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CONSENSUS STATEMENT

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Real-world evidence to advance knowledge in pulmonary hypertension: Status, challenges, and opportunities. A consensus statement from the Pulmonary Vascular Research Institute's Innovative Drug Development Initiative's Real-world Evidence Working Group

Kellie Morland[1] | **Christian Gerges**[2] | **Jean Elwing**[3] | **Scott H. Visovatti**[4] | **Jason Weatherald**[5] | **Kari R. Gillmeyer**[6,7] | **Sandeep Sahay**[8] | **Stephen C. Mathai**[9] | **Athénaïs Boucly**[10,11,12] | **Paul G. Williams**[13] | **Sivadasanpillai Harikrishnan**[14] | **Evan P. Minty**[15] | **Lukas Hobohm**[16,17] | **Arun Jose**[3] | **Roberto Badagliacca**[18] | **Edmund M. T. Lau**[19,20] | **Zhi-Cheng Jing**[21] | **Rebecca R. Vanderpool**[4] | **Charles Fauvel**[22] | **Jose Leonidas Alves Jr.**[23] | **Geoff Strange**[24] | **Tomas Pulido**[25] | **Junyan Qian**[26] | **Mengtao Li**[26] | **Valentina Mercurio**[27] | **Jason G. E. Zelt**[28] | **Victor M. Moles**[29] | **Meghan M. Cirulis**[30,31] | **Sylvia M. Nikkho**[32] | **Raymond L. Benza**[33] | **C. Gregory Elliott**[30,31]

Correspondence
Kellie Morland
Email: kmorland@unither.com

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Abstract

This manuscript on real-world evidence (RWE) in pulmonary hypertension (PH) incorporates the broad experience of members of the Pulmonary Vascular Research Institute's Innovative Drug Development Initiative Real-World Evidence Working Group. We aim to strengthen the research community's understanding of RWE in PH to facilitate clinical research advances and ultimately improve patient care. Herein, we review real-world data (RWD) sources, discuss challenges and opportunities when using RWD sources to study PH populations, and identify resources needed to support the generation of meaningful RWE for the global PH community.

KEYWORDS
administrative claims data, electronic health records, patient-generated health data, real-world data, registries

For affiliations refer to page 14.

INTRODUCTION

Traditional randomized clinical trials (RCTs) are recognized as powerful tools for developing scientific evidence regarding therapeutic interventions. RCTs guide regulatory approval of new drugs and devices, and they are the foundation of clinical guidelines. Yet RCTs recruit highly selected populations and manage them in controlled settings, which makes it difficult to generalize the results of RCTs to larger, diverse populations encountered in clinical practice.[1] Increasingly, clinicians, regulators, payers, and the pharmaceutical industry recognize the utility of real-world evidence (RWE) to complement the knowledge gained from RCTs.[2]

Recent legislation and regulatory mandates have accelerated RWE generation.[3,4] In the United States (US), the 21st Century Cures Act, passed by Congress in 2016, required the Food and Drug Administration (FDA) to develop a framework for evaluating RWE to support drug approval and postapproval evaluations. In response, the FDA has based several drug approvals on RWE.[5,6] Similarly in Europe, the European Medicines Agency (EMA) has advocated for the use of RWE in regulatory decision making and has accepted RWE when evaluating new marketing authorization applications and extensions of indications.[7]

Since the First World Symposium on Pulmonary Hypertension (WSPH) convened in 1973, the understanding of pulmonary hypertension (PH) and, more recently, disorders grouped in the clinical classification of pulmonary arterial hypertension (PAH), have benefited greatly from RCTs and analyses of real-world data (RWD). RCTs provided the evidence necessary for regulatory approval of 15 PAH-specific medications. RWD fueled the derivation and validation of risk stratification tools[8,9] used to assess patients diagnosed with PAH, and RWD provided the key data for current treatment guidelines for PAH patients who show vasoreactivity at the time of a diagnostic right heart catheterization.[10,11] Similarly, RWD from registries yielded additional insights into the safety, side effects, and efficacy of PAH-specific medications not identified during RCTs.[12] Analyses of RWD also provided an understanding of the natural history, epidemiology, healthcare delivery practices, quality of life, and long-term outcomes related to large and diverse PAH patient cohorts over decades.[13–19]

It is against this backdrop that we explore the continuing role that RWD plays in our understanding of PH. In the sections that follow, we review RWD sources, discuss challenges and opportunities when using RWD sources to study PH populations, and identify resources needed to support the generation of meaningful RWE for the global PH community.

DEFINITIONS AND DATA SOURCES

RWE is clinical evidence regarding the use and potential benefits or harms of an intervention derived from the analysis of RWD (Table 1). RWD is defined as information relating to patient health status or healthcare delivery that is routinely collected through a wide variety of sources. For this discussion, we limit ourselves to the main data sources defined by regulatory authorities: administrative claims data, electronic health records (EHRs), registries, and patient-generated data outside of clinical trials.[2,3] Appropriate analysis of RWD requires a fundamental understanding of the purpose and strengths and weaknesses of the varied sources of RWD (Table 2).

Administrative claims data

Administrative claims data are generated within a healthcare system to reimburse medical services. Every patient encounter generates claims data that include diagnostic and procedural codes for services rendered in inpatient and outpatient settings and pharmacy dispensing data. Because these data are generated for billing and not patient care, administrative claims lack important clinical, laboratory, and functional health information that are relevant for analyzing populations. Furthermore, coding included on claims for reimbursement purposes may not always reflect the medical condition of a patient. Despite these limitations, claims data provide an opportunity to evaluate morbidity related to procedures, medical treatments, and other healthcare resource utilization.[22–25] In some countries, population-level vital statistics registries can also be linked to claims databases or to other RWD sources using unique identifiers, which can permit mortality analyses.[26–29] Claims data also provide large sample sizes with longitudinal follow-up to generate RWE related to adherence to medical care plans. Moreover, claims data may contain information on practice patterns not captured by other sources of RWD.

EHRs

EHRs represent longitudinal data in an electronic format that are collected during the routine delivery of healthcare. EHRs capture a broad group of patients, and EHRs are widely available in developed countries.[22,24,30–32] Furthermore, a patient's EHR often includes data from all facets of their inpatient and outpatient care, including laboratory results, medication records, pathology reports, procedures, and clinical notes. As such, EHRs allow a very

TABLE 1 Definition of RWD and RWE by FDA and EMA.

