Design of the REVEAL Registry for US Patients With Pulmonary Arterial Hypertension

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The Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) has been designed to meet the need for current information about patients with pulmonary arterial hypertension (PAH). The main objectives of REVEAL are to better define and understand PAH and to assess the consequences of treatment strategies. REVEAL is collecting clinically relevant data from 3500 consecutively enrolled patients with confirmed PAH diagnoses. Outcomes will be evaluated longitudinally and compared according to the baseline classification of PAH. The primary outcome for group comparisons will be survival. Collected data include World Health Organization functional class, 6-minute walk distance, cardiopulmonary exercise testing, pulmonary function test results, hemodynamic measurements, functional status, hospitalizations, and death. REVEAL will be the richest source of data on patients with World Health Organization group I PAH.

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IPAH = idiopathic pulmonary arterial hypertension; NHLBI = National Heart, Lung, and Blood Institute; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; REVEAL = Registry to Evaluate Early and Long-term PAH Disease Management; RHC = right heart catheterization; SNAP = Surveillance of North American Pulmonary Hypertension; SOPHIA = Surveillance of Pulmonary Hypertension in America; WHO = World Health Organization

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Improvements in our understanding of pulmonary arterial hypertension (PAH) during the past 25 years can be attributed in large part to clinical data acquired in the Patient Registry for the Characterization of Primary Pulmonary Hypertension, a nationwide US database established in 1981 and supported by the National Heart, Lung, and Blood Institute (NHLBI).[1,2] In addition to providing a clinical and demographic description of the patient population, the registry determined that the 3-year probability of survival was 50% among its cohort of 187 patients who were treated before the availability of approved pulmonary vascular–targeted therapy.[1] By describing a precisely defined subpopulation of patients with pulmonary hypertension (PH), the registry helped determine the emphasis and direction of clinical research. The survival information has formed the basis of comparison for subsequent studies of outcome, including long-term clinical drug studies.

The data from the NHLBI study are constrained by the era in which they were collected, the relatively small number of patients included, and the tightly delineated scope of the disease studied. More recently, recognition of these limitations has led to efforts to update and expand our understanding of pulmonary hypertensive conditions. Two new registries were established in the early 2000s: a French registry of patients with PAH, which provides 1-, 2-, and 3-year survival data[3] and a Chinese registry of patients with idiopathic PAH (IPAH) and familial PAH,[4] which studies the survival of patients who are treated exclusively with conventional therapies, such as diuretics, calcium channel blockers, and oral anticoagulants. The Surveillance of North American Pulmonary Hypertension (SNAP)[5] and the Surveillance of Pulmonary Hypertension in America (SOPHIA)[6] registries were developed to address the question of whether prior exposure to anorexigens was associated with the development of PAH.

In contrast, the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) will provide an extensive and updated picture of the natural history of a more broadly defined scope of PAH and the effects of current therapy. This project will use appropriate analysis to identify key clinical features of PAH and to predict outcomes on the basis of the presentation of disease and its response to a spectrum of therapeutic strategies.

TABLE 1. **REVEAL Study Objectives**[a]

1.	To characterize the demographics and clinical course of the patient population diagnosed as having WHO group I PAH
2.	To evaluate differences in patient outcomes according to WHO group I classification subgroup
3.	To compare outcomes in patients who do and do not meet prespecified traditional hemodynamic criteria for the diagnosis of PAH
4.	To identify clinical predictors of short-term and long-term outcomes
5.	To assess the relationship between PAH medications (individually and in combination) and patient outcomes
6.	To report temporal trends in treatments and outcomes for patients with newly diagnosed PAH
7.	To collect timely and relevant data that will assist in the evolving research needs of the PAH community

[a] PAH = pulmonary arterial hypertension; REVEAL = Registry to Evaluate Early and Long-term PAH Disease Management; WHO = World Health Organization.

