# FDA Advisory Committee Briefing Document
# Cardiovascular and Renal Drugs Advisory Committee
# July 29, 2010

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**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**
Division of Cardiovascular and Renal Products

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**MEMORANDUM**

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DATE: July 2, 2010

FROM: Norman Stockbridge, MD, Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I, CDER, FDA

TO: Chair, Members and Invited Guests
Cardiovascular and Renal Drugs Advisory Committee (CRDAC)

RE: Overview of the July 29, 2010 CRDAC Meeting to discuss the use of hemodynamics as a measure of drug effectiveness in pediatric patients with pulmonary arterial hypertension and the amendment of Pfizer's Written Request.

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Dr. Lisa Mathis will provide background on the Pediatric Written Request process and its legal basis. In short, a Pediatric Written Request is a contract between the FDA and a sponsor. The fulfillment of the contract results in an additional 6 months of exclusivity. The contract terms specify performance criteria, but they cannot make successfully distinguishing drug from control be a contract term. Instead, the terms need to be defined to ensure that a meaningful result is obtained.

Pfizer's Written Request for sildenafil was originally crafted at a time when Pfizer had some data suggesting it might be useful in pulmonary arterial hypertension (PAH), but the development program for that use was in its infancy. Consequently, the original Written Request for studying the use in PAH was crafted to support an entire development program in children.

As additional information was developed, (in particular, following approval for use in adults with PAH), the Written Request has been amended, five times so far. At this meeting, the Advisory Committee is being asked to opine whether we should amend this Written Request one more time.

The current Written Request calls for the conduct of a single placebo-controlled study with a long-term open-label follow-up. To ensure that a failed study would yield useful information, the Written Request calls for a late, blinded assessment of variance, and then a resizing, if necessary, to ensure power to exclude a treatment effect considered of marginal clinical significance if the true treatment effect were zero.

Pfizer concluded that the trial was infeasible, short of its enrollment goals. Had they nonetheless found a treatment effect on the original end point of exercise capacity, they could have petitioned FDA to amend the Written Request to allow them to file with the smaller sample size; there is precedent for such an action. In fact, the sponsor's analyses support no such appeal (FDA has not reviewed their results). Therefore, as the Written Request is currently constructed, Pfizer has failed to fulfill the terms and has no obvious remedy.

Independent of any consideration about Pfizer's Written Request, but mindful of difficulties conducting PAH studies in children, the Agency has been reviewing its aggregated data from development programs in adults with PAH, looking at possible surrogate markers. Dr. Satjit Brar will describe his efforts in this regard. His work clearly shows an association between a hemodynamic marker and exercise in adults with PAH. The relationship seems to be consistent across drugs of several classes and in control groups.

Thus, the Advisory Committee will be asked to examine the case for considering a hemodynamic marker as a surrogate for a very limited use—extending to a new population the indication for a drug known to be effective in treating PAH. Secondly, the Advisory Committee will be asked whether it believes that Pfizer's Written Request should be amended to be based on their ability address hemodynamic effects in children.

DRAFT Questions for the Advisory Committee Members - July 29, 2010

Topic 1: Use of change from baseline in Pulmonary Vascular Resistance Index (PVRI) as a primary endpoint in pediatric PAH trials.

Currently, there are no suitable measures for assessing effectiveness for the possible approval of drugs for pulmonary arterial hypertension (PAH) in the pediatric population. While the 6-minute walk distance (6MWD) is the most frequently used primary endpoint for adults with PAH, the application of this test not feasible in pediatric patients. A potential efficacy measure for pediatric PAH has been established by comparing results obtained in adults on hemodynamic markers and exercise capacity from 13 separate trials of different therapies in three different drug classes. The relationship shown between the effects on hemodynamics and 6MWD serves as a basis for determining what constitutes a clinically beneficial hemodynamic effect. This information could be used to evaluate other adult populations who are unable to perform exercise capacity testing. In addition, if it can be concluded that the PAH disease state is similar between adults and pediatrics, we are proposing that hemodynamic measures can be used for regulatory approval in pediatric populations for PAH therapies already approved in adults.

1. With the information obtained from the analysis of PAH adult trials, is it reasonable to conclude that change from baseline in PVRI predicts a change from baseline in exercise capacity for adults?

2. Does the committee agree that the PVRI measure can be used to assess treatment effect where exercise capacity cannot be measured in clinical trials?

3. Considering the inability of younger children to perform exercise testing and the potential value of PAH treatments for such children, the use of PVRI as an effectiveness measure is attractive. Doing so, however, requires that the PAH disease in adults classified as WHO Group I be similar to the disease commonly seen in the pediatric population. Does the committee agree that the disease in these populations is indeed similar?

4. Does the committee agree that change from baseline and placebo in PVRI can be used to demonstrate evidence of effectiveness and to derive dosing in the pediatric PAH population?

    a. If no, what additional information would be necessary to qualify the use of PVRI in pediatric trials?

    b. If yes, does the committee agree that the model describing the 6MWD vs. PVRI relation could be used to derive a treatment effect size (assuming that a target for 6MWD is a 10% improvement over placebo)?

    c. Please discuss trial design considerations that might be important in pediatric PAH populations, including minimally important effect size and appropriate statistical power for a PAH trial.

Topic 2: Written Request (WR) for the development of sildenafil in pediatrics

Pediatric clinical studies for sildenafil were initiated in the Summer of 2003. Since then, FDA and Pfizer had ongoing communication regarding the design and conduct of the development program and the challenges associated with conducting clinical trials in the pediatric PAH population. Issues such as endpoints and study interpretability were discussed along with the unique difficulties associated with the recruitment of pediatric PAH clinical trials. During the time that the pediatric development program was progressing, more became understood about pediatric PAH, and significant data on the use of sildenafil in adults with PAH became available. As a result, the WR has undergone updates since December of 2001 to reflect the additional knowledge gained. When considering the ongoing challenges associated with conducting a pediatric PAH program, Pfizer has asked that some aspects of the pediatric program be modified and has proposed amendment of the sildenafil pediatric WR. A summary of the WR history and modifications can be reviewed in the Sponsor's Written Request Summary.

1. If the committee has reservations related to questions #3 and 4 of Topic 1 above, does having some exercise information in older pediatric populations support extrapolation of information into younger pediatrics?

2. Given the relationship between hemodynamics and 6MWD in adults across different classes of drugs, the ability to extrapolate from WHO Group I adults to pediatric populations and the findings reported by Pfizer in pediatric PAH patients, does the committee agree that:

    a. approval for future studies in pediatrics can be based on assessment of hemodynamics (for drugs already approved in adults)? Is this only for children too young to be able to perform exercise testing?

    b. sildenafil's WR can be amended to base approval on the evaluation of hemodynamic data?