FDA[20]	EMA[21]
RWD: Data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources	**RWD**: Routinely collected data relating to a patient's health status or the delivery of healthcare from a variety of sources other than traditional clinical trials
RWE: Clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD	**RWE**: Information derived from analysis and/or synthesis of RWD

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration; RWD, real-world data; RWE, real-world evidence.

granular examination of a patient's medical profile. However, since the primary intent of EHR data is to facilitate individual patient management rather than research, missing data remains a limitation of EHRs.

Registry data

Patient registries are collections of data for a group of people who share a common characteristic (e.g., PAH).[33] Patient registries capture clinical data uniformly over time to evaluate the incidence and prevalence, demographics, and outcomes of real-world patients with the condition of interest. Patient registry cohorts are large and generally more diverse than populations enrolled in RCTs, but registry data are uncontrolled and observational. Consequently, registry data may be biased by patient selection and reporting, missing data, and analytic errors.

Patient-generated health data (PGHD)

PGHD are created, recorded, or gathered by or from patients. Examples of PGHD include biometric data[34] obtained from wearable or implantable devices and data gathered from social media. While medical use of data from social media is limited, use of biometric data generated from wearable and implantable devices has garnered much attention, stimulated, in part, by the need for remote monitoring during the COVID pandemic.

Advances in digital technology created a plethora of PGHD from wearable devices such as smartwatches and activity trackers. These personal wearables capture important biometric data, including heart rate, ECG, oxygen saturation, sleep quality, and step count/activity, which may provide a more comprehensive picture of patients than episodic measurements made in clinics and hospitals. A recent review describes (1) wearable devices and associated machine learning (ML) techniques, (2) research studies that have investigated the role of wearable devices in the early detection and treatment of cardiovascular conditions (e.g., atrial fibrillation or heart failure), and (3) some of the challenges and opportunities related to the use of PGHD from wearable devices.[35]

Although noninvasive biometrics generate a wealth of data, the use of these data remains limited by several concerns. For example, the tendency of individuals to modify their behavior when they are being observed (the Hawthorne effect) may limit the value of biometric data collected from wearables and other readily visible sources. Biometric data from implantable devices may overcome the Hawthorne effect, but implantable devices introduce risks that must be counterbalanced by clear clinically relevant benefits.[36]

Regional and global resource disparities also limit the value of PGHD. Many sources of biometric RWD require access to expensive devices and platforms, such as devices paired with smartphones, reliable internet access, and a stable power grid, which are widely available in resource-rich regions but are not feasible or practical for implementation in resource-poor environments, introducing systemic bias to the collection of these data.

GENERAL CHALLENGES WHEN UTILIZING RWD

There are general challenges related to the utilization of RWD.[22,23,30,31] RWD are often large, difficult to locate and access, and potentially cost-prohibitive to process and use. EHR data are the most resource-intensive source of RWD with respect to data extraction, curation, and validation. Investigators may require data engineering and analysis resources to clean and restructure data from source systems, engineer features through methods like natural language processing (NLP), and implement analytic methods that scale effectively to process large heterogeneous data sets. These steps can significantly inflate the total costs of RWD acquisition and utilization.[37] Furthermore, legal, regulatory, and financial barriers may limit the availability and use of some of the largest sources of EHR and claims data

TABLE 2 Summary of RWD sources.

Data source	Description	Data elements	Advantages	Disadvantages
Administrative claims	• Retrospective and longitudinal clinical and economic outcomes data at the patient level intended for reimbursement purposes	• Clinical diagnosis (ICD-9/ICD-10 codes) • Patient encounters • Medications • Procedure information (CPT codes)	• Large and diverse populations • Typically contain information on diagnoses, procedures, and treatments that may not be captured elsewhere	• Nonrandomized • Developed for reimbursement; may not accurately capture population or outcomes of interest
Electronic health records	• Structured and unstructured data intended to document patient care	• Laboratory tests • Detailed clinical data collected during patient encounters and procedures	• Large patient populations with extensive clinical data	• Unformatted • Unstandardized • Often incomplete • Limited availability in low- and middle-income countries
Registries	• Observational, retrospective, and/or prospective cohort data	• Limited by the data elements that are included/excluded and the availability of data	• Large and diverse populations • Often longitudinal and specific to disease of interest	• Risk of bias in patient selection, reporting, and missing data • Failure to include diverse sites as enrollment limits generalizability
Patient-generated health data	• Generated by the patient outside of medical settings	• Many data points across time frames of data capture	• Unique RWD not typically captured elsewhere	• Clinical utility is incompletely defined • Concern for Hawthorne effect to modify biometric data • Resource availability may affect access to biometric data

Abbreviations: CPT, Current Procedural Terminology; ICD, International Classification of Diseases; RWD, real-world data.

(e.g., Veterans Administration database, Centers for Medicare & Medicaid Services). Without pre-existing agreements or significant financial resources, it remains difficult to obtain and utilize RWD from large national sources of RWD, a limitation not unique to the US.[38,39]

Regulations and laws concerning the acquisition, transfer, and utilization of RWD differ.[22–25,30–32,39] These regulations and laws can have significant implications for the use of RWD. For example, the types of RWD available to researchers and the rules governing the use of these data differ markedly between countries, particularly for informed consent, opt-in versus opt-out of data collection, and anonymization. Such differences in national regulations and laws impair the integration of RWD from multiple national sources.

A related concern involves data privacy and patient rights, as RWD often contains personal health information that may not be adequately anonymized, creating a conflict between data transparency and patient privacy. Concerns regarding patient privacy, data security, and disclosure of sensitive health information not only affect the acquisition and use of RWD but also vary across geographic locations.

One final challenge relates to the lack of standardization of data formats.[22–25,31,32] This lack of standardization significantly complicates the ability to share, integrate, and analyze RWD. Further compounding the problem, many sources of RWD are electronic, and they are acquired on unique proprietary platforms that compete directly in free markets. Competing proprietary platforms often limit or actively discourage effective communication with one another. The lack of harmonization between different RWD sources, combined with heterogenous standards for data entry and formatting, is currently the greatest challenge in the use of RWD.

Fortunately, the US federal government recently took an important step to address the challenge of standardization. The Office of the National Coordinator for Health Information Technology issued a regulation that addressed both the technical obstacles and the economic problems caused by the competitive nature of the US healthcare system. The regulation requires providers to share EHRs, and it provides stiff financial penalties as consequences for EHR vendors and health information networks that obstruct information exchange. Similar initiatives are underway to allow for EHR interoperability across the European Union.[40,41] Even with these steps to advance standardization in Europe and the US, adoption of global standards for RWD is likely years away.