REGISTRY DESIGN

REVEAL is a multicenter, observational, US-based registry designed to study the longitudinal (2006–2012) clinical course and disease management of patients with PAH. Each of the 54 participating sites received institutional review board approval. The first 2977 consecutive patients were enrolled from March 1, 2006, through September 30, 2007, and will be followed up prospectively for a minimum of 5 years from the date of study enrollment. An additional 500 patients with newly diagnosed PAH are being enrolled. Data collection is Web-based, with follow-up information entered at quarterly intervals regardless of patients' naturally occurring visit schedules. The 7 objectives included in the protocol are provided in Table 1. The first objective will be addressed with baseline data alone, whereas the next 4 involve prospectively collected outcome data. The sixth objective was added through a protocol amendment concurrent with the decision to extend enrollment for patients with newly diagnosed PAH. The final objective is an acknowledgement that the database may later be used for research goals that could not be fully anticipated at the study's inception.

All consecutively screened consenting patients diagnosed as having World Health Organization (WHO) Group I PAH (Table 2)[7] and meeting specific hemodynamic criteria based on prior right heart catheterization (RHC) were enrolled at each center. Patients older than 3 months were eligible for enrollment regardless of prior treatments. Although patients could be enrolled at any time after diagnosis, those enrolled within 3 months of diagnostic RHC are defined as having newly diagnosed PAH.

Inclusion criteria consisted of documentation of the following hemodynamic parameters obtained by RHC, performed at any time before study enrollment: (1) mean pulmonary arterial pressure of more than 25 mm Hg at rest or more than 30 mm Hg with exercise; (2) mean pulmonary arterial wedge pressure (PCWP) or left ventricular end-diastolic pressure of 18 mm Hg or less, measured contemporaneously with pulmonary arterial pressure; (3) pulmonary vascular resistance of 240 dynes $\times$ s $\times$ cm^{-5} or higher (to convert to Wood units, divide by 80); and (4) a clinical diagnosis of PAH according to the clinical investigators' judgment guided by generally accepted definitions. Although participants in investigational clinical trials were included, data collected during the blinded phase of clinical trials were excluded from the registry.

Patients were excluded if RHC was not performed, hemodynamic criteria were not met, the clinical presentation was inconsistent with a diagnosis of PAH, or informed consent was withheld.

TABLE 2. **REVEAL-Eligible Pulmonary Hypertension Entities (Bolded) of the 2003 Third World Symposium of Pulmonary Hypertension**

1. Pulmonary arterial hypertension (PAH)	2. Pulmonary hypertension with left heart disease
1.1. Idiopathic (IPAH)	2.1. Left-sided atrial or ventricular heart disease
1.2. Familial (FPAH)	2.2. Left-sided valvular heart disease
1.3. Associated with (APAH):	3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
1.3.1. Collagen vascular disease	3.1. Chronic obstructive pulmonary disease
1.3.2. Congenital systemic-to-pulmonary shunts	3.2. Interstitial lung disease
1.3.3. Portal hypertension	3.3. Sleep-disordered breathing
1.3.4. Human immodeficiency virus infection	3.4. Alveolar hypoventilation disorders
1.3.5. Drugs and toxins	3.5. Chronic exposure to high altitude
1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)	3.6. Developmental abnormalities
1.4. Associated with significant venous or capillary involvement	4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
1.4.1. Pulmonary veno-occlusive disease (PVOD)	4.1. Thromboembolic obstruction of proximal pulmonary arteries
1.4.2. Pulmonary capillary hemangiomatosis (PCH)	4.2. Thromboembolic obstruction of distal pulmonary arteries
1.5. Persistent pulmonary hypertension of the newborn	4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
	5. Miscellaneous: sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

From *J Am Coll Cardiol*.[7]

Patients were enrolled after providing informed consent. To maintain patient confidentiality in accordance with the Health Insurance Portability and Accountability Act, each patient was assigned a unique patient-identifying number when enrolled in the registry.

Included patients were asked to provide demographic information, and baseline characteristics were collected (Table 3). Serial follow-up data from routinely performed studies were recorded, as were data from hospitalizations, including discharge diagnoses and/or death (including cause of death), changes in PAH medications, and documentation of other major medical events, eg, lung or heart-lung transplant or atrial septostomy (Figure 1).

