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RESEARCH ARTICLE

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# Kids Mod PAH trial: A multicenter trial comparing mono- versus duo-therapy for initial treatment of pediatric pulmonary hypertension

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**Abstract**

Pulmonary hypertension (PH) is a significant health problem that contributes to high morbidity and mortality in diverse cardiac, pulmonary, and systemic diseases in children. Evidence-based advances in PH care have been

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challenged by a paucity of quality endpoints for assessing clinical course and the lack of robust clinical trial data to guide pharmacologic therapies in children. While the landmark adult AMBITION trial demonstrated the benefit of up-front combination PH therapy with ambrisentan and tadalafil, it remains unknown whether upfront combination therapy leads to more rapid and sustained clinical benefits in children with various categories of PH. In this article, we describe the inception of the Kids Mod PAH Trial, a multicenter Phase III trial, to address whether upfront combination therapy (sildenafil and bosentan vs. sildenafil alone) improves PH outcomes in children, recognizing that marked differences between the etiology and therapeutic response between adults and children exist. The primary endpoint of this study is WHO functional class (FC) 12 months after initiation of study drug therapy. In addition to the primary outcome, secondary endpoints are being assessed, including a composite measure of time to clinical worsening, WHO FC at 24 months, echocardiographic assessment of PH and quantitative assessment of right ventricular function, 6-min walk distance, and NT-proBNP levels. Exploratory endpoints include selected biomarkers, actigraphy, and assessments of quality of life. This study is designed to pave the way for additional clinical trials by establishing a robust infrastructure through the development of a PPHNet Clinical Trials Network.

**KEYWORDS**
bosentan, children, multicenter randomized control trial, pulmonary arterial hypertension, sildenafil

## INTRODUCTION

Pediatric pulmonary hypertension (PH) is a significant health problem that contributes to high morbidity and mortality in diverse cardiac, pulmonary, and systemic diseases in children.[1] PH, which is often life-threatening and progressive, is a formidable health care cost burden, accounting for over three billion dollars in hospital charges in 2012 with a more than three-fold rise in fewer than 5 years.[2] Etiologies of PH are diverse, and include primary PH or pulmonary arterial hypertension (PAH), and secondary forms of PH, including PH related to left-sided heart conditions, lung disease, chronic thromboemboli, and others. Evidence-based advances in the care of children with PH have been challenged by a limited number of multidisciplinary care centers, relatively small numbers of patients at each center, paucity of quality endpoints for assessing clinical course, and the lack of robust clinical trial data to guide pharmacologic therapies.[3–5]

Furthermore, despite the availability and approval of multiple PH-targeted pharmaceutical therapies for adults, data regarding the use of these agents remains extremely limited for children. To date, two agents—bosentan and sildenafil—have been approved by the U.S. Food and Drug Administration (FDA) to treat PH in children. To date, there has only been one pediatric randomized controlled trial for sildenafil in PAH (which did not include secondary forms of PH) and none for bosentan, thus FDA approval was largely dependent on extrapolation from adult data.[6] Given the morbidity and mortality associated with pediatric PH, off-label treatment without clearly defined goals occurs routinely.

Current pharmaceutical therapies for the treatment of PH fall into three classes based on major signaling pathways, namely prostacyclin (PGI2), nitric oxide (NO)/cyclic GMP, and endothelin (ET). However, no single class of drug is consistently effective in treating all patients, suggesting that no dominant pathogenic pathway has yet been demonstrated in all types of pediatric PH. Data from the adult AMBITION trial demonstrated the benefit of up-front combination therapy with the endothelin receptor antagonist (ERA) ambrisentan and the phosphodiesterase type 5 inhibitor (PDE5i) tadalafil in World Symposium on Pulmonary Hypertension (WSPH) Group 1 PH patients (Group 1 comprises those

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with PAH).[7,8] Specifically, the risk of the first event of clinical failure (defined as the first occurrence of a composite of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response) was 50% less in those who received combination therapy compared to those who received monotherapy with either ambrisentan or tadalafil.

Despite these promising findings in adults, it remains unknown whether upfront combination therapy leads to more rapid and sustained clinical benefits in children with various categories of PH, including WSPH Groups 1 and 3 PH (Group 3 comprises those with lung disease-related PH). Extrapolation of results from adult studies to children may not be appropriate as there are marked differences between the etiology and therapeutic response between adults and children with PH.[9,10] Members of the Pediatric Pulmonary Hypertension Network (PPHNet) designated this key question regarding the potential benefits of upfront combination therapy in children as the highest priority for a randomized control trial to improve the care for all children with pediatric PH (not limited to PAH alone) and led to the inception of the Kids Mod PAH Trial, a multicenter Phase III trial, to address this question.