CHALLENGES WHEN UTILIZING RWD TO STUDY PH

There are several unique challenges to consider when using RWD to study PH. First, the diagnosis of PH requires accurate measurement of pulmonary hemodynamics during right heart catheterization. These measurements are fundamental for the physiologic classification of PH.[42] Misclassification of PH diagnoses remains a common problem, and RWD sources such as EHRs are not designed to assess the quality and accuracy of hemodynamic data.

Second, definitions of PH and pulmonary vascular disease (PVD) have evolved.[10,43,44] PH was once diagnosed when right heart catheterization confirmed a mean pulmonary artery (PAmean) pressure of at least 25 mmHg. In 2018, the Task Force on Hemodynamic Definitions of the sixth WSPH modified this definition to include patients with a PAmean pressure >20 mmHg. Another revised definition accompanied the 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines for the Diagnosis and Treatment of PH wherein the definition of PVD was changed from a pulmonary capillary wedge pressure (PCWP) ≤15 mmHg with a pulmonary vascular resistance (PVR) ≥3 Wood units to a PCWP ≤15 mmHg with PVR ≥2 Wood units.[45] These changes in the definitions challenge investigators who collect and analyze RWD to study PH and PVD.

Third, the clinical classification of PH based on RWD remains challenging. The classification of PH has evolved from the early differentiation of PH into primary PH and secondary PH to the current World Health Organization (WHO) clinical classification of PH. These changes in the clinical classification require investigators to make careful adjustments when analyzing and reporting data, as illustrated by Frost et al.[46] Furthermore, the nonspecific signs and symptoms of PH and the presence of related comorbidities, such as chronic obstructive pulmonary disease or chronic pulmonary emboli, challenge analysis of patients with PH because these patients often have mixed causes of PH. In the PVDOMICS study, preliminary analysis showed that over a third of patients had mixed causes of PH and could not be assigned to a single WSPH group.[47]

Fourth, the diagnostic tests required to establish the clinician's classification of PH may confound investigators seeking to use RWD for the study of PH. Several tests are recommended in addition to diagnostic right heart catheterization, including ventilation and perfusion lung scans, high-resolution chest computed tomography, pulmonary function tests, and infectious and immunologic tests, to identify potential etiologies of PH. A survey

of centers in the US showed that guideline-recommended tests were often not completed.[48] Outside of the US, resource disparities, operator preference, and even social and cultural attitudes surrounding certain tests (e.g., blood testing for human immunodeficiency virus [HIV] or hepatitis C virus is stigmatized in certain regions of the world) may foster incomplete evaluation of PH.

Recent efforts to study PAH have exposed several of these challenges for the use of RWD. A study to estimate the global prevalence, incidence, and mortality of PAH reported a 175-fold variation in the estimated incidence and a 40-fold difference in the estimated prevalence of PAH across 37 countries.[49] While these differences may exist in part due to local/regional factors, such as the higher prevalence of methamphetamine use-related PAH in the Western world and the higher prevalence of congenital heart disease-related PAH in developing countries, the authors concluded that no known risk factor was of sufficient strength to explain this extreme variability. Rather, these variations occurred due to a lack of a generalized approach to the diagnosis and classification of PAH.

CURRENT STATUS OF RWD IN PH AND OPPORTUNITIES FOR IMPROVEMENT

Administrative claims data

It is well documented that the use of administrative claims data in a PH population is primarily limited by challenges related to aligning the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) diagnostic codes with the five clinical classification groups of the WSPH.[50] Several algorithms have been developed to improve discrimination of patients with PAH in claims data.[50–52] A systematic review of PAH algorithms concluded that ICD codes alone performed poorly, with positive predictive values ranging from 3.3% to 66.7%.[50] Algorithms that are multicomponent and include the presence of PAH medications, diagnostic codes, and procedural codes improve performance.[50,52,53] The development and validation of algorithms outside of Group 1 PH are especially challenging in part because therapies approved for the treatment of PAH are used on and off-label for the treatment of other PH groups (e.g., PH in interstitial lung disease, chronic thromboembolic pulmonary hypertension [CTEPH]). Compounded with the lack of specificity in diagnostic codes, researchers are limited in their ability to discriminate patients within the five clinical classification groups in claims data. While some attempts have been made to develop algorithms for Groups 3 and 4 PH,[54,55] additional work is needed and validation through medical record review will be required. Further, an opportunity may exist for clinical experts to define the standards for coding in their specialty by collaborating with the standard-setting organizations.

EHRs

The granular nature of EHRs has provided several areas of opportunity for PH researchers. As one example, EHRs can be used to evaluate prescribing patterns and clinical monitoring of patients with Group 3 PH, as demonstrated by Johnson et al.[56] Perhaps the most exciting opportunity for EHRs lies in the application of ML techniques to better identify PH populations. In a multistage ML experiment, Schuler et al. demonstrated that the successive application of random forest models can be used in combination with human validation to create clean training cohorts of patients with PAH that were large enough to train ML-based case definitions.[57] Furthermore, Schuler et al. demonstrated that these definitions could be applied to an EHR database to create cohorts that identify additional patients with known risk factors for PAH.[57] This highlights the possibility that such approaches could be used to find PAH further upstream in the diagnostic process and more effectively create site-based registries. Given the different clinical care processes that might exist at each site, such algorithms may not be generalizable to all expert PH centers.

Registry data

Among RWD sources available to investigators, national PH registries have contributed the most RWE (Table 3), particularly for patients diagnosed with PAH or CTEPH. In the 1980s, the US National Institutes of Health Primary Pulmonary Hypertension (PPH) Registry established the natural progression of PPH (primarily idiopathic PAH [IPAH] and heritable PAH) in an era preceding the advent of PAH-targeted therapies.[58,59] Subsequently, RWD generated from thousands of patients enrolled in PH registries around the world provided crucial long-term epidemiologic data,[8,60–62] including the identification of a significant increase in median survival from 2.8 years at the end of the 20th century to more than 7 years in a more contemporary treatment era.[14,58] RWD also changed the early belief that IPAH (formerly known as PPH) develops primarily

TABLE 3 PH registries.