TABLE 3. **Baseline Variables Collected for Enrolled Patients**[a]

Parameter	Specific categories
Date of birth	DD/MM/YYYY
Sex	Male or female
Race	Specify
Zip code	Specify
Diagnosis	See Table 2
Vital signs	Blood pressure, heart rate, weight, height
Nursing service use	Saw/did not see PAH nurse
NYHA/WHO functional class	I, II, III, or IV
Patient employment status	Including reason for unemployment
Student status	Student or nonstudent
Living status	Independent, assisted, dependent
Symptoms	Type
	Onset
PAH-specific medications	Type
	Dose
	Start and stop dates
	Administration route
	Start and stop reasons
Concomitant medications	List
Major comorbidities	List
Clinical trial status	Specify
Chest radiography	Indicate if performed
Electrocardiography	Indicate if performed
Doppler echocardiography	Transthoracic
	Agitated saline shunt study
	Transesophageal
6-Minute walk distance	Borg dyspnea score
Cardiopulmonary exercise test	Indicate if performed
Pulmonary function tests	Indicate if performed
Ventilation/perfusion lung scintigraphy	Indicate if performed
Computed chest tomography	Standard
	High-resolution
	Contrast-enhanced
Invasive hemodynamic parameters	Baseline
	Vasodilator study

[a] NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; WHO = World Health Organization.

STATISTICAL AND DATA ANALYSES

To determine the appropriate sample size for the initial enrollment period (ignoring the supplemental enrollment of patients with newly diagnosed PAH), the study was powered to identify survival differences in moderate-sized subgroups. If 2 subgroups reflect 15% and 25% of patients, respectively, a total sample size of 3000 patients is sufficient to detect a 20% reduction in mortality (ie, 40% vs 32%) with 80% power and an α level of .05. In this example, a total enrolled population of 3000 patients would yield sample sizes for the 2 treatment cohorts of 450 patients and 750 patients, respectively. On the basis of a simple χ^2 test and a 2-sided α level of .05, REVEAL would have 80% power to detect a 20% reduction in mortality.

In practice, we expect to use the Cox proportional hazards regression model to account for variable length of follow-up and multivariate analysis to adjust for nonrandom treatment assignments. Furthermore, because of the inclusion of patients with newly diagnosed PAH (qualifying RHC diagnosis, ≤3 months before enrollment) as well as those with previously diagnosed PAH (qualifying RHC diagnosis, >3 months before enrollment), the observed mortality rate is likely to be somewhat different than in a sample that included only patients with newly diagnosed PAH. Adjustments will be required to include both patients with newly diagnosed PAH and those with previously diagnosed PAH in a single analysis. Nonetheless, the sample size based on the χ^2 test provides reasonable assurance that the study is powered for the types of comparisons that are most likely to be of interest. Although enrollment of patients with newly diagnosed PAH will continue after we have enrolled 3000 patients, this initial set of patients will be the analysis cohort for most of the study objectives. To analyze temporal trends, we will need a larger number of patients with newly diagnosed PAH who are recruited over a longer time; therefore, we will continue to recruit these patients after the first 3000 patients are enrolled.

To identify predictors of outcomes, multivariate Cox proportional hazards regression[8,9] and linear regression models will be used, starting with clinically relevant variables judged to have a biologically plausible association with outcomes. Because the cohort includes patients with both newly and previously diagnosed PAH, methods that account for left truncation (survivor bias) will be used.[10] For example, to estimate the survival curve, a patient who was enrolled 2 years after diagnosis and followed up for 4 years contributes to the estimated hazard from year 2 through year 6 but provides no data about the probability of surviving to 2 years. Thus, the early portion of the survival curve is estimated exclusively from patients with newly diagnosed PAH, whereas patients with previously diagnosed PAH contribute information about the probability of surviving an additional period, conditional on having