**U.S. Food and Drug Administration**
**Center for Drug Evaluation and Research**
**BREIFING INFORMATION FOR CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE MEETING**
**July 29, 2010**

# *Use of ΔPVRI for Dosing Recommendations of Adult-Approved Drugs in Pediatric PAH Patients*

Advisory Committee for Cardiovascular and Renal Drugs
July 29, 2010

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## Executive Summary

The current report describes a systematic investigation of the relationship between hemodynamic measures and exercise capacity in WHO Group I adult patients with pulmonary arterial hypertension (PAH). The intent of the investigation is to determine whether hemodynamic endpoints can be used as evidence of effectiveness in pediatric PAH trials. The following are major findings and recommendations from the investigation:

- Changes in hemodynamic measures predict change in exercise capacity in adult patients; this conclusion is based on data from 13 trials (n=1096 subjects, WHO Group I).
- It is reasonable to use of effect of a drug on PVRI to establish a drug's effectiveness in patients who are unable to perform a reliable exercise capacity test (e.g., pediatric patients <7 years old).
- Reasonable dosing recommendations can be derived by measuring change from baseline in comparison to placebo in PVRI. The report proposes the use of hemodynamic measures as a basis for regulatory approval for treatments of PAH in the pediatric population (**Figure 6**).

For the pooled analysis, a significant relationship was observed between the change in hemodynamic measures (ΔCI, ΔmPAP, ΔRAP, ΔSVRI, and ΔPVRI) and change in exercise capacity, Δ6MWD (univariate, p-value all $< 0.05$). Importantly, the relationship (estimated slope) between ΔPVRI and Δ6MWD was consistent across all trials using different drug classes (Appendix II). All other hemodynamic parameters did not show consistent trends across trials.

The WHO Group I (idiopathic/familial PAH etiology) is considered to represent similar populations in children and adults. The disease similarity is supported by similar pathophysiology, etiology, and clinical presentation in the adult and pediatric populations with PAH. Pediatric patients are expected to have responses to therapeutic intervention that are similar to adults. Hemodynamic evaluation has long been the "gold standard" for diagnosis and assessment of disease severity in PAH, even when Δ6MWD has been the usual measurement of drug effectiveness. It has long been discussed that the 6MWD measurement in a young pediatric population is not feasible. Given the diagnostic utility of hemodynamic measures and the observed relation of hemodynamic changes to changes in 6MWD, it is reasonable to use the hemodynamic measures to assess treatment effect in young pediatric patients with PAH.

## Public Health Need

Currently, there are no suitable endpoints for approval of drugs for pulmonary arterial hypertension (PAH) in pediatrics. The 6-minute walk distance (6MWD) used to measure sub-maximal exercise tolerance is the most frequently used primary endpoint for adults with PAH. Moreover, the 6MWD test has been shown to predict morbidity and mortality from cardiopulmonary diseases (1). Although this test is convenient and administered with ease in adults, the application of the 6MWD test is irreproducible and unreliable in pediatric patients, especially those under 7 years of age (2). On these grounds, additional parameters to determine the effectiveness of treatments for PAH are needed in pediatric patients.

# Introduction

Pulmonary arterial hypertension (PAH) is a complex, progressive condition consequent of constrained blood flow through the pulmonary arterial circulation with increased pulmonary arterial pressure that may result in right-heart failure and death. Although the disease is rare, increasingly frequent reports of confirmed cases suggest that more patients (both pediatrics and adults) have PAH than was previously recognized. Recent documentation provides a thorough summary of the pathology/pathogenesis, epidemiology, classification, diagnosis and treatment of this complex disorder (3-6). Advances in the understanding of PAH have led to increased recognition of the disease and to the important identification of several different pharmacologic approaches to treatment. Currently in the U.S., several drugs in each of three pharmacological classes have been approved for PAH, including phosphodiesterase-5-inhibitors (sildenafil and tadalafil), endothelin receptor antagonists (bosentan and ambrisentan), and prostanoids (epoprostenol, iloprost, and treprostinil). These therapies have attempted to address the pulmonary vascular pressure dysfunction by targeting the vasoconstriction and vasoproliferation associated with the condition. In the effectiveness trials used for registration for all three classes of drugs, exercise capacity, measured as the six-minute walk distance (6MWD), has been used as the primary end point, where all of the existing drugs have exhibited similar improvements. In addition to its prognostic ability (7) and the association of exercise capacity to mortality (3), the 6WMD test is relatively easy to administer. The available information supports the utility of the 6MWD in PAH trials as a reasonable measure of symptomatic benefit and this measure of exercise capacity has been the basis for the evaluation of treatment effect in PAH patients.

The presumed pathophysiologic cause in the impairment of exercise capacity, and other symptoms in PAH patients, is the elevated pulmonary arterial pressures caused by pulmonary vascular pathology. Cardio-pulmonary hemodynamics, such as measurements of systemic and pulmonary blood pressures and saturations, pulmonary capillary wedge pressure, right atrial pressure, and cardiac output by thermodilution or Fick method (6), are used to diagnose and assess the severity of PAH. The diagnosis of PAH requires hemodynamic confirmation with a complete right heart catheterization. In addition to defining the identity and presence of disease, cardio-pulmonary hemodynamics have prognostic value (3) and are known to be independent predictors of survival of patients with PAH (8). Moreover, all currently approved medical therapies are directed at decreasing the vasoconstriction and vasoproliferation within the pulmonary vasculature, which is perceived as the fundamental cause of PAH. Nonetheless, in studies with adults, the hemodynamic measures have not been accepted by themselves as surrogate endpoints on which approval would be based. In considering the use of drugs in pediatric PAH, it has been recognized that children, especially those < 7 years, cannot perform a reliable 6MWD test, and the question has arisen as to whether hemodynamic effects could be used a basis for approval in pediatric patients. As cardio-pulmonary hemodynamics are indicative of PAH diagnosis and are measures of the disease progression, it appears logical that standard hemodynamic measurements in patients with PAH would correlate with clinical state, functional class, and exercise capacity.

This investigation was designed to examine the possible use of hemodynamic effects as a basis for approval by evaluating the quantitative relationship between hemodynamic measures and exercise capacity in adults, with the intention of extrapolating the information to pediatrics. According to FDA's pediatric decision tree (9), such extrapolation could be supported if the

disease is similar in pediatrics and adults. Evaluation of the pathophysiology, diagnostic assessment, hemodynamic definition, and symptoms of the disease indicate that PAH disease is indeed similar for adults and pediatrics. A comprehensive PAH disease state comparison between adults and pediatrics have been summarized in the Sponsor's briefing document (10).