For this study, the agents selected were sildenafil (PDE5i) and bosentan (ERA). Use and dosing are guided by pediatric case series, AHA/ATS guidelines, the European Medicines Evaluation Agency pediatric guidelines, our published systematic review, and extensive clinical experience.[11–14] As known interactions between sildenafil and bosentan may lead to reduction in availability of sildenafil and to increased availability of bosentan,[15,16] pharmacokinetics are being assessed as part of this study. There are no approved endpoints for pediatric PH trials, and to this end, the study includes a variety of novel and innovative secondary and exploratory endpointsfor pediatric PH. For example, time to clinical worsening and actigraphy, which are not age dependent, are being evaluated.

## STUDY HYPOTHESES

The primary goal of this study is to compare upfront combination therapy (sildenafil and bosentan) to a common pediatric approach of single agent (monotherapy) in children newly diagnosed with WSPH 1 and WSPH Group 3 PH. The monotherapy arm for this study is sildenafil since a placebo arm would have a substantial risk for morbidity and mortality due to untreated progression of PH. We hypothesize that upfront combination therapy is superior to monotherapy as assessed by the primary endpoint of WHO functional class (FC) 12 months after initiation of study drug therapy. WHO FC is a commonly used standard for assessing PH disease status which can be utilized in children[11,17,18] and is being treated as a four-level ordinal scale with expert adjudication.

## STUDY PROTOCOL

This randomized, open-label, pragmatic, superiority trial is currently recruiting 100 subjects (50 in each therapy arm) from 12 pediatric PH centers in North America. Eligibility criteria include a diagnosis of PH by cardiac catheterization within the 4 weeks before screening, age ≥3 months to <18 years, WSPH PH Groups 1 or 3, and current WHO FC II or III (slight or marked limitations of physical activity). PH is defined by cardiac catheterization by the following standard criteria: mean pulmonary artery pressure >25 mmHg and/or pulmonary vascular resistance index (PVRI) > 3 Wood units*$m^2$, and pulmonary capillary wedge pressure (or left ventricular end-diastolic pressure) ≤15 mmHg.[11] Revised criteria for PA pressure >20 mmHg from the sixth WSPH were not used for this study due to incomplete validation in children at the time of study initiation.[10] Alternatively, for infants less than 1 year of age with concern for Group 3 PH for whom cardiac catheterization is considered too high risk by the expert clinical team's assessment, the following criteria must be met: two separate echocardiograms clearly demonstrating PH per standard criteria (these are detailed in Table 1); absence of clinical or imaging

**TABLE 1** Diagnostic criteria for PH by echocardiography for the Kids MoD PAH study.

**Echocardiographic metrics (three of the following are needed):**

- Early diastolic pulmonary regurgitant gradient >20 mmHg
- Right ventricular hypertrophy (qualitative as mild to severe)
- Right atrial enlargement (scales for age will be provided)
- Elevated right ventricular systolic pressure
  - >35 mmHg on at least two reliable spectral Doppler envelopes during the echocardiogram and in the setting of normal for age-documented systolic blood pressure

  OR
  - >50% systemic using systolic blood pressure at the time of the echocardiogram.
- Flattening or (right to left) bowing of the interventricular septum (qualitative or by elevated end-systolic eccentricity index)[19,20]
- Diminished RV function (RV fractional area change <35%) and/or TAPSE below published normal range for age and weight (TAPSE Z-score < −2)[21,22]

Abbreviations: PH, pulmonary hypertension; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.

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evidence of left heart dysfunction; unequivocal lack of pulmonary venous stenosis on the two separate echocardiograms and/or CT angiography or cardiac magnetic resonance imaging if there are concerns; and no evidence of hemodynamically significant left-to-right shunt lesions.

Randomization is stratified by WSPH group (1 or 3) to ensure balance of WSPH groups. In addition to the primary outcome, secondary endpoints are being assessed, including a composite measure of time to clinical worsening (TTCW), WHO FC at 24 months, echocardiographic assessment of PH and quantitative assessment of right ventricular function, 6-min walk distance (for participants ≥8 years), and NT-proBNP levels. Exploratory endpoints include actigraphy (the use of wearable devices to measure physical activity) and assessments of quality of life (PedsQL).[23,24] In an optional biospecimen component of the study, biomarkers of pulmonary vascular disease (interleukin 6 and suppression of tumorigenicity 2) will be analyzed.[25,26] Additional specimens to be banked include DNA, peripheral blood mononuclear cells, plasma, serum, RNA, miRNA, and urine.

A flow diagram of the study is provided in Figure 1.