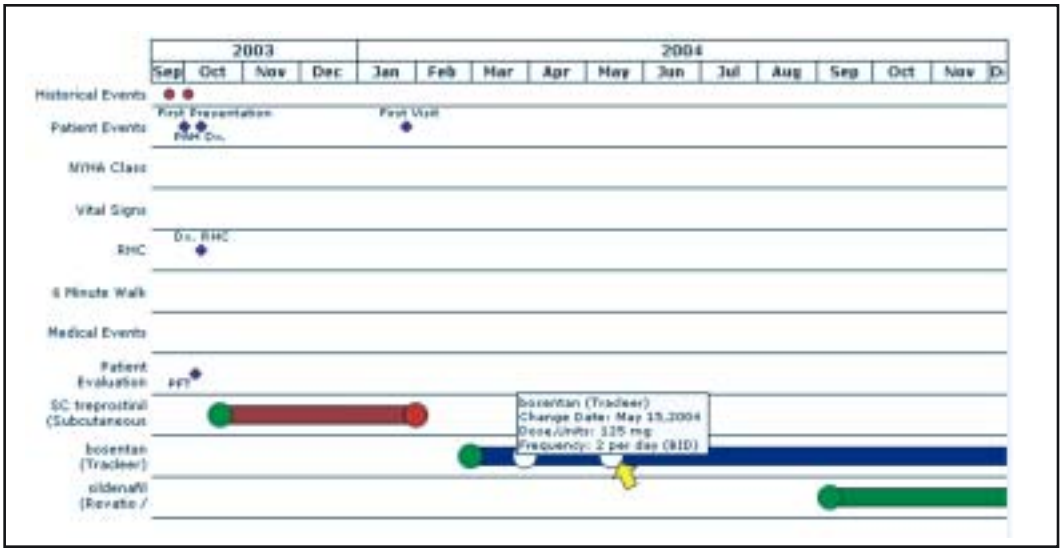

FIGURE 1. Gantt chart illustrating a typical patient's viewable clinical and medication history during an interval from September 10, 2003, to December 10, 2004. Information in the text box appears when cursor hovers over an event circle. Created by MedNet Solutions, Minnetonka, MN. Dx = diagnosis; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PFT = pulmonary function test; RHC = right heart catheterization.

survived for the time since diagnosis. To assess the relationship between medications and outcomes, propensity score methods[11-14] will be used to adjust for the chance that a patient may be given one treatment vs another.

A prespecified set of candidate predictor variables for long-term outcome have been identified from the data collected at baseline and through retrospective evaluation. The primary data used to assess the relationship between medications and outcomes will be collected at initial treatment; however, treatment patterns (including sequential or simultaneous combinations of medications) will also be evaluated. Outcomes will be compared using time-to-event methods and repeated measures models. Analyses will be stratified by patients with newly diagnosed PAH (enrolled in registry ≤3 months after diagnostic RHC) vs those with previously diagnosed PAH (enrolled in registry >3 months after diagnostic RHC). Time-to-event methods and repeated measures models will be used to compare outcomes of patients who meet prespecified traditional hemodynamic criteria for the diagnosis of PAH vs those who do not.

To determine diagnostic stringency, an analysis will be done to determine the extent to which the test data support the clinical diagnosis of PAH; patients diagnosed as having PAH but also having a mean PCWP of more than 15 mm Hg but less than or equal to 18 mm Hg will be included in the analysis. Outcomes will be evaluated longitudinally and compared according to the baseline WHO group I classification. An increasing number of patients who meet all criteria for PAH except for a mean PCWP of more than 15 mm Hg are being referred to PH centers and are being treated with PAH medications. We have included these patients, who were not included in previous registries, in REVEAL to assess their outcomes with PAH treatments. A separate analysis will compare cohorts of patients who do and do not meet the strict quantitative classical definition of PAH according to prespecified hemodynamic criteria (ie, PCWP ≤15 mm Hg vs >15 to ≤18 mm Hg). These analyses will be stratified by timing of PAH diagnosis (newly vs previously diagnosed), by WHO group I classifications, and by hemodynamic criteria.