Registry (reference)	Study cohort/eligible age[a]	Duration and study design	Number of centers[b]	Number of patients[c]
NIH registry[58,59]	IPAH and HPAH, age >6 months	1981–1985, prospective	32	187
US PHC[68,69]	Group 1 PH, age ≥18 years	1982–2004, retrospective 2004–2006, prospective	3	578
Scottish-SMR[70]	Group 1 PH (IPAH, CHD-PAH, and CTD-PAH), age 16–65 years	1986–2001, retrospective	N/A	374
Netherlands[71]	All PH groups, children	1991–2005, retrospective	2	3263
Gi-PH-Reg[72]	All PH groups	1993–2011, prospective	1	2067
Mayo Clinic[73]	Group 1 PH, age ≥18 years	1995–2004, prospective	1	484
Israel[74]	All PH groups, age 16–90 years old	1998–2005, prospective	1	191
Spanish (REHAP)[75]	Group 1 PH and group 4 PH, age ≥14 years	1998–2006, retrospective 2007–2008, prospective	31	1028
Slovakia[76]	Group 4 PH	1998–2014, retrospective	1	81
Switzerland[77,78]	All PH Groups	1999–2012, prospective	13	996
Chinese-1[79]	IPAH and HPAH	1999–2004, prospective	1	72
Chile[80]	Group 1 PH	1999–2005, prospective	2	17
Czech Republic[81]	PAH, age ≥18 years	2000–2006, retrospective 2007, prospective	Four diagnostic centers + a national network of echocardiographic center	191
Swedish (SPAHR)[82,83]	Group 1 PH and group 4 PH, age ≥18 years	2000–2008, retrospective 2008–ongoing, prospective	7	640
The United Kingdom and Ireland[84]	IPAH, HPAH, and anorexigen-associated PAH	2001–2009, prospective	8	482
ASPIRE[85]	All PH groups	2001–2010, prospective	1	1344
French[13,86]	Group 1 PH, age ≥18 years	2002–2003, prospective	17	674
Chile[87]	Group 1 PH and Group 4 PH	2003–2005, prospective	1	29
Argentina[88]	Group 1 PH	2004–2012, prospective	1	134
France[89]	All PH groups, children	2005–2006, prospective	21	50
China-pSS-PAH[90]	Primary Sjogren's syndrome-associated PAH	2005–2014, retrospective 2014–2017, prospective	9	103

(Continues)

TABLE 3 (Continued)

Registry (reference)	Study cohort/eligible age[a]	Duration and study design	Number of centers[b]	Number of patients[c]
US REVEAL[14,60,91]	Group 1 PH, age ≥3 months	2006–2009, prospective	55	3515
China-SLE-PAH[92]	Systemic lupus erythematosus-associated PAH	2006–2016, prospective	14	310
Chinese-2[93]	IPAH and CTDPAH	2007–2009, retrospective	5	276
Latvia[94]	Group 1 PH and group 4 PH, age ≥18 years	2007–2016, prospective	1	174
COMPERA[15,95,96]	All PH groups	2007–ongoing, prospective	41	10910[b]
Portugal[97]	Group 1 PH and group 4 PH, age >18 years	2008–2010, prospective	5	79
South Korea (KORPAH)[98]	Group 1 PH	2008–2011, prospective	35	625
Japan (JAPHR)[99]	Group 1 PH	2008–2013, prospective	8	189
Brazil[100]	Group 1 PH	2008–2013, retrospective	1	178
Columbia[101]	Group 1 PH, ≥18 years	2008–2014, retrospective	5	398
TOPP[102]	Group 1 PH, aged ≥3 months and <18 years	2008–2015, prospective	33	531
Spain (REHIPED)[103]	All PH groups, children	2009–2012, prospective	21	225
China-CTEPH[104,105]	Group 4 PH, age 14–85 years	2009–2018, prospective	18	593
Argentina (HINPULSAR)[106]	Group 1 PH	2010–2011, prospective	31	124
Egypt[107]	Group 1 PH and Group 4 PH, adults >18 years	2010–2016, prospective	1	65
PAPUCO Study[108]	All PH groups	2011–2014, prospective	9	220
Indonesia (COHARD-PH)[109]	Congenital heart disease-related PH, ≥18 years	2012–2019, prospective	1	411
Argentina (RECOPILAR)[110]	All PH groups, age >3 months	2014–2016, prospective	Multicenter across 23 provinces	627
PPHNet[111]	All PH groups, age <18 years	2014–2020, prospective	8	1475
Ukraine[112]	Group 1 PH and Group 4 PH, age ≥18 years	2014–2018, prospective	1	281
India (KERALA)[113–115]	All PH groups, age >18 years	2015–2016, prospective	50	2003
Mexico (REMEHIP)[116,117]	Group 1 PH and Group 4 PH, age >2 years	2015–2017, prospective	23	796
USPHSR[118]	Group 1 PH, age ≥18 years	2015–2018, prospective	15	499
United Arab Emirates (UAEPH)[119]	All PH groups	2015–2021, retrospective	1	164
PHAR[120–123]	Group 1 PH and Group 4 PH, all ages	2015–ongoing, prospective	69	1200[d]

TABLE 3 (Continued)

Registry (reference)	Study cohort/eligible age[a]	Duration and study design	Number of centers[b]	Number of patients[c]
Poland (BNP-PL)[124]	Group 1 PH	2018, prospective	21	970
Poland[125]	Group 1 PH and Group 4 PH, children	2018, prospective	8	87
PVRI GoDeep[126]	All PH groups	2020–ongoing, retrospective and prospective	8, global	15,742[e]

Abbreviations: CHD, congenital heart disease; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; N/A, not applicable; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PAPUCO, Pan African Pulmonary Hypertension Cohort; PPHNet, Pediatric Pulmonary Hypertension Network.

[a]Eligible age is noted for those registries that list specific age criteria in the methodology section of the referenced publications.

[b]The number of centers enrolling patients may change over time for those registries that are ongoing.

[c]Unless otherwise indicated, the number of patients reflects the population reported in the initial publication of the registry data; subsequent publications may have different patient counts reflecting changes in enrollment over time.

[d]Reflects population reported in a March 2022 article; as the registry is ongoing, the patient count will continue to change.

[e]Reflects population reported on the website as of May 2022; as the registry is ongoing, the patient count will continue to change.

in young women without comorbidities[46] by showing that IPAH also affects older women and men with cardiovascular comorbidities.[16,63] RWD from PH registries also were instrumental in the derivation and validation of PAH risk assessment tools that are now emphasized in guidelines for the treatment of PAH,[45,64] including the ESC/ERS, the French or COMPERA 2.0 noninvasive method, and the US REVEAL 2.0 and REVEAL Lite scores.[9,45,65–67]

Although the majority of registry data describe populations of adult PH patients, pediatric registries of patients with PH have provided important insights into the nature and natural history of PH in children.[103,111,127] These registries have shown the importance of PH caused by lung disorders in children. One contemporary pediatric registry, the Pediatric Pulmonary Hypertension Network (PPHNet) Registry, reported that PH due to lung disorders such as bronchopulmonary dysplasia constituted more than one-half of the registry population.[111]

Registry data also create opportunities to enrich current and future PAH clinical trials.[128] Event-driven primary endpoints are increasingly used in PAH clinical trials, substantially increasing the size, duration, and cost of these trials. The FDA has advocated the use of prognostic enrichment of event-driven clinical trials by preselecting a patient population with an increased likelihood of experiencing the trial's primary endpoint. Risk assessment tools, derived from RWD, identify patients who are likely to experience a clinical worsening event for trial enrichment.