# Hemodynamic Determinants of Exercise Capacity in PAH

The primary objective was to examine the relationship between hemodynamic measures and 6MWD in adult patients, using previously collected data from NDA submissions. Specifically, the investigation was performed in order to:

- determine whether there are systemic and pulmonary hemodynamic measures that are predictive of 6MWD;
- explore whether there are combinations of hemodynamic measures that are predictive of change in 6MWD; and
- evaluate potential clinical factors that may influence the relationship between hemodynamic measures and 6MWD.

The establishment of such a relationship in adults would be considered as a basis for using hemodynamic measures to evaluate treatment effect where exercise capacity cannot be measured in clinical trials.

## ***Methodology***

To assess which hemodynamic measures show a relation to 6MWD, the following approach for the analysis was employed:

Step 1: For individual and pooled trial data, a relationship between individual hemodynamic measures and 6MWD was explored via regression analysis. Individual hemodynamic measures were rank ordered with respect to the significance of the relationship with 6MWD.

Step 2: For the pooled trial data, linear combinations of all hemodynamic measures were explored for determination of the best model that predicts a change in 6MWD.

Step 3: The hemodynamic measures that showed a significant relationship with 6MWD, on a trial level and pooled data, were further scrutinized. The following additional analyses were performed:

- A sensitivity analysis was conducted by the systematically removing extreme values to determine if the relationship between hemodynamic measure and exercise capacity was influenced by outliers.

- The slope estimates of the relationship between hemodynamic measures and 6MWD were evaluated for consistency across trials.

- For the individual trials, the relationship between treatment induced changes (change from baseline and control; double delta) in hemodynamic measure and exercise capacity was evaluated.

The choice of an appropriate hemodynamic measure was based on the significant and consistent relationship of a particular hemodynamic measure to predict a change in 6MWD.

***Sources of Data***

A total of 13 PAH trials conducted in adults were included in the analysis from the data submitted to the agency. The selected trials included data from PAH therapies with three major mechanisms-of-action: prostacyclins, endothelin-receptor antagonists and PDE5 inhibitors. All individual patient level datasets were gathered to generate analysis datasets.

***Identification and selection of studies***

The studies involving the adult PAH patient population were used (phase II/III investigations) for analysis. Further refinement of the analysis dataset was governed by the following criteria:

- Data from patients categorized as WHO Group I of all NYHA severities were used in the analysis. This WHO group classification is primarily based on the inflammatory etiology of PAH, the major cause for PAH in pediatric patients.
- The trials included in the analysis were required to have measurements of hemodynamics and clinical measures at ≥2 separate times over the trial period (at baseline and at least one measurement after start of treatment).
- The data included for analysis included those patients that have completed protocol (per-protocol data) as opposed to data obtained via imputation at the end of study (i.e., LOCF).

***Primary analysis variables***

As the primary purpose of this investigation was to assess the utility of PAH hemodynamic measures in lieu of exercise capacity, the following measures analyzed:

Clinical measurements: The clinical outcome measures evaluated included: six-minute walk distance (6-MWD).

Hemodynamic measures (pulmonary and systemic): The measures evaluated included: cardiac output (CO, L/min), cardiac index (CI, L/min/$m^2$), mean pulmonary arterial pressure (mPAP, mmHg), pulmonary capillary wedge pressure (PCWP, mmHg), right atrial pressure (RAP, mmHg) and mean arterial pressure (MAP, mmHg).

Composite hemodynamic measures: Useful hemodynamic variables that were calculated from the individual measures included: pulmonary vascular resistance (PVR, dyne*sec/$cm^5$), systemic

vascular resistance (SVR, dyne*sec/cm$^5$) and their corresponding indices (PVRI and SVRI). PVR is a composite of CO, mPAP and PCWP while SVR is a composite of MAP, RAP and CO. These measures were used as secondary endpoints in PAH trials and may represent the underlying pathophysiology of PAH.

Baseline measures: Baseline information was tabulated from all PAH clinical trials to evaluate their effects on the relationship between hemodynamic measures and 6MWD. This information included demographic characteristics and baseline hemodynamic measures.

## ***Data Analysis***

The relationship between change from baseline in hemodynamic measures and change from baseline in 6MWD was evaluated. The following considerations were given in preparing the dataset:

- Baseline was defined as the last measurement carried out before the start of study treatment.
- To match hemodynamic measurement and 6MWD, both 6MWD and hemodynamic assessment had to be measured within the same clinical visit (day).
- The hemodynamic and 6MWD measurements assessed were obtained prior to the first dose of the day (trough measurements).

For each individual study, an analysis included all patients who were on active treatment or control (placebo or alternative therapy). For all relationships, Δ6MWD was considered as the response variable and Δhemodynamic variable was considered the predictor variable. Linear regression between Δ6MWD and each individual hemodynamic variable (individual or composite) was performed to allow comparison between trials and therapies. For each regression model, slope and the corresponding 95% confidence interval were derived. Parameter estimates for the regressions were evaluated for statistical significance ($\alpha = 0.05$) and for consistency between trials. Individual trial summaries were generated for comparison among trials and therapies. Subsequently, a pooled analysis incorporating all trials was conducted. Using the same methodology, the pooled analysis was conducted to corroborate the results of the individual trials. For the pooled data evaluation, the regression analysis was further scrutinized to determine the influence of extreme observations on the relationship. A sensitivity analysis was performed by systematically removing observations at the extremes for independent variable.

Step-wise multivariate regression was performed to determine which combination of hemodynamic measures resulted in the best model fit. For exploration of the best model, forward inclusion and backward exclusion of all pertinent hemodynamic measures was performed and the hemodynamic parameter was retained upon statistical significance (for forward inclusion, $p < 0.05$, for 1 degree of freedom and backward exclusion, $p < 0.01$, for 1 degree of freedom). The final model was further scrutinized via covariate analysis in the similar technique used for multiple-linear regression (forward inclusion, backward exclusion). Covariate analysis was implemented on the slope parameter and included demographics and disease state information (e.g., age, gender, BSA, baseline walk distance, and NYHA classification). Prior to model building, hemodynamic measures were assessed for redundancy.

The hemodynamic parameters that yielded the best model fit were further evaluated to determine how well changes in hemodynamic measures predict changes in 6MWD induced by treatment. For each trial comprising a control arm, the difference between the treatment and control group in the Δ6MWD (the treatment effect of the drug, double-delta) was plotted against the difference between the treatment and control group in ΔPVRI for each dose level within the trial. A linear regression model, between ΔΔPVRI vs. ΔΔ6MWD was fit to determine if a relationship exists.