To report temporal trends in treatments and outcomes for patients with newly diagnosed PAH, the proportion of patients receiving specific treatments within 3 months and within 1 year of diagnosis will be estimated by calendar year of diagnosis. Similarly, event rates in the first year after diagnosis will be estimated by calendar year of diagnosis. Although most outcome analyses will include patients with newly diagnosed PAH and those with previously diagnosed PAH, the temporal trends analyses will focus exclusively on patients with newly diagnosed PAH to distinguish true changes in practice vs cohort effects.

OUTCOMES AND POTENTIAL CONTRIBUTIONS

In keeping with the specified objectives of the study, results will include detailed information about the demo-

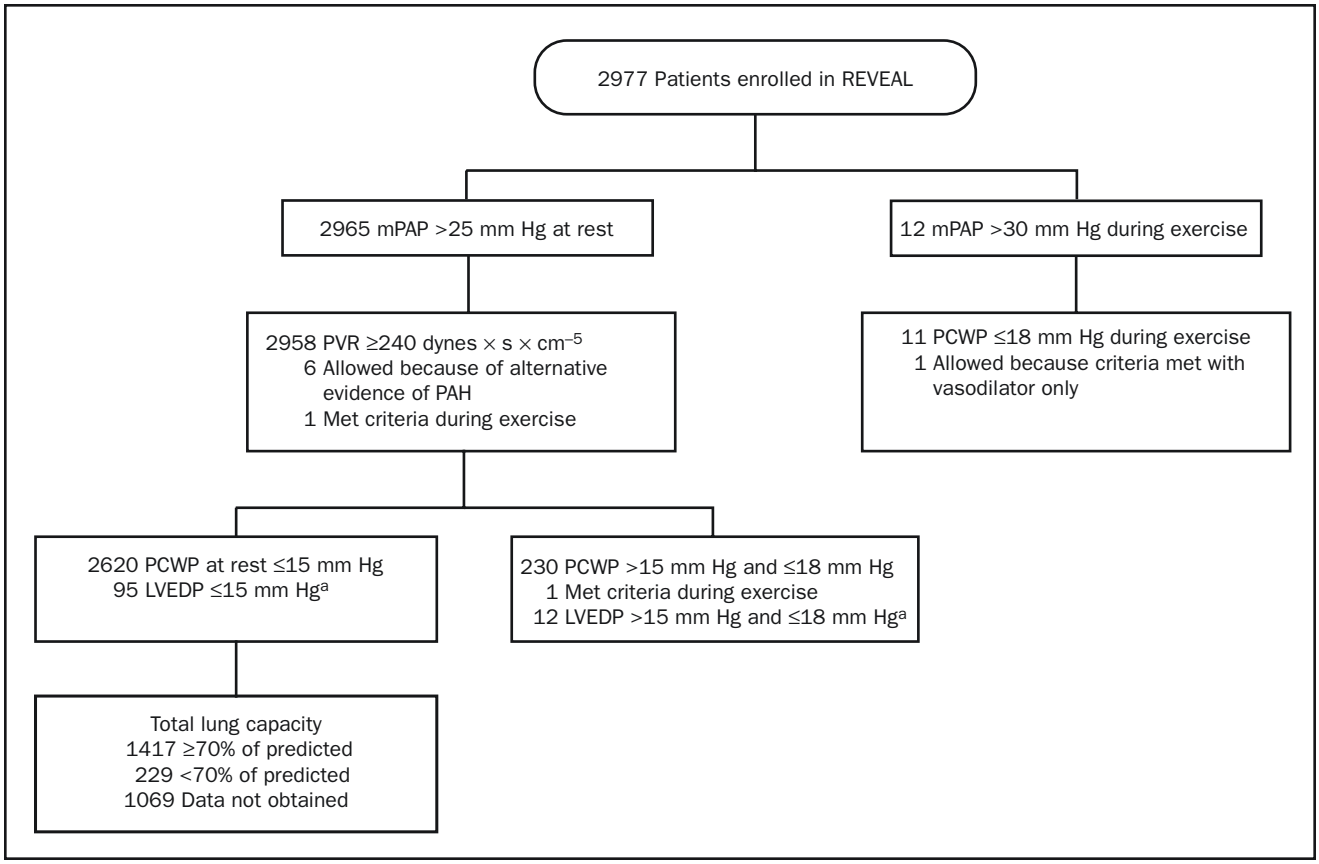

FIGURE 2. Characteristics of the initial 2977 patients enrolled in the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL). LVEDP = left ventricular end-diastolic pressure; mPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance.
[a] For patients with unreliable or unobtainable PCWP, criterion was met by LVEDP.

graphics of patients currently diagnosed as having PAH. Coupled with results of specific diagnostic tests, the demographic data should provide insights into the degree to which clinicians adhere to classically accepted criteria in diagnosing PAH and prescribing therapy. Figure 2 depicts some key baseline characteristics of the 2977 patients enrolled to date and distinguishes between those who meet classical criteria (1417) and those who do not (ie, those without confirmation of absence of pulmonary restriction, with PCWP >15 mm Hg, or with PAH only during exercise). Information should also emerge elucidating constellations of symptoms and coexisting conditions, potentially modifying the diagnosis of PAH and its management. Characteristics of treatment regimens will reveal which practice patterns are used in the 21st century and the extent to which they comply with current recommendations.

Long-term follow-up data will inform us of how baseline characteristics and treatment decisions affect outcomes. The primary outcome for treatment comparisons will be survival. Other outcomes of interest will include time to clinical worsening, functional status, and exercise capacity assessed by the 6-minute walk test.

In contrast to clinical drug development studies, which enroll discrete subpopulations of patients with PH under carefully controlled conditions, REVEAL will incorporate a larger and more diverse population of patients exposed to a wide range of treatments. Current controlled drug studies are challenged by the relatively small number of patients available to participate in the many trials investigating medications and combinations thereof. Studies comparing one treatment approach with another are even more difficult to design or carry out. Consequently, the results of this registry will provide information about the efficacy of treatment strategies that are not likely to be feasibly examined by other methodologies, such as controlled clinical drug studies.