RWD from PH registries have also allowed the analysis of treatment patterns within risk groups, retrospective validation of guidelines, and generation of innovative and often complex treatment strategies for future RCTs.[129,130] For example, a retrospective analysis of French registry data suggested a benefit of initial combination therapy in intermediate-risk, but not low-risk, patients diagnosed with PAH.[129] Furthermore, analysis of data from French referral centers suggested that initial triple-combination therapy, including a parenteral prostanoid, was associated with improved survival in treatment-naïve patients at high risk for mortality,[129] in line with a previous RWD pilot study.[131]

In addition to the contributions of past and current registries, more work is needed to address the paucity of registry data in regions with limited resources. As illustrated by investigators in sub-Saharan Africa and South America,[132,133] alternative algorithms to identify disease may be required. Nevertheless, investigators have already provided important data to allow the international community to better understand unique challenges and opportunities to advance the diagnosis

and treatment of PH in regions with limited resources.[108,134,135] For example, the Pan African Pulmonary Hypertension Cohort, a multinational registry of 254 consecutive patients diagnosed with PH from nine centers in four African countries, describes baseline characteristics and three-year survival of an HIV-infected cohort newly diagnosed with PH and identifies the common concurrence of chronic lung disease (tuberculosis) and hypoxia with HIV-associated PAH.

More work is also needed to provide data from registries that enroll patients diagnosed with Groups 2, 3, and 5 PH, as well as PH due to a combination of disorders (e.g., chronic lung disease and chronic pulmonary embolism).

To further address these unmet needs, the Pulmonary Vascular Research Institute (PVRI) established the Global Deep Phenotyping PH Meta-Registry (PVRI-GoDeep; NCT05329714). PVRI-GoDeep is poised to become a global hub and RWD mart for PH research. This meta-registry is expected to encompass >25,000 patients with PH spanning all continents, offering rare geographical and ethnic profiles of patients affected by PH. The architects of GoDeep developed a strategy a priori to address the global disparities in PH epidemiologic data, employed a standardized framework and strict diagnostic criteria, and leveraged multiple EHR data sets to create a large, robust source of PH RWD. Although PVRI-GoDeep investigators faced multiple challenges (Table 4), the ongoing success of PVRI-GoDeep demonstrates how careful planning can effectively overcome many challenges, create a novel source of PH RWD, and lay the groundwork for generating high-quality RWE that directly informs improvements in the care of PH patients.[126]

Patient-generated biometric data

Unlike patient registries that have an established role in understanding PH, patient-generated RWD from biometric sources have only recently begun to contribute to the study of PH. Many available metrics, such as heart rate variability, heart rate recovery, step count, exercise intensity, and accelerometry, have been explored in relation to PH disease severity, and outcomes but are yet to be incorporated into risk stratification models.[136–139] The 6-min walk distance (6MWD), an established metric for clinical trials of PAH therapies, can now be measured at a point in time or estimated longitudinally by several smart devices and applications with relative accuracy and reliability.[140]

Accelerometry is a new source of patient-generated data for PH populations. In a recent study of pediatric patients with PAH, Zijlstra et al. found that physical activity, as assessed by accelerometers, correlated with indices of disease severity (including 6MWD) and predicted clinical deterioration.[141] Given the importance of quantifying PH patients' functional limitations, accelerometry may yield complementary or surrogate information for 6MWD.[35,141] A recent decision by the FDA to accept accelerometry as a primary endpoint for a phase 3 clinical trial shows that accelerometry has the potential to become a common endpoint for PH clinical trials.[142,143]

Similarly, implantable devices may provide valuable RWD to advance the understanding and care of patients with PH. For example, the CardioMEMS heart failure system, an implantable pulmonary artery pressure monitor, records changes in pulmonary artery pressure. Investigators tested CardioMEMS in patients with PH due to left heart disease. The CHAMPION and MEMS-HF trials independently demonstrated that management guided by CardioMEMS reduced pulmonary artery pressure and reduced heart failure hospitalizations in patients with left heart failure.[144–147]

More recent data suggest opportunities to apply data from CardioMEMS in the management of precapillary PH. Benza and colleagues implanted CardioMEMS in 26 patients with PAH with WHO functional class III symptoms. The study had no device-related short- or long-term serious adverse events.[148,149] CardioMEMS provided data regarding variability and trends in pulmonary artery pressure and other calculated measures (proprietary algorithm) and was able to identify pre-hospitalization changes in stroke volume, cardiac output, and pulmonary artery pressure as a patient developed right ventricular failure.[148] The presence of CardioMEMS reduced the use of invasive right heart catheterization by 50%,[149] and it was also used to successfully transition three patients from intravenous treprostinil to oral selexipag in the home setting.[150] As implantable hemodynamic monitoring gains interest, increased use in clinical trials (such as the ongoing ARTISAN trial [NCT05203510]) and clinical settings will proffer more information and clarity on how to use RWD from implantable devices like CardioMEMS.

RESOURCES NEEDED TO PROVIDE MEANINGFUL RWE TO THE GLOBAL PH COMMUNITY

RWD clearly provides opportunities to enhance our understanding of PH and improve care for patients with PH. However, innovative solutions are still necessary to overcome the challenges inherent to the acquisition and

TABLE 4 Successful approaches and remaining challenges of PVRI-GoDeep registry initiative.

RWD challenge	Approach	Remaining barriers
Regulatory/legal landscape	• Multiple stakeholders involved in steering committee • Centralized database	Data transfer between institutions and across borders
Multiple large data sources	• Local processing at each site followed by automatic anonymization and addition to central database	Integration with multiple EHR platforms
Data security/privacy	• Data protection via anonymization • Electronic encryption for data transfer	Data access use rules for data sharing and utilization
Data standardization	• Common parameter list for "essential" data • Local and central data validation strategies	Heterogeneity in data sources and practice patterns across sites (e.g., magnetic resonance imaging or right heart catheterization)

Abbreviations: EHR, electronic health record; PVRI, Pulmonary Vascular Research Institute; RWD, real-world data.

use of RWD. Here we offer specific recommendations to improve current RWD data sources, discuss newer methodologies to generate RWE, and discuss opportunities for the expansion of regulatory policies that will be vital to generate high-quality RWE for the global PH community.