SAS 9.2 (The SAS Institute, Cary, NC) was used for data mining and organization. S-PLUS 7.0 (Insightful, Seattle, WA) and R (version 2.10.1; http://www.r-project.org) were used for model diagnostics, graphical inspection and statistical analysis.

## ***Results***

The clinical and demographic characteristics of the patients used for the analysis are provided in **Table 1** below. Out of a total of 1934 subjects from 13 trials, a total of 1453 (75.1%) patients had complete and matching hemodynamic and 6MWD information. Of this subset, the analysis comprised of 1096 patients who were diagnosed with WHO Group I PAH. Majority of patients (~92%) had moderate to severe PAH disease at baseline (NYHA class II and III). Approximately, ~40% were on placebo or alternative therapy while ~60% were randomized to active treatment.

**Table 1:** Patient characteristics for pooled analysis of n = 13 PAH trials.

| | median (range) / N (%) |
|---|---|
| Age, years | 50 (18 – 83) |
| BSA, $m^2$ | 1.77 (1.25 – 2.66) |
| Gender | |
| Male | 290 (26.4%) |
| Female | 806 (73.6%) |
| NYHA Class | |
| I | 5 (0.4%) |
| II | 324 (29.7%) |
| III | 689 (62.9%) |
| IV | 76 (6.9%) |
| Treatment arm | |
| Control | 444 (40.5%) |
| Active | 652 (59.5%) |
| Trial Duration | |
| 12 weeks | 386 (35.2%) |
| 16 weeks | 611 (55.7%) |
| 24 weeks | 99 (9.0%) |
| Baseline walk distance, meters | 368 (60 – 480) |
| **Total analyzed** | **1096** |

*Each Hemodynamic Variable as a Correlate of Δ6MWD (Univariate Analysis)*

The slope estimates and the 95% confidence intervals obtained from the univariate regression analysis are provided in Appendix II. In the pooled analysis, a statistically significant relation was observed between all Δhemodynamic measures and Δ6MWD, with the exception of mean arterial pressure (MAP). The corresponding slope parameter estimates and plots of ΔCI, ΔRAP, ΔSVRI and ΔPVRI vs. Δ6MWD are provided in **Table 2** and **Figure 1,** respectively.

**Table 2**: Results from univariate regression of Δ6MWD and Δ hemodynamic measures for pooled analysis.

| Hemodynamic parameter | Slope estimate (95% conf interval) | p-value |
|---|---|---|
| CI | 25.1 (18.6, 31.5) | <0.001 |
| MAP | -0.10 (-0.32, 0.13) | NS |
| mPAP | -1.7 (-2.2, -1.2) | <0.001 |
| PCWP | -1.0 (-1.9, -0.09) | 0.031 |
| RAP | -3.0 (-3.9, -2.2) | <0.001 |
| PVRI | -0.032 (-0.039, -0.024) | <0.0001 |
| SVRI | -0.015 (-0.021, -0.009) | <0.0001 |

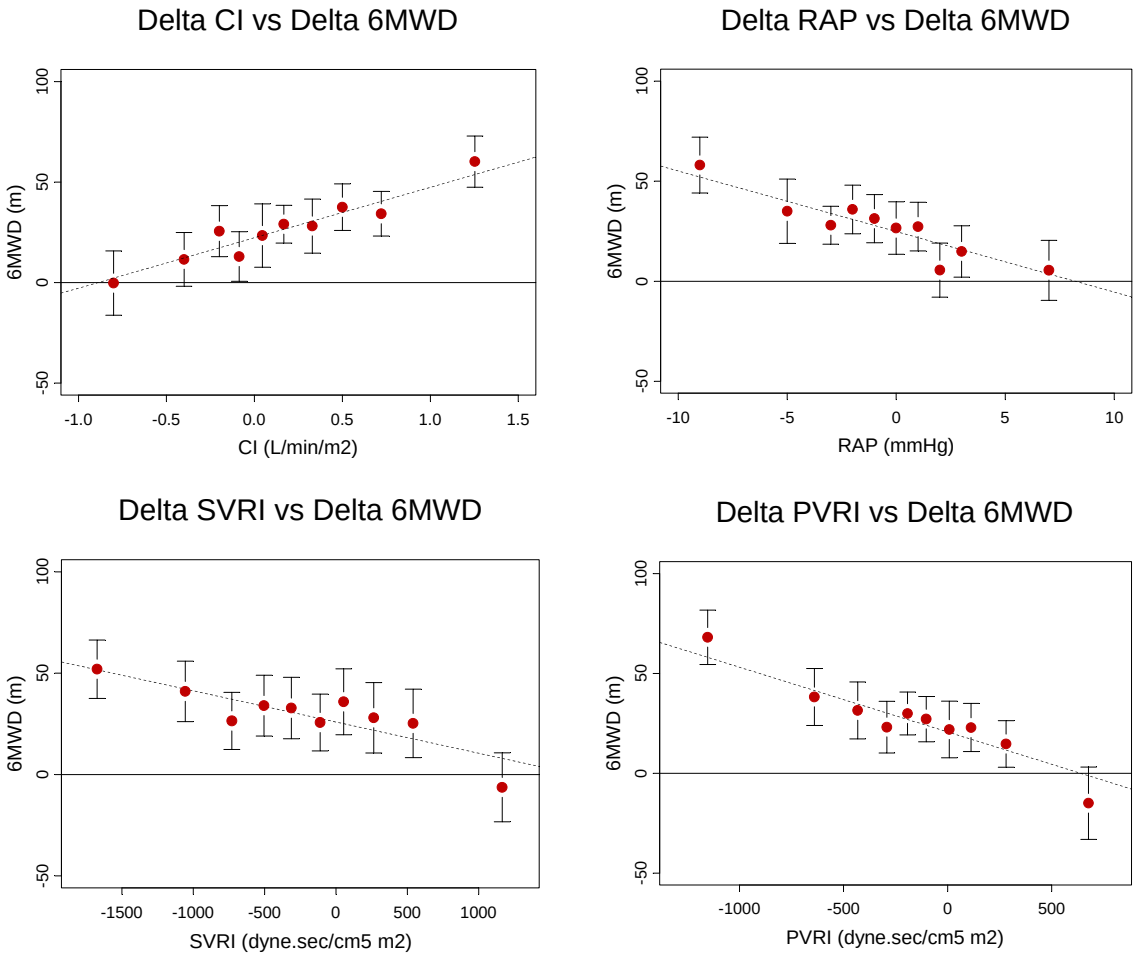


**Figure 1**: Plots of ΔCI, ΔRAP, ΔSVRI, and ΔPVRI vs. Δ6MWD. Observations were binned by hemodynamic measure percentiles (10 bins, deciles) so that an approximate equal number of patients composed each percentile (n ~ 100 subjects per bin). The points represent the median Δhemodynamic measure per bin and the corresponding mean Δ6MWD (with 95% confidence interval). The dotted line represents the linear regressor for all n=1096 observations.