COMPARISON WITH OTHER REGISTRIES

Our ability to understand the nature of PAH and to design appropriate treatment recommendations has been hampered historically by the relative infrequency of the disease and the resulting paucity of participants in clinical studies. Moreover, the geographic distribution of the patients means that no single clinician or institution is likely to see enough patients to develop an accurate comprehension of the disease spectrum or of treatment efficacy and safety. As a result, the definition of PAH is derived from somewhat arbitrary working definitions, such as the enrollment criteria for the NHLBI registry, or is based largely on consensus. In addition, as pharmaceutical options for treatment multiply, treatment regimens have become more complex. Because of the variability of clinical drug studies and the absence of "head-to-head" trials in various subsets (often limited by the number of patients required for comparison trials), decisions about therapy in certain clinical scenarios cannot be evidence based. "Approved" therapies are widely used in conditions that have not been rigorously studied, and "unapproved" and unstudied combinations of medications are used in many patients. REVEAL has been designed to provide data to at least begin to rectify these shortcomings.

An important departure of this registry from previous study designs is its broadening of the enrollment criteria to include some patients who do not satisfy traditional definitions of PAH but who nevertheless frequently present to PH specialists and are treated (rightly or wrongly) as patients with PAH. REVEAL includes patients whose hemodynamics are outside the usual definition of PAH, specifically those who have evidence of a component of pulmonary venous hypertension (mean PCWP, >15 to ≤18 mm Hg). It also includes those who do not exhibit all characteristics of classically defined PAH but are judged by a clinician to meet sufficient clinical criteria to be diagnosed as having PAH. Finally, this prospective registry will gather data on demographics and treatment outcomes for 3500 children and adults with PAH who are similar to those seen routinely in clinical practice. No previous registry has been this large or included such a sizable number of pediatric patients

The importance of this approach cannot be overstated. The effect of this liberalized definition of PAH on treatment outcomes could help us identify which patients should receive treatment and determine which treatments are the safest and most beneficial. Indeed, increasing the inclusiveness of enrollment may permit a pivotal redefinition of PAH itself. If responsiveness to treatment does not appear to vary between "classic" PAH and PAH as more liberally defined in the registry, then serious consideration should be given to adjusting the definition.