Recommendations to improve current RWD sources for PH populations

1. *Support global PH registries*: Currently, there are PH registries in individual countries and multinational registries.[151] Past registries overrepresented Western countries and underrepresented other regions of the world. Global PH registries can provide a better understanding of the epidemiology of PH worldwide, address global disparities in PH care, and foster global collaborative research. PVRI has begun this work by establishing the GoDeep initiative as a platform that can be continuously supported and improved.
2. *Ensure harmonization and integrity of data collection*: Specific data dictionaries and standards must be established to define quality control, data validation, and transparency of data-processing methods. A novel approach in this regard is to adopt a common data model (CDM) that dictates the organization of tables, standard vocabularies, and mappings used within an observational health data set (Figure 1). By organizing data in identical ways, data do not need to move across organizational firewalls to be analyzed collectively. Analysis code, configured against the CDM, can be distributed among participating centers and executed behind an organization's firewall, at which point only the aggregate, inherently deidentified results are shared. This approach circumvents obstacles to data movement across firewalls and allows large cohorts to be studied rapidly. For example, a CDM approach characterized 4.5 million COVID patients across three continents and demonstrated the hazard of combining azithromycin and hydroxychloroquine early in the pandemic.[152] Within the PH community, investigators have already converted registries into CDM formats.[153]
3. *Develop a standard software platform for data collection*: Such tools must be processed, handled, and stored in accordance with Regulation (EU) 2016/679 (General Data Protection Regulation) and be compliant with FDA 21 CFR Part 11 to protect personal data from unauthorized or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss. PAHTool is a commercially available database software that is already used by several registries worldwide for data collection.[154]
4. *Include medical imaging in future electronic databases of clinical data*: This requires the exchange of extensive image data, image processing, and storage of results. Normal picture archiving and communication systems are used to store and retrieve data following institutional regulations, but picture archiving and communication systems are not designed for clinical research. Innovative solutions for managing the storage, retrieval, and processing of medical image data should include features specific to clinical research.
5. *Support development and adoption of EHRs in low- and middle-income countries (LMICs)*: Fewer than half of all countries have a national EHR system,[155] and adoption in LMICs is often limited to specific programs for infectious diseases.[156] The WHO published guidance in 2006 on EHR implementation in developing countries that details the necessary

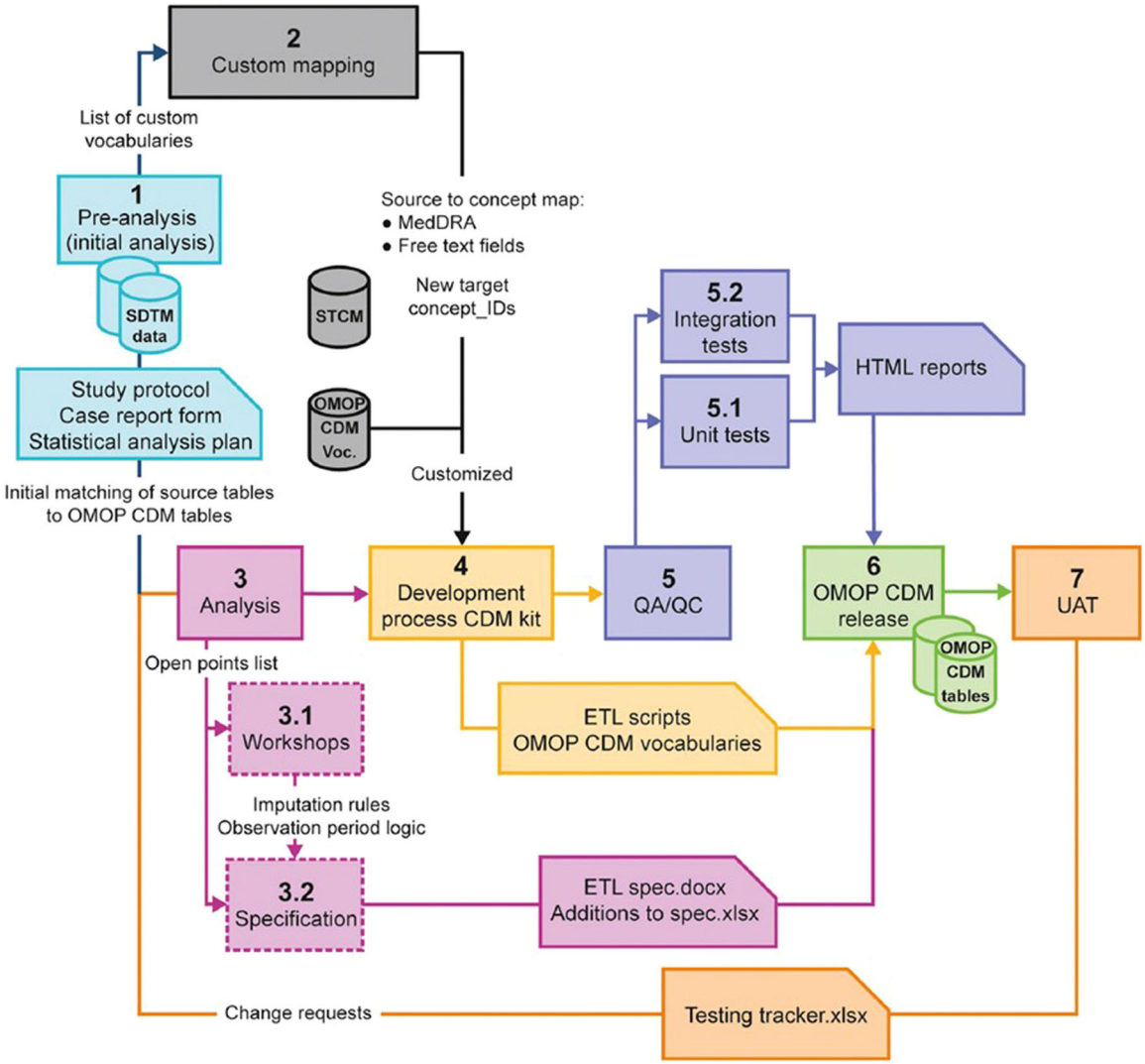

FIGURE 1 Proposed flow chart of mapping data from three different pulmonary hypertension registries into a CDM (3). This figure was reproduced under Creative Commons 4.0 International License. CDM, common data model; ETL, extract, transform, load; OMOP, observational medical outcomes partnership; QA, quality assurance; QC, quality control; SAP, statistical analysis plan; SDTM, study data tabulation model; UAT, user acceptance testing. *Source*: Biedermann et al.[153]

functions and features of an EHR system, the required workforce training to implement an EHR, and the technological infrastructure essential for implementation. Yet EHR implementation in LMICs remains a work in progress, and there is limited research on evidence-based implementation strategies to enable the successful integration of EHRs into health systems.[157,158] Continued research to understand barriers and facilitators to EHR adoption in LMICs will be vital to support efforts to build and scale EHRs effectively.