For individual trials, ΔmPAP, ΔPCWP and ΔSVRI resulted in a statistically significant relation with Δ6MWD for fewer than 50% of the trials analyzed. A positive relation with cardiac index (ΔCI) was observed for all trials and was statistically significant in >50% of the trials. However, pulmonary vascular resistance index (ΔPVRI) showed a significant negative relation (Figure 2) with Δ6MWD across trials. ΔPVRI showed a significant relation in 12 of the 13 trials, with the 95% confidence intervals overlapping among majority of trials. A forest plot comprising the ΔPVRI slope estimates and 95% confidence intervals for the individual and pooled 13 trials is included in **Figure 2** below.

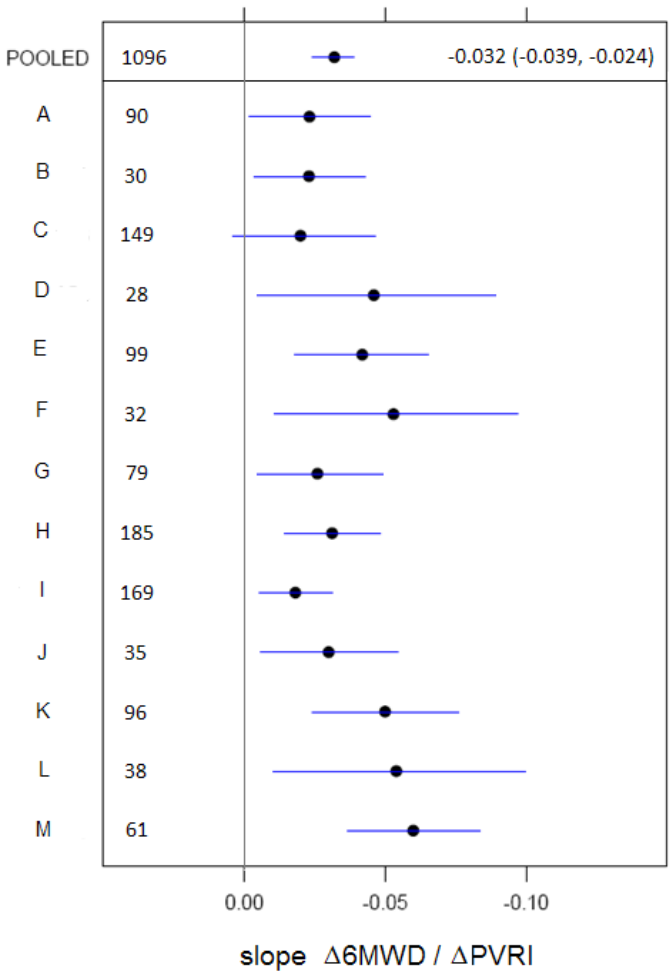


**Figure 2**: Slope estimates (± 95% confidence interval) of ΔPVRI vs. Δ6MWD for individual trials and pooled analysis (N = number of subjects included for the analysis). Horizontal line demarcates zero slope.

Evaluation of the ΔPVRI vs. Δ6MWD relationship between the three drug classes and control/placebo resulted in no statistically significant difference ($p < 0.05$) between slopes suggesting that the relation is independent of drug mechanism of action. A forest plot comprising the ΔPVRI slope estimates and 95% confidence intervals for the pooled arms for endothelin receptor antagonists (ERA), PDE5 inhibitors, prostacyclins, and control (i.e., placebo) arms is included in **Figure 3** below.

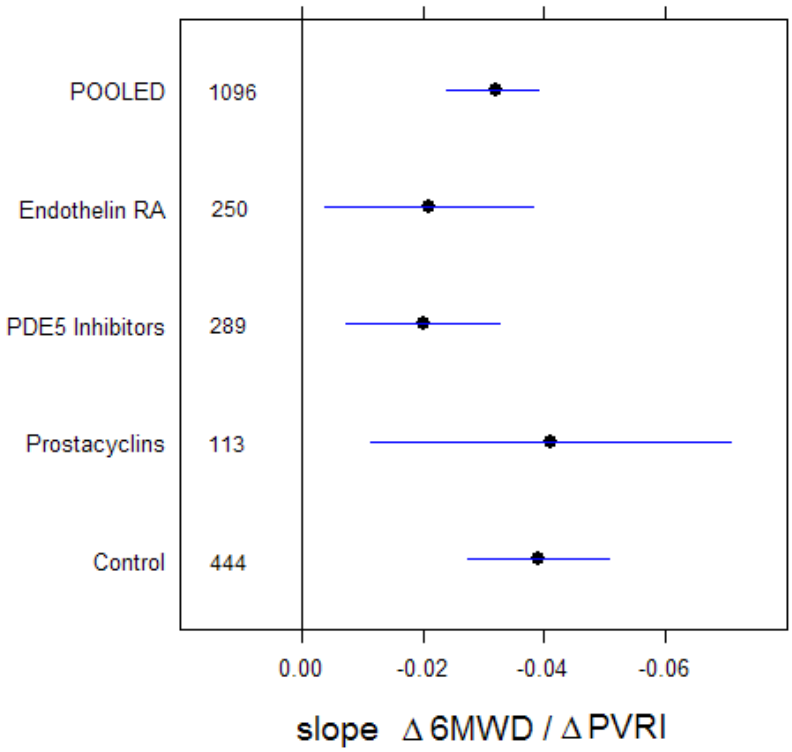


**Figure 3**: Slope estimates (± 95% confidence interval) of ΔPVRI vs. Δ6MWD between drug classes and control (i.e., placebo) (N = number of subjects included for the analysis). Horizontal line demarcates zero slope.

*Combination of Hemodynamic Measures as Correlates of Δ6MWD (Multivariate analysis)*

Stepwise multivariate regression resulted in both ΔRAP and ΔPVRI as being significant predictors of Δ6MWD. The forward inclusion and backward exclusion was done by selecting among all possible linear regression models of Δ6MWD as a function of ΔCI, Δ PVRI, ΔSVRI, ΔRAP. As ΔPCWP and ΔmPAP make up the composite ΔPVRI, and were collinear variables, they were not included in the modeling process. A linear combination of change in PVRI and change in RAP was identified as the best predictor of Δ6MWD, in which:

$$\Delta 6MWD = 23.17 - 1.89\ \Delta RAP - 0.0301\ \Delta PVRI \quad (\text{p-value for model} < 0.0001)$$

Compared to adults, pediatrics with PAH generally have better preserved RAP at diagnosis (11). As ΔPVRI showed a consistent and significant relation across trials, and the utility of RAP evaluation in pediatric PAH may be limited, the relationship between ΔPVRI and Δ6MWD, only, was further scrutinized.