The differences between REVEAL and other major registries[1-6,15] are illustrated by the entry criteria shown in Table 4. The NHLBI's Patient Registry for the Characterization of Primary Pulmonary Hypertension[1,2] enrolled fewer than 200 patients who were diagnosed as having primary pulmonary hypertension (now called PAH) at 32 US clinical centers between July 1, 1981, and December 31, 1985, and were followed up through August 8, 1988. Demographic data and measurements of hemodynamic variables, pulmonary function, and gas exchange variables were obtained at baseline. Patients were followed up at 6-month intervals for survival. Thus, the NHLBI registry provides survival data for IPAH alone (but not for other outcomes or for PAH associated with other conditions) at a time when the standard of care did not include current approved PAH therapies.

In France, 674 consecutive patients with PAH seen between October 2002 and October 2003 at 17 university hospitals were enrolled in a registry.[3] Baseline and 1-year survival results were recently reported, and the planned period of follow-up is 3 years.

In China, a registry was established of patients with IPAH and familial PAH.[4] From 1999 to 2004, 72 patients were enrolled in the study and had their demographic, clinical, and hemodynamic data recorded. The registry will be used to study outcomes in patients treated only with conventional medications (diuretics, digoxin, calcium channel blockers, oxygen, and oral anticoagulants) because the newer PAH-approved pharmacotherapies were not readily available.

A retrospective registry collected data from 5 centers in Switzerland.[15] Data from 106 patients with severe PH (New York Heart Association class III or IV) were analyzed up to December 1999. Pulmonary hypertension was defined as mean pulmonary arterial pressure of greater than 25 mm Hg at rest. Clinical and hemodynamic parameters from RHC were collected, as well as age at diagnosis and patients' treatments.

Several registries were established to document any association between PH and previous exposure to anorexigens. The SNAP study gathered data from patients seen from September 1, 1996, to December 31, 1997, at 12 referral centers in North America.[5] The study included 579 patients: 205 with IPAH and 374 with secondary PH. The objective of the study was to follow up the patients prospectively and to document their exposure to medications, particularly anorexigens. Patients with secondary PH were to serve as controls for the patients with IPAH. The SOPHIA working group was established to detect changes in the incidence of PAH, to characterize patients with primary (now referred to as idiopathic PAH) vs noncardiac secondary PH (now classified as group III-V

TABLE 4. **Patient Inclusion and Exclusion Criteria of Major PAH Registries**[a]