## COLLABORATIONS AND INTERACTIONS

A key structural element of this study is the collaboration between a Clinical Coordinating Center (Johns Hopkins University) and an independent Data Coordinating Center (DCC: Duke University). This cooperation is essential for maintaining data integrity, reporting of adverse events, conducting analyses, and dissemination of findings. The logistics of this trial have been greatly aided by additional collaborations with the National Center for Advancing Translational Sciences—funded

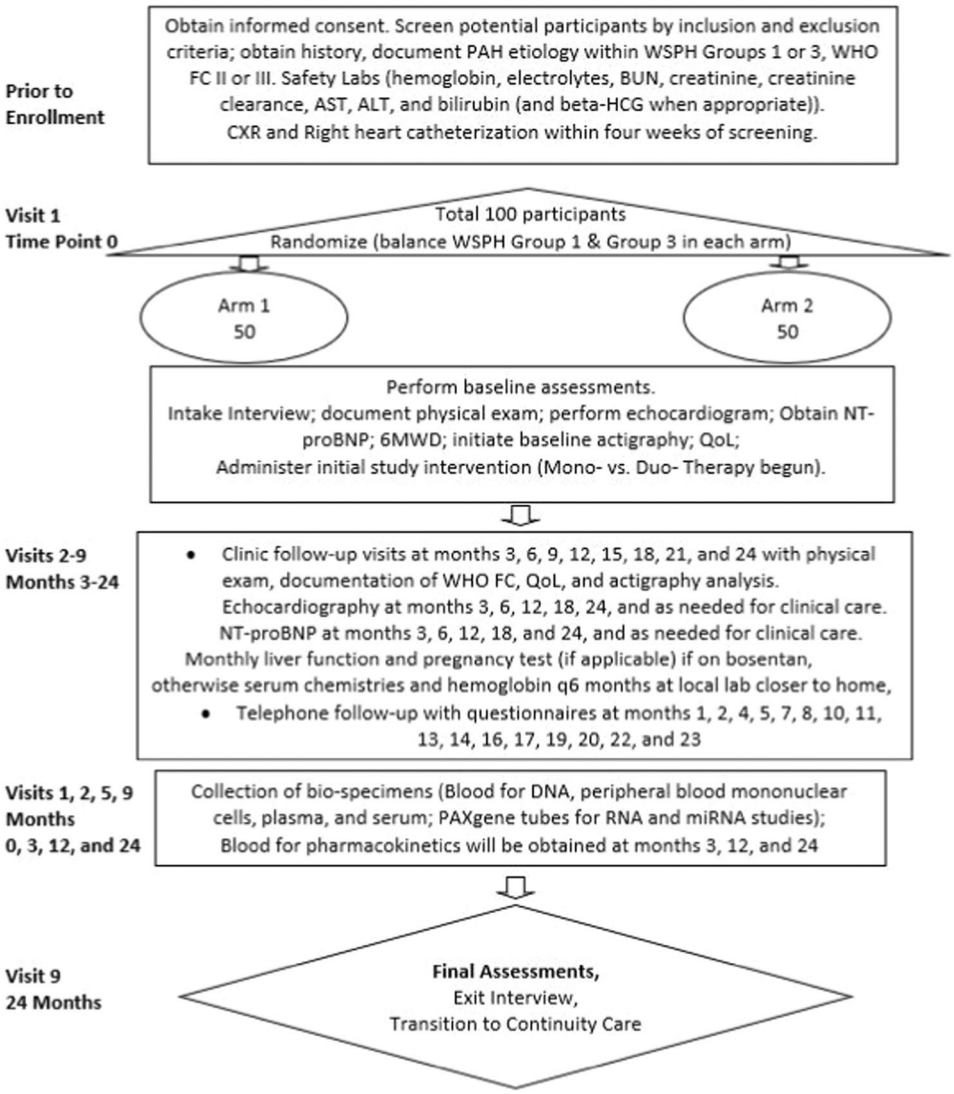


**FIGURE 1** Flow diagram of the Kids MoD PAH trial.

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Trial Innovation Network (TIN), Johns Hopkins and Duke University/Vanderbilt University Trial Innovation Centers (TICs), Vanderbilt Recruitment Innovation Center (RIC), and the research team from the Division of Brain Injury Outcomes Clinical Trials Coordinating Center at Johns Hopkins. Indeed, project design began with a Comprehensive Consult from the TIN that featured formative input from the above-mentioned TICs and RIC. Additionally, this study benefits from a close collaborative approach to study implementation and conduct with the Lung Division of National Heart, Lung, and Blood Institute (NHLBI) as this study has been funded through a competitive UG3/UH3 Cooperative Agreement grant from NHLBI.