*Sensitivity Analysis of ΔPVRI versus Δ6MWD*

The association between ΔPVRI and Δ6MWD was further examined as a consistent and significant relationship was observed with this particular hemodynamic variable. To assess whether the extreme observations influenced the relationship, the observations that comprised the 1st and 10th deciles were removed. The linear regression was performed on the truncated dataset and the slope estimates were compared to the complete dataset for ΔPVRI. The plots depicting the regressions for the truncated dataset are shown in **Figure 4**, while **Table 3**. summarizes the slope comparison between the truncated and complete datasets. The relationship between ΔPVRI vs. Δ6MWD is still significant and consistent after the exclusion of extreme observations.

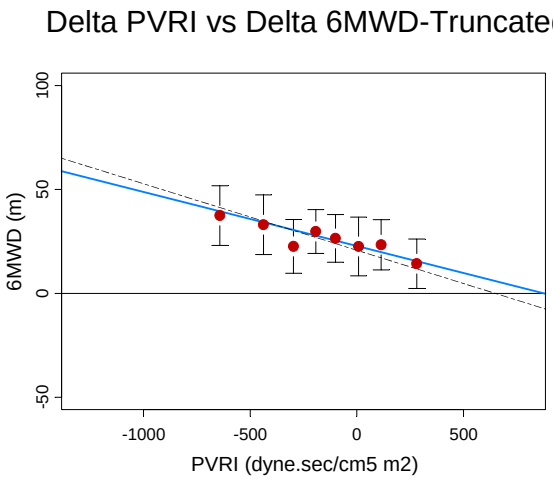


**Figure 4**: Plot of ΔPVRI vs. Δ6MWD. Observations were binned by hemodynamic measure percentiles (8 bins, octiles) so that an approximate equal number of patients composed each percentile. The dotted line represents the linear regressor for all n=1096 observations while the blue solid line represents the regressor about the truncated dataset (n =774).

**Table 3**: Results from univariate regression of ΔPVRI vs. Δ6MWD for pooled analysis for entire and truncated dataset.

| dataset (N) | Slope estimate (95% conf interval) | p-value |
|---|---|---|
| complete (1096) | -0.032 (-0.039, -0.024) | <0.001 |
| truncated (774) | -0.026 (-0.041, -0.011) | 0.006 |

*Evaluation of Treatment Induced Changes in Hemodynamic Measures Predicting Changes in Δ6MWD*

For assessment of the treatment effect between control and active arms, ΔPVRI were evaluated as predictors of Δ6MWD. The mean double-delta plots are provided in **Figure 5** below. A significant relationship was observed with ΔΔPVRI as a function of ΔΔ6MWD. The treatment induced changes in ΔPVRI are able to explain treatment induced changes in Δ6MWD.

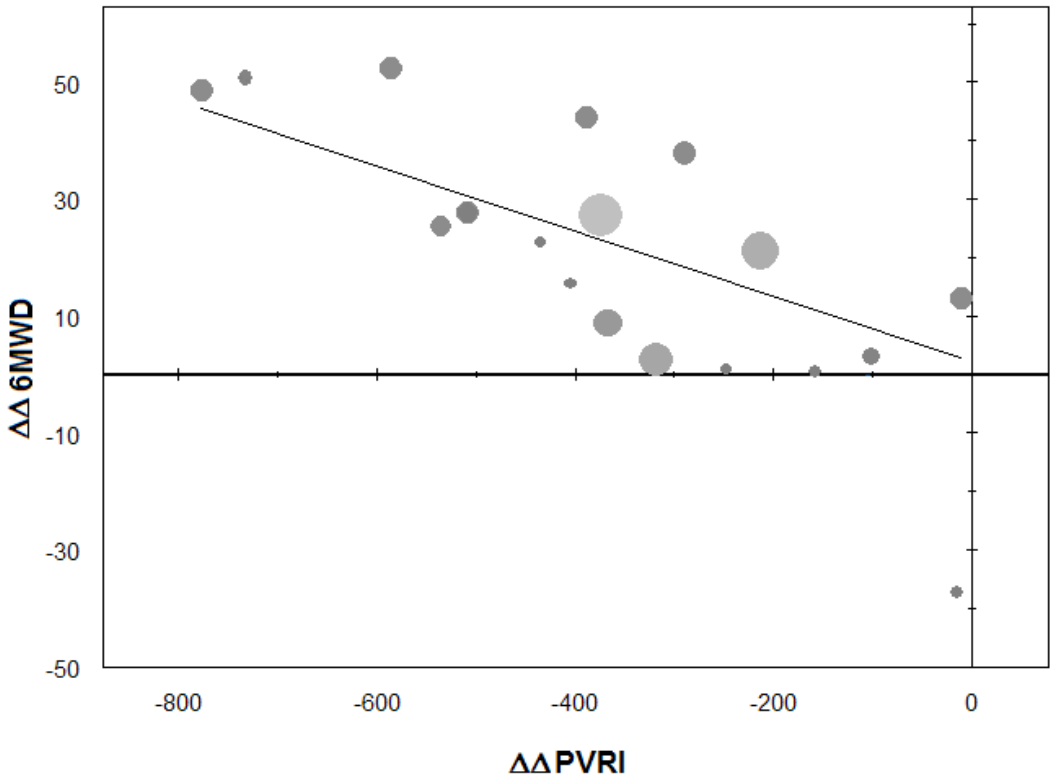


**Figure 5**: Plot ΔΔPVRI vs. ΔΔ6MWD. Observations represent the mean difference between control and active arms for hemodynamic measure and 6MWD (n=18 different dose levels for 12 trials). The size and color of each point represents the number of subjects in the trial arm with complete data (the larger and darker, the more number of subjects). The solid line represents the linear regressor for all n=18 observations.

## ***Discussion***

In adult PAH trials, a significant relationship was observed between Δhemodynamic measures and Δ6MWD. ΔPVRI was found to be a significant and consistent predictor of exercise capacity across 13 PAH trials. For ΔPVRI, a negative relation was observed, with an improvement in pulmonary pressure (decrease) yielding an improvement in 6MWD (increase). The treatment effect (placebo-corrected change from baseline) on PVRI was found to have a similar significant negative relation with the treatment effect on 6MWD. The other hemodynamic measure that showed a significant relationship with 6MWD was ΔRAP (an improvement in RAP yielded an

improvement in 6MWD). RAP was not further scrutinized as right heart function is generally better in pediatrics compared to adults, limiting the translation of this analysis to the pediatric population (11;12). Interestingly, the ΔPVRI relationship was consistent across PAH trials using treatments of differing mechanisms of action (PDE5 inhibitors, endothelin receptor antagonists and prostacyclins), suggesting that the ΔPVRI measure may be useful to assess treatment effect regardless of therapy class.