6. *Support WHO efforts to optimize the use of health service data to affect PH outcomes*: Based on several surveys during recent years, the WHO has provided guidance about the optimization of health service data, including (a) data use for policy and action, (b) data and evidence to drive policy and planning, (c) data access and sharing, and (d) strong country-led governance of data (Figure 2). Such a large and comprehensive data set exchange across databases represents an opportunity to improve our understanding of patients' phenotypes, expanding the collection of meaningful information for all PH categories.

Methods to improve RWD analysis for PH populations

Advanced computational methods that replicate human cognitive processes are being developed and applied across the spectrum of human medicine, from the development of diagnostics and therapeutics to

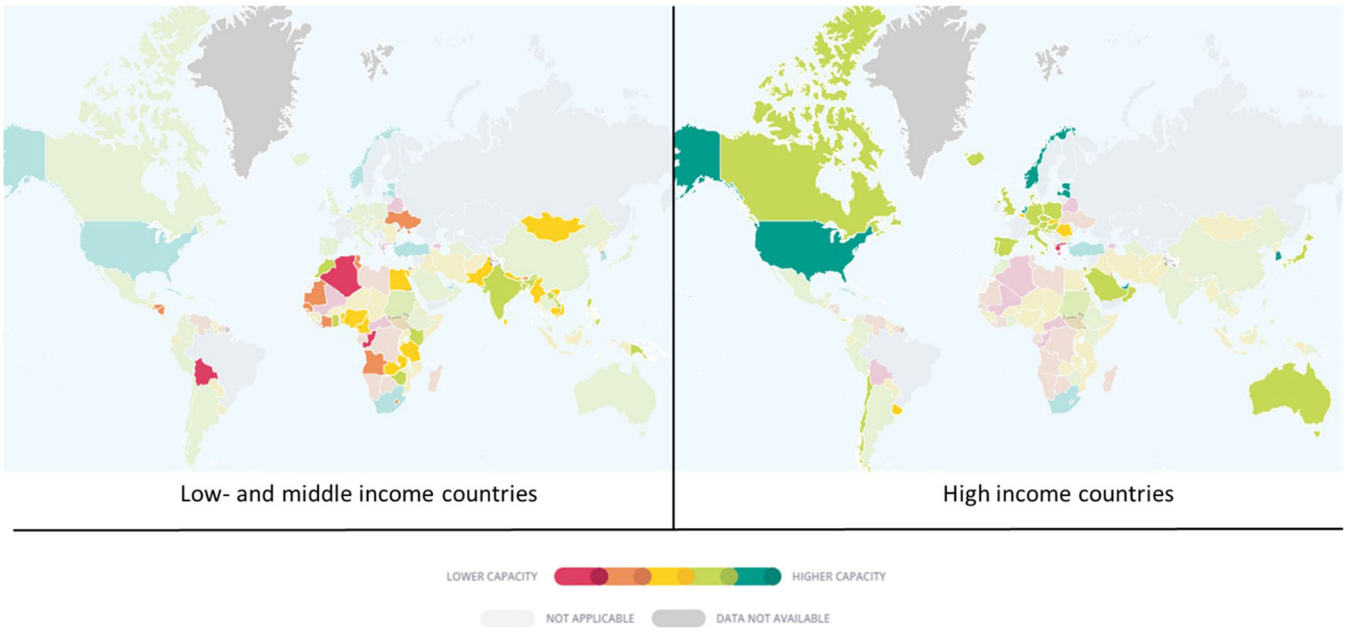

FIGURE 2 Comparison of capacities regarding ability of countries to provide data for policy and action uses. *Source*: World Health Organization. Map Production: Public Health Information and Geographic Information Systems (GIS).

population health management and healthcare regulation. Broadly referred to as artificial intelligence (AI), these emerging technologies can serve as powerful tools to improve data quality and expand the applicability of RWD in PH.

ML refers to the development of algorithms that learn from input data to automatically make predictions or infer patterns in complex data. Once developed, these ML algorithms can be used as decision-support tools. The potential applications of ML to RWD in PH are nearly endless. For example, ML algorithms have been created to more accurately identify PH and PH subgroups within EHR and claims data,[57,159] to detect patients with PH earlier in their disease course using commonly collected clinical data,[160,161] to improve PH risk stratification,[162] and to automate echocardiogram interpretation.[163] ML algorithms could expand relevant expertise to low-income countries and other areas with expert provider shortages. Despite the promises of ML, more work is required to validate performance characteristics, expand generalizability, and improve the transparency of ML algorithms.[164]

NLP is a collection of automated methods that can be used to extract unstructured data (e.g., clinical notes, imaging reports) and translate them into structured data elements, substantially reducing the time required for manual expert review. NLP is particularly relevant for RWD sources, as more than 80% of EHR data are unstructured.[165] NLP has been applied in a variety of clinical contexts, including detecting potential adverse drug events not identified through standard reporting systems,[166] screening candidates for clinical trial eligibility,[167] and improving the identification of diseases,[168] among others. While NLP has been widely employed in other cardiovascular and pulmonary diseases,[169] at present, its use in PH remains limited.

Robotic process automation uses automation technology to perform repeated tasks, speeding processing time and reducing human error. In the context of RWD, robotic process automation can be used to quickly capture, interpret, and process large volumes of data from RWD sources, including EHRs, claims data, mobile applications, or social media.

Combining AI technologies can create even more powerful tools to harness RWD in PH. For example, robotic process automation could be used to extract and process waveforms from right heart catheterizations in EHR data, which could then be combined with other clinical data and fed into ML algorithms to predict the presence of PH and determine PH subgroups. As the research community continues to expand and refine these technologies, their value in utilizing RWD in PH will continue to grow.