This study heavily leverages the working relationships of PPHNet. PPHNet is an association of medical professionals from PH centers focused on the clinical, research, and educational aspects of PH in children. All 12 study sites are members of PPHNet. Preliminary data for study design were provided by the PPHNet Registry, which has enrollment of nearly 1500 pediatric PH patients[9]; similarly, biospecimens collected during this study will be stored and analyzed through the PPHNet Biospecimen Laboratory Depot (PPHNet *BOLD*). NHLBI provided critical momentum to the PPHNet through U01 HL12118 which made it possible to compile the PPHNet Registry—an important foundation of the current study.[9]

In an effort to develop and test new endpoints for pediatric PH, define new pediatric PH phenotypes, conduct secondary analyses, and build infrastructure for future pediatric PH clinical trials, several working groups have been established to foster collaborations and share expertise. The working groups focus on primary and secondary outcomes for the study (i.e., WHO FC and echocardiography), exploratory outcomes (i.e., quality of life, actigraphy, and adherence), and phenotyping (i.e., artificial intelligence/predictive modeling and biomarkers), and a participant-facing mobile application[27] for improving the interface with the study team (and hence retention). Members of these groups are drawn from the core study teams and investigators at study sites and other PH centers. They have contributed to the development of the protocols used in this study and published details of their work will be forthcoming in other venues to serve the broader PH community.

## PLANNED ANALYSES

The primary outcome measure is the change in WHO FC class from baseline to 12 months analyzed as a binary variable using a two-proportion test. For the WHO FC binary variable, improvement/no deterioration is defined as WHO FC lower than or equal to baseline WHO FC and deterioration is defined as a WHO FC greater than baseline. Secondary and exploratory outcomes are to be analyzed using standard longitudinal methods.

## DISCUSSION

This study has several unique strengths that add to its overall value. This is the first NIH-sponsored investigator-initiated trial of drug therapy for pediatric PH in North America. Second, it includes subjects with PH related to respiratory disease (WSPH Group 3), a novelty compared to adult studies with only PAH. In contrast to adult populations with PH,[28] the percentage of children with PH associated with respiratory disease is much higher and this is a group of PH patients that has not been well-studied to date in any age group.[9] The study also offers subjects voluntary participation in an established pediatric repository for biobanking. This core will be able to carry out standardized proteomic and genomic profiling to aid understanding of the mechanisms of pediatric PH and assist with generating more detailed phenotypes. Finally, any multicenter study that recruits small numbers of subjects from each center is at risk for data variability. To minimize this, careful attention was paid during study design to formulating standardized data collection, expert adjudication of screening criteria and the primary endpoint, batch analyses of study samples, and data harmonization through the DCC. Current challenges to this study's recruitment efforts include two that are worthy of note: COVID-19-associated attitudes toward scientific inquiry[29] and a trend toward initiation of PH-directed therapies by providers before referral to pediatric PH centers (with or without cardiac catheterization data). Both issues are being addressed through outreach and education at the levels of colleagues and the public.

While the primary goal of this study is to conduct a multicenter randomized control trial of initial combination therapy versus monotherapy in children with PH, this study has several other important secondary goals. This study is designed to pave the way for additional clinical trials and other studies by establishing a robust infrastructure for such work through the development of a PPHNet Clinical Trials Network. Toward that end and an existential goal in itself, career and leadership development for junior and mid-level faculty continue to be high priorities.[30] Additionally, this study will test a variety of endpoints through its secondary and exploratory outcomes for use in future clinical studies. Again, the field has been hampered by a lack of valid endpoints for pediatric PH studies.[11] This study will also test the

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utility of a variety of biomarkers through banked samples, which will improve our understanding of the mechanisms underlying pediatric PH and provide for more accurate phenotyping. Looking further, efforts toward endpoint innovation through Kids MoD PAH are investments in improving the pediatrics clinical research enterprise in general and efforts to launch and complete successful multicenter randomized clinical trials in particular, as they will provide validation for new modalities and metrics for assessing the toll of cardiopulmonary and other chronic diseases on children.

Research will be disseminated through traditional forums such as peer-reviewed publications and presentations at national meetings. Data will be archived for future research. Biobanking will provide a key resource for this study and for future work in the field.

## AUTHOR CONTRIBUTIONS

*Study conception and design*: Lewis H. Romer, Steven H. Abman, Erika B. Rosenzweig, Joseph M. Collaco, and Daniel F. Hanley. *Draft manuscript preparation*: Joseph M. Collaco and Lewis H. Romer. All authors reviewed the results and approved the final version of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets have yet been generated for the current study.

## ETHICS STATEMENT

This study has been approved by the Johns Hopkins University School of Medicine IRB (Protocol Number: IRB00300590) and includes written consent and assent.

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