These relations are physiologically plausible. Progressive remodeling of the pulmonary arteriolar vessels, a hallmark in PAH pathogenesis, causes an increase in hemodynamic pressures, yielding increases in right ventricular afterload. As a result, symptoms of PAH arise from the inability to adequately increase pulmonary blood flow for oxygen demand during exercise (6MWD). Thus, measurements of pulmonary vascular pressures and blood flow quantify both the disease process and its main functional consequence. Improvement of pulmonary pressures (PVRI) yielded an improvement in 6MWD, which coincides with exercise physiology. Therefore, the results of this systematic investigation are supported by theoretical understanding of the disease. Since the hemodynamic goal is to bring pulmonary artery pressure back toward normal, a success on hemodynamic endpoint does indicate effectiveness of drug in PAH.

## Pediatric development of PAH therapies from adult information

Once changes in hemodynamic measures are accepted as valid surrogates of 6MWD for drugs that have established efficacy in adults, ΔPVRI can be used to assess treatment effect in pediatric studies, so long as it is reasonable to consider the disease to be pathophysiologically similar in adults and children. In this report, we also provide a potential path forward to use hemodynamic measure in pediatric clinical trial as primary endpoint. **Figure 6** provides conceptual framework that can be used in regulatory decision making and designing pediatric PAH trials for drugs that are already approved in adults.

Currently, in the clinical development of therapies for *adult* PAH, approval is based on an improvement in Δ6MWD on treatment compared to placebo. Currently, the dose selection for pivotal trials is usually based on hemodynamic measures, namely PVRI. The doses that yield a beneficial effect on the hemodynamics are carried onward to the larger phase 3 trials. In the larger registration trials, hemodynamic measures are still obtained but are considered important secondary endpoints in assessing treatment effect. For pediatric development of a PAH therapy approved for adults, a relationship between 6MWD and hemodynamic measure should be established in adults for that particular therapy. It is imperative that dose ranging studies be performed in pediatrics to achieve different degrees of hemodynamic benefit. Reference would be made to the adult relationship to derive dosing based on the targeted benefit in exercise capacity.

We have established a relationship between hemodynamic measures and 6MWD in adults, showing hemodynamic measures (PVRI) that can be used to assess treatment effect in pediatrics. In the clinical development for pediatric PAH, the goal will be to show statistically significant treatment on hemodynamic effect(s) that correspond to clinically significant effects on exercise function. Trial designs that compare dose of the test drug to a control (such as placebo), compare

on-drug versus off-drug effects (withdrawal) and dose-ranging have been typically used for pediatric studies. In this case, the goal is not only to demonstrate a treatment effect but also to find dose(s) that elicit an effect on Δ6MWD in adults at the approved doses. Dose ranging studies may be the most reasonable approach to achieve differing degrees of hemodynamic changes. Regulatory approval can be based on the changes in hemodynamic measures compared to placebo or a suitable control. To derive rational dosing in pediatrics, the quantitative relationship between hemodynamics and 6MWD may be used to predict desired clinical benefit on exercise capacity

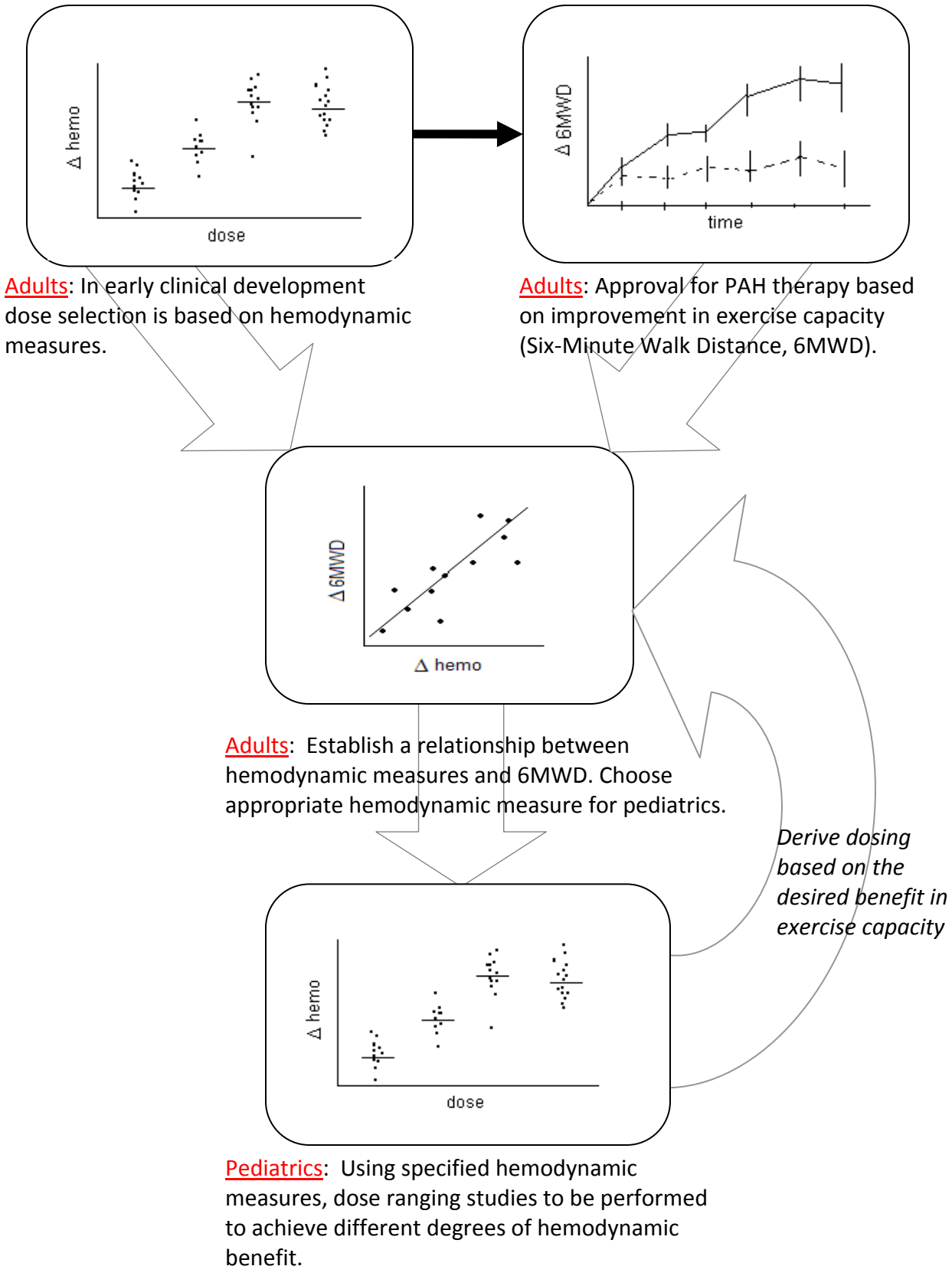


**Figure 6**: Approach for pediatric development of PAH therapies from adult information.

# CONCLUSION

The change in PVRI should be used as a measure of treatment effect in pediatric PAH patients. This recommendation is based on the following notions:

- Pulmonary arterial hypertension in adults and patients is similar in clinical presentation, etiology (WHO Group I), and pathophysiology.

- PVRI is routinely measured for diagnosis in patients with PAH (both adults and pediatrics). An increase in PVRI is hallmark of the PAH disease.

- PVRI is considered an independent predictor of mortality in PAH patients.

- The pulmonary vasculature is the primary target for PAH therapies and PVRI is the closest physiological measure that reflects the dynamics of the pulmonary vasculature.

- A relationship between change in PVRI and a change in 6MWD was observed in a systematic analysis of hemodynamic and 6MWD data from 1096 patients, across 13 independent trials and drugs with 3 different mechanisms of action.

- The use of PVRI is supported by *a priori* physiological reasoning. An improvement in PVRI yields an improvement in exercise capacity.

- Treatment induced changes in PVRI are able to explain treatment induced changes in exercise capacity.

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# APPENDIX I - LIST OF ABBREVIATIONS

| | |
|---|---|
| CI | Cardiac Index |
| CO | Cardiac Output |
| MAP | Mean Arterial Pressure |
| mPAP | Mean Pulmonary Arterial Pressure |
| PCWP | Pulmonary Capillary Wedge Pressure |
| PVR | Pulmonary Vascular Resistance |
| PVRI | Pulmonary Vascular Resistance Index |
| RAP | Right Atrial Pressure |
| SVR | Systemic Vascular Resistance |
| SVRI | Systemic Vascular Resistance Index |
| 6-MWD | Six-Minute Walk Distance |
| NYHA class | New York Heart Association Classification |
| WHO class | World Health Organization Pulmonary Hypertension Classification |

# APPENDIX II – Univariate regression slope estimates FOR ALL TRIALS.

Univariate regression slope estimates [upper and lower 95% CI] of Δhemodynamic measurement vs. Δ6MWD for all individual PAH trials along with pooled results. Shading signifies statistically significant slope and all pooled results were statistically significant.

| | TRIAL | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *hemodynamic measurement* | *A* | *B* | *C* | *D* | *E* | *F* | *G* | *H* | *I* | *J* | *K* | *L* | *M* | *POOLED* |
| *mPAP* | -1.3 [-2.7, 0.13] | -1.7 [-3.6, 0.27] | -1.1 [-2.4, 0.22] | -0.99 [-3.9, 1.9] | -6.33 [-10.4, -2.3] | -2.3 [-3.4, -1.1] | -0.97 [-2.8, 0.88] | -2.1 [-3.3, -0.9] | -1.4 [-2.6, -0.19] | -1.9 [-6.0, 2.1] | -1.0 [-3.1, 1.1] | -1.4 [-5.1, 2.2] | -4.4 [-6.6, -2.2] | -1.7 [-2.2, -1.2] |
| *PCWP* | 0.12 [-2.5, 2.7] | -1.1 [-4.5, 6.7] | -1.3 [-3.8, -1.3] | -2.2 [-7.4, 3.1] | -9.06 [-15.7, -2.4] | -0.45 [-3.0, 3.1] | -0.93 [-3.1, 1.2] | -0.49 [-2.3, 1.3] | -0.98 [-3.4, 1.4] | -1.6 [-7.7, 4.5] | -1.7 [-5.8, 2.3] | -14.9 [-32.4, 2.5] | -1.2 [-2.1, 4.4] | -1.03 [-1.9, -0.09] |
| *CI* | 37.96 [16.4, 59.5] | 12.51 [-15.3, 40.3] | 13.72 [-4.84, 32.3] | 63.12 [9.6, 116.7] | 50.8 [3.88, 97.69] | 22.0 [1.74, 42.3] | 10.97 [-14.1, 36.1] | 16.67 [4.93, 28.4] | 20.73 [4.87, 36.6] | 19.77 [12.5, 27.1] | 32.41 [0.65, 65.5] | 55.8 [-8.1, 119.7] | 44.1 [19.3, 68.9] | 25.1 [18.6, 31.5] |
| *PVRI* | -0.023 [-0.04, -0.002] | -0.02 [-0.04, -0.003] | -0.02 [-0.04, 0.01] | -0.05 [-0.09, -0.001] | -0.05 [-0.09, -0.01] | -0.04 [-0.07, -0.02] | -0.026 [-0.05, -0.001] | -0.03 [-0.05, -0.01] | -0.02 [-0.03, -0.005] | -0.03 [-0.05, -0.005] | -0.05 [-0.07, -0.03] | -0.05 [-0.09, -0.01] | -0.06 [-0.08, -0.03] | -0.032 [-0.039, -0.024] |
| *SVRI* | 0.0059 [-0.01, 0.03] | -0.006 [-0.01, -0.003] | NA | NA | -0.047 [-0.073, -0.022] | NA | -0.002 [-0.019, 0.016] | -0.003 [-0.015, 0.009] | -0.011 [-0.02, -0.003] | -0.015 [-0.04, 0.012] | -0.009 [-0.03, 0.01] | -0.044 [-0.08, -0.001] | -0.039 [-0.05, -0.02] | -0.0154 [-0.021, -0.009] |
| *RAP* | -1.89 [-6.0, 1.22] | -3.56 [-5.31, -1.61] | -4.27 [-9.31, 0.77] | -3.46 [-6.17, -0.76] | -5.18 [-10.5, -0.1] | -2.63 [-5.46, -0.03] | -3.37 [-5.7,-0.98] | -3.29 [-5.02, -1.57] | -1.84 [-3.26, -0.38] | -1.49 [-8.45, 5.46] | -3.67 [-7.24, -0.099] | -6.14 [-10.1, -2.4] | -3.02 [-6.2, -0.17] | -3.03 [-3.89, -2.17] |