Opportunities to improve regulatory policies to support the acquisition, use, and value of RWD

There are many opportunities to improve regulatory policies to support the acquisition, use, and value of RWD. For example, data from RCTs should be shared, particularly in

rare diseases. Existing research data can be utilized to answer questions beyond those planned in the original study, to analyze outcomes that were not included in the primary analysis, to enable individual participant data meta-analysis, and to investigate new methodologies for analyzing data. In addition, published results can be independently validated. However, data ownership, the confidentiality of personal information, and data protection represent areas of concern that may prevent data sharing. For this purpose, detailed methods for creating deidentified, anonymized data sets in compliance with current data protection laws have been previously described.[170] Further, clear regulations are needed that define data ownership.

In the field of PH research, patient-level pooled analyses of deidentified data sets from RCTs have been performed.[171,172] However, clinical trial data sets are not uniformly available upon request. Mandatory submission of deidentified clinical trial data from RCTs as part of submissions to regulatory agencies (e.g., FDA, EMA, Health Canada) would create resources for expanded use of RCT data.

Recently, global regulatory agencies endorsed a joint statement calling for international collaboration to enable the generation and use of RWD and RWE for regulatory decision making.[173] However, challenges remain, including heterogeneous data sources, different levels of data quality, and various governance models for data sharing and access. Global networks such as the Data Analytics and Real-World Interrogation Network (DARWIN EU) are currently under construction to address these challenges.

Although RWD from international sites can be valuable, the fitness of international RWD for use in regulatory decision making is limited by important differences in healthcare systems. Challenges in PAH recognition and management are well-reported in LMICs.[135] For example, PH-left heart disease (Group 2 PH) was the most common cause in PH registries from LMICs.[135] Thus, using data from other countries for regulatory decision making might require additional analyses that consider the differences in medical practice, healthcare delivery, and data reliability. Furthermore, for a rare disease such as PAH, the ability to draw causal inferences from RWD/RWE requires robust methodologic approaches to account for the variability of data sources and the relatively small effect size of treatments in PAH.

SUMMARY AND RECOMMENDATIONS

Over the past 50 years, RWD has contributed greatly to our understanding of the epidemiology, risk stratification, and treatment of PH. RWE complements data from RCTs. Recent regulatory support has elevated the importance of RWD sources, including administrative claims data, EHRs, registry data, and PGHD, in the modern healthcare environment. The increasing reliance upon RWD and RWE will require the development of meaningful quality standards for study designs. Recent legal and regulatory requirements mandate new approaches to gathering, storing, protecting, and analyzing RWD. The collection, storage, and analysis of RWD will require that investigators overcome both general challenges and challenges specific to the study of PH.

Development of CDM and AI applications and expansion of EHRs to LMICs are among the most important steps necessary to advance global understanding and treatment of PH. Moving forward, multi-stakeholder participation is necessary to accelerate the understanding of PH disease states among initiatives that further develop the framework necessary for the responsible collection, analysis, interpretation, and sharing of RWD.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the concept or design of the work; drafted the article or revised it critically for important intellectual content; approved the version to be published; and participated sufficiently in the work to take public responsibility for appropriate portions of the content.

AFFILIATIONS

[1]Global Medical Affairs, United Therapeutics Corporation, Research Triangle Park, North Carolina, USA

[2]Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Vienna, Austria

[3]Division of Pulmonary, Critical Care, and Sleep Medicine, University of Cincinnati, Cincinnati, Ohio, USA

[4]Division of Cardiovascular Medicine, The Ohio State University, Columbus, Ohio, USA

[5]Department of Medicine, Division of Pulmonary Medicine, University of Alberta, Edmonton, Canada

[6]The Pulmonary Center, Boston University Chobian & Avedisian School of Medicine, Boston, Massachusetts, USA

[7]Center for Healthcare Organization & Implementation Research, VA Bedford Healthcare System and VA Boston Healthcare System, Bedford, Massachusetts, USA

[8]Division of Pulmonary, Critical Care & Sleep Medicine, Houston Methodist Hospital, Houston, Texas, USA

[9]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[10]Faculté de Médecine, Université Paris-Saclay, Le Kremlin-Bicêtre, France

[11]Service de Pneumologie et Soins Intensifs Respiratoires, Centre de Référence de l'Hypertension Pulmonaire, Hôpital Bicêtre, Assistance Publique Hôpitaux de Paris, Le Kremlin Bicêtre, France

[12]National Heart and Lung Institute, Imperial College, London, UK

[13]Center of Chest Diseases & Critical Care, Milpark Hospital, Johannesburg, South Africa

[14]Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India

[15]Department of Medicine & O'Brien Institute for Public Health, University of Calgary, Calgary, Canada

[16]Department of Cardiology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

[17]Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

[18]Department of Clinical, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Policlinico Umberto I, Rome, Italy

[19]Department of Respiratory Medicine, Royal Prince Alfred Hospital, University of Sydney, Camperdown, New South Wales, Australia

[20]Faculty of Medicine and Health, University of Sydney, Camperdown, New South Wales, Australia

[21]State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[22]Service de Cardiologie, Centre de Compétence en Hypertension Pulmonaire 27/76, Centre Hospitalier Universitaire Charles Nicolle, INSERM EnVI U1096, Université de Rouen, Rouen, France

[23]Pulmonary Division, Heart Institute, University of São Paulo Medical School, São Paulo, Brazil

[24]School of Medicine, The University of Notre Dame Australia, Perth, Western Australia, Australia

[25]Ignacio Chávez National Heart Institute, México City, Mexico

[26]Department of Rheumatology and Clinical Immunology, Chinese Academy of Medical Sciences & Peking Union Medical College, National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Ministry of Science & Technology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital (PUMCH), Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Beijing, China

[27]Department of Translational Medical Sciences, Federico II University, Naples, Italy

[28]Department of Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Canada

[29]Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan, USA

[30]Division of Pulmonary and Critical Care Medicine, University of Utah, Salt Lake City, Utah, USA

[31]Department of Pulmonary and Critical Care Medicine, Intermountain Medical Center Murray, Salt Lake City, Utah, USA

[32]Global Clinical Development, Bayer AG, Berlin, Germany

[33]Mount Sinai Heart, Icahn School of Medicine at Mount Sinai, New York, New York, USA

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ETHICS STATEMENT

All authors conform to the International Standard for Authors. There are no ethical concerns.

ORCID

Kellie Morland https://orcid.org/0000-0003-1800-7983
Kari R. Gillmeyer https://orcid.org/0000-0002-5333-259X
Sandeep Sahay https://orcid.org/0000-0002-0672-1680
Lukas Hobohm https://orcid.org/0000-0002-4312-0366
Zhi-Cheng Jing https://orcid.org/0000-0003-0493-0929
Sylvia M. Nikkho https://orcid.org/0000-0003-1245-2656
Raymond L. Benza https://orcid.org/0000-0001-9627-6236

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