonization of data with other studies using additional methodologies with appropriate safeguards in place. The Global Unique IDentifier (GUID) is a computer-generated alphanumeric code that is unique to each research participant, derived from subject information that does not change over time.[11] The GUIDs for research subjects could be generated by other studies and harmonized with the data from the PHAR. Data with GUIDs (without PII) are considered "de-identified." PHAR has included GUID generation and the possibility and processes for future data sharing and collaborative multistudy analyses in the patient consent process.

Table 3. PHAR – Governance

Committee	Membership
Steering Committee	**Steven M. Kawut, MD, MS** (Chair) University of Pennsylvania **Daniel C. Grinnan, MD** Virginia Commonwealth University **Wendy M. Hill, MSN, NP-C** Cedars Sinai **Ronald J. Oudiz, MD** Harbor-UCLA Medical Center **Linda Santos** Patient Representative **Corey E. Ventetuolo, MD, MS** Brown University
Liaison Committee	**Roham T. Zamanian, MD** (Chair) Stanford University **David B. Badesch, MD** University of Colorado Denver **Todd M. Bull, MD** University of Colorado Denver **Theresa Crisostomo** Patient Representative **Steven D. Nathan, MD** Inova Fairfax Hospital **Jeffrey S. Sager, MD, MSCE** Cottage Health System
Data Access/Publications and Presentations Committee	**Peter J. Leary, MD, MS** (Chair) University of Washington **H. James Ford III, MD** University of North Carolina **Steven M. Kawut, MD, MS** University of Pennsylvania **Richard A. Kronmal, PhD** University of Washington **Stephen C. Mathai, MD, MHS** Johns Hopkins University **Corey E. Ventetuolo, MD, MS** Brown University
Data and Clinical Coordinating Center *University of Washington*	Richard A. Kronmal, PhD (Co-PI) Kayleen Williams, MPH (Co-PI) Kristina Blank, MPH Stephen Daniel, PhD Zach Drager Peter J. Leary, MD, MS Jerry Watson

The PHAR has a transparent and publicly documented organizational structure (see Table 3). The PHAR Steering Committee oversees the objectives and direction of the PHAR, legal/ethical decisions, fulfilling obligations to patients, and satisfying interests to a diverse group of stakeholders. The Liaison Committee is charged with maintaining relationships with centers, providing feedback and ongoing advice on operations and patient/provider insights, and developing tools for monitoring satisfaction with registry conduct and the accessibility of staff. The Data Access/Publications and Presentations Committee (P&P) is responsible for ensuring access to registry data, defining the process by which investigators access data and perform and propose analyses, ensuring proper de-identification of data prior to release, reviewing paper proposals, and reviewing and approving abstracts and manuscripts before submission. The Data and Clinical Coordinating Center (DCC) at the Collaborative Health Studies Coordinating Center of the University of Washington built and maintains the data capture system, CRFs, and rules; manages study committee and study administration documentation; trains site personnel; disseminates reports; and participates in the analysis of study data.

PHAR Committee members each serve 3-year terms. Nominations, including self-nominations, are accepted annually for committee membership from an autumn announcement to the PHCCs, PH Clinicians and Researchers membership network, PH Professional Network, and patient community.

The core mission of the PHAR is aligned with that of the overall PHCC: that is, to improve outcomes in PH patients. The main purposes of the PHAR are to measure process and outcome variables, leading to improvements in quality of care, and establish benchmarks for health outcomes. Summary data are available to each contributing center in "real time" using a secure website. Each PHCC can

Table 4. Projects to Date

Meeting	Abstract Title	Link
American Thoracic Society (ATS) – 2016 Annual Congress	Evaluation of Quality of Care and Quality of Life of Pulmonary Hypertension (PH) Patients Seen in PH Care Centers: Pulmonary Hypertension Association Registry (PHAR) Study Design	http://bit.ly/PHAR1
American Thoracic Society (ATS) – 2017 Annual Congress	Characterization of Hispanics with Pulmonary Hypertension in the U.S.: The Pulmonary Hypertension Association Registry	http://bit.ly/PHAR2
	Determinants of Health-Related Quality of Life in PAH: Data from the Pulmonary Hypertension Association Registry	http://bit.ly/PHAR3

review their summary data regarding evaluation, disease and severity mix; use of therapies; and outcomes compared to all other sites, allowing for quality improvement initiatives.

The PHAR data could also lead to new understandings of PAH and CTEPH. Individuals from one of the following groups may submit paper proposals to perform analyses using the PHAR dataset: a) PHAR Principal Investigators (or members or trainees on their teams) who have contributed data to the registry; b) members of the PHAR Coordinating Center; and c) representatives of the PHA. All concept proposals are formally reviewed by the P&P Committee and require approval prior to data analysis. The DCC may execute the analysis, depending on the needs of the proposal and the proposing investigators, or (following establishment of a Data Use Agreement) release de-identified data to the investigators for analysis. A representative from each center providing data to the PHAR has been included on the projects to date (Table 4, and at www.PHAssociation.org/recent-research-and-the-pha-registry).

The PHAR provides the opportunity to make important inroads into identifying and providing the best care for patients with PAH and CTEPH. The PHAR provides an infrastructure for PHCCs to participate in local, regional, and national quality improvement initiatives as well as research endeavors. The participation of patients, caregivers, and health professionals and the support of the PHA make the PHAR a unique multi-stakeholder patient registry in the PH disease state. Improvement of care processes and outcomes of PH patients will be the ultimate milestones of success.

References

1. Galiè N, Humbert M, Vachiéry JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J*. 2015;46(4):903-975.
2. Altman DG, Bland JM. Missing data. *BMJ*. 2007;334(7590):424.
3. Jensen H, Benn CS, Lisse IM, Rodrigues A, Andersen PK, Aaby P. Survival bias in observational studies of the impact of routine immunizations on childhood survival. *Trop Med Int Health*. 2007;12(1):5-14.
4. Rubinstein YR, McInnes P. NIH/NCATS/GRDR® Common Data Elements: A leading force for standardized data collection. *Contemp Clin Trials*. 2015;42:78-80.
5. Hamilton CM, Strader LC, Pratt JG, et al. The PhenX Toolkit: get the most from your measures. *Am J Epidemiol*. 2011;174(3):253-260.
6. Yorke J, Corris P, Gaine S, et al. emPHasis-10: development of a health-related quality of life measure in pulmonary hypertension. *Eur Respir J*. 2014;43(4):1106-1113.
7. Smith I, Billings C, Kiely D, Yorke J, Armstrong I. Extended Evaluation Of EmPHasis-10 Quality Of Life Questionnaire In PH. *Am J Respir Crit Care Med*. 2016;193:A6465.
8. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34(3):220-233.
9. Loosman WL, Hoekstra T, van Dijk S, et al. Short-Form 12 or Short-Form 36 to measure quality-of-life changes in dialysis patients? *Nephrol Dial Transplant*. 2015;30(7):1170-1176.
10. US Department of Health & Human Services, Office of the Secretary, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report*. 1979. https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf. Accessed April 2018.
11. Johnson SB, Whitney G, McAuliffe M, et al. Using global unique identifiers to link autism collections. *J Am Med Inform Assoc*. 2010;17(6):689-695.