Reference, dates of patient enrollment	Inclusion criteria	Hemodynamic parameters	Exclusion criteria
REVEAL, current, March 1, 2006-September 30, 2007	Consecutive infant, adolescent, or adult patients newly or previously diagnosed as having WHO group I PAH at 54 participating US institutions	Documented by RHC anytime before study enrollment mPAP >25 mm Hg at rest *or* mPAP >30 mm Hg with exercise *and* PCWP ≤18 mm Hg *and* PVR ≥240 dynes × s × cm^{-5}[b]	Not meeting inclusion criteria
NHLBI registry,[1,2] July 1, 1981-December 31, 1985	Patients (>1 y) diagnosed as having PPH (corresponding to IPAH) at 32 US clinical centers	mPAP >25 mm Hg at rest *or* mPAP >30 mm Hg with exercise	Not meeting inclusion criteria
National French registry,[3] October 2002-October 2003	Consecutive patients (≥18 y) newly or previously diagnosed as having WHO group I PAH (excluding PVOD and PCH) at 17 French university hospitals	mPAP >25 mm Hg at rest *and* PCWP <15 mm Hg at RHC	Known severe pulmonary function abnormalities (defined as PFT results for FVC, TLC, or FEV_1 <60%)
Swiss registry[15]	Retrospective data collection from patients presenting before 1999 with PH and no identifiable cause at 4 Swiss university centers and 1 defined geographical area	mPAP >25 mm Hg at rest	Secondary causes of PH
SNAP registry,[5] September 1, 1996-December 31, 1997	Every patient presenting to 12 participating centers in North America with an RHC-confirmed diagnosis of PAH	mPAP >25 mm Hg *or* invasive or echocardiographic PASP >40 mm Hg	Evidence of heart disease on the left side or valvular heart disease
SOPHIA registry,[6] January 1998-June 2001	Every patient (≥18 y) presenting to 13 participating centers with a new RHC-confirmed diagnosis of PAH	Not stated	Evidence of heart disease on the left side or PCWP >15 mm Hg
Chinese registry[4] 1999-2004	Consecutive patients with idiopathic and familial PAH at 2 Chinese hospitals	mPAP >25 mm Hg *or* echocardiographic RVSP >40 mm Hg	Not stated

[a] FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary arterial pressure; NIH = National Institutes of Health; PAH = pulmonary arterial hypertension; PASP = pulmonary artery systolic pressure; PCH = pulmonary capillary hemangiomatosis; PCWP = pulmonary capillary wedge pressure; PFT = pulmonary function test; PH = pulmonary hypertension; PPH = primary pulmonary hypertension; PVOD = pulmonary veno-occlusive disease; PVR = pulmonary vascular resistance; REVEAL = Registry to Evaluate Early and Long-term PAH Disease Management; RHC = right heart catheterization; RVSP = right ventricular systolic pressure; SNAP = Surveillance of North American Pulmonary Hypertension; SOPHIA = Surveillance of Pulmonary Hypertension in America; TLC = total lung capacity; WHO = World Health Organization.

[b] To convert to Wood units, divide by 80.

pulmonary hypertension), and to determine whether any associations exist between PH and various drugs, including anorexigens.[6] Between January 1998 and June 2001, 1335 patients newly diagnosed as having PH at 13 tertiary PH centers were enrolled. Patients were required to have objective evidence of PH from an RHC performed at a SOPHIA center. The study looked only at rate of new diagnoses of PH, not at long-term outcomes.

The trial design of REVEAL directly addresses a number of challenges common to observational studies. First, because our study enrolls existing patients, it runs a substantial risk of survivor bias because no observation can be made about patients who do not survive long enough to enroll. Therefore, our results will be most useful for direct comparisons with patients who currently have PAH, both those in whom the disease has been recently diagnosed and those who have been living with the disease for many years. To validate the results for patients with newly diagnosed PAH, we will perform subset analyses, which have inherently weaker power due to smaller sample sizes. Patients who have survived with the disease for an extended period will be represented in the registry to a greater degree than one would expect from a random sample of patients with newly diagnosed PAH. Therefore, our results may not be entirely generalizable to patients with undiagnosed PAH or to patients who have not yet been referred to a PH practice.

Second, the same test results will not be available for all patients at the same time points, and some patients will have no follow-up testing. Furthermore, due to patient participation in blinded studies, there will be gaps in the data. The inclusion of patients participating in open-label studies results in a seminaturalistic approach because inclusion of these patients reflects real-world practice patterns in PAH (ie, many patients with PAH are enrolled in clinical trials). However, it is well appreciated that patients

enrolled in clinical trials may receive better overall care than those who are not. Patients' follow-up schedules may not be completely naturalistic because they are dictated by open-label trial protocols; however, including protocol-mandated visits is the only way to obtain an appropriately broad and representative picture of today's PAH practices.

CONCLUSION

With an enrollment of approximately 3500 adults and children, REVEAL promises to be the richest source of data in the world on WHO group I PAH, enabling the collection of information on demographics, treatments, and outcomes.

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