

# The evolving landscape of pulmonary arterial hypertension clinical trials

## Web Appendix

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*The Redesigning Pulmonary Arterial Hypertension Clinical Trials Task Force of the 18<sup>th</sup> Global Cardio Vascular Clinical Trialists Forum*

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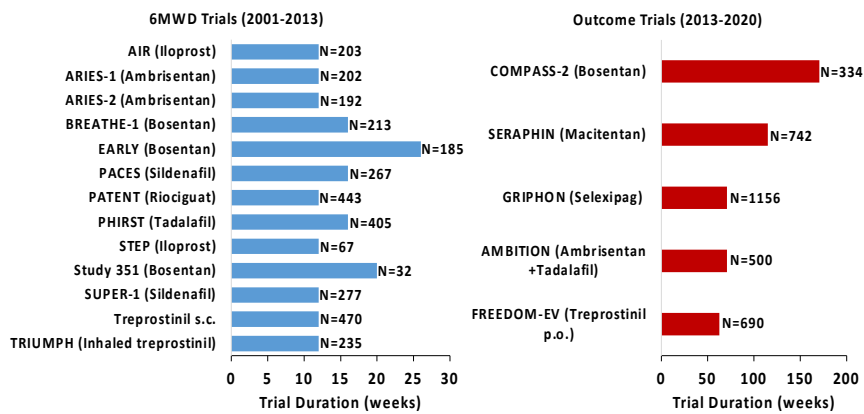
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**e-Figure 1. Duration and size of pulmonary arterial hypertension randomized controlled trials.**

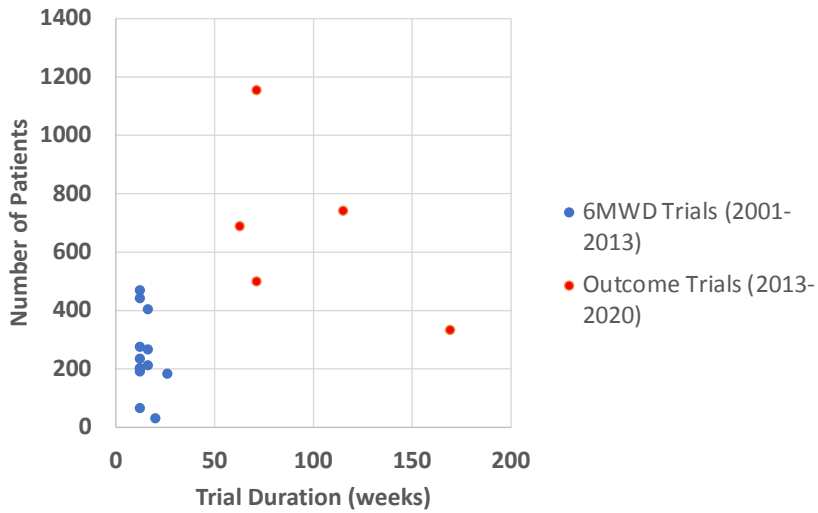
A) Pulmonary arterial hypertension clinical trials in the era of 6-minute walk distance primary endpoint studies and studies that have used clinical outcome primary endpoints.

B) Plot of trial size vs duration. Abbreviations: p.o. – per os, s.c. - subcutaneous

**A**

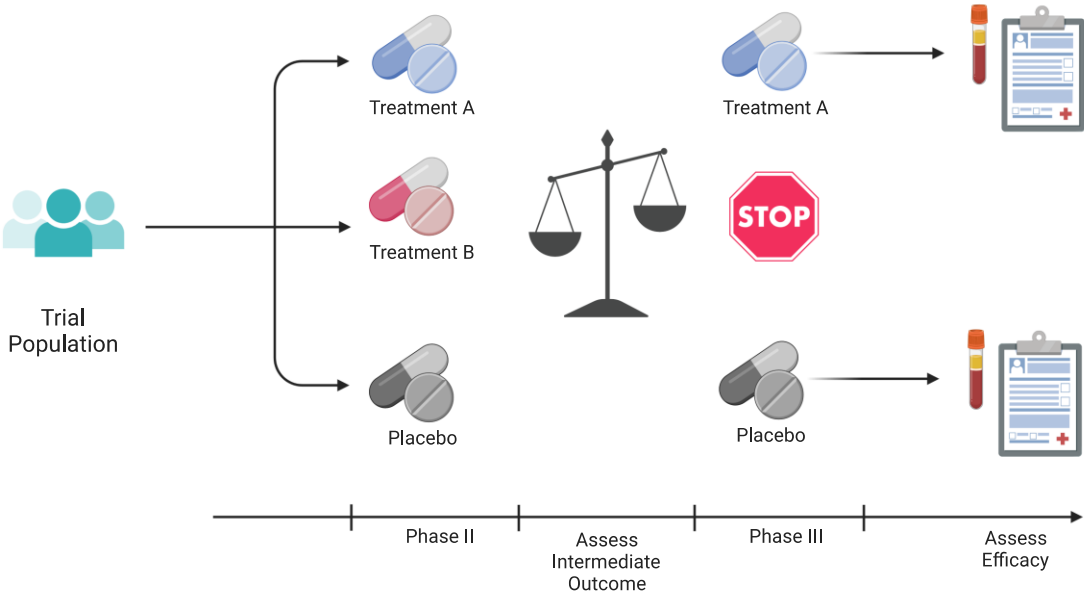


**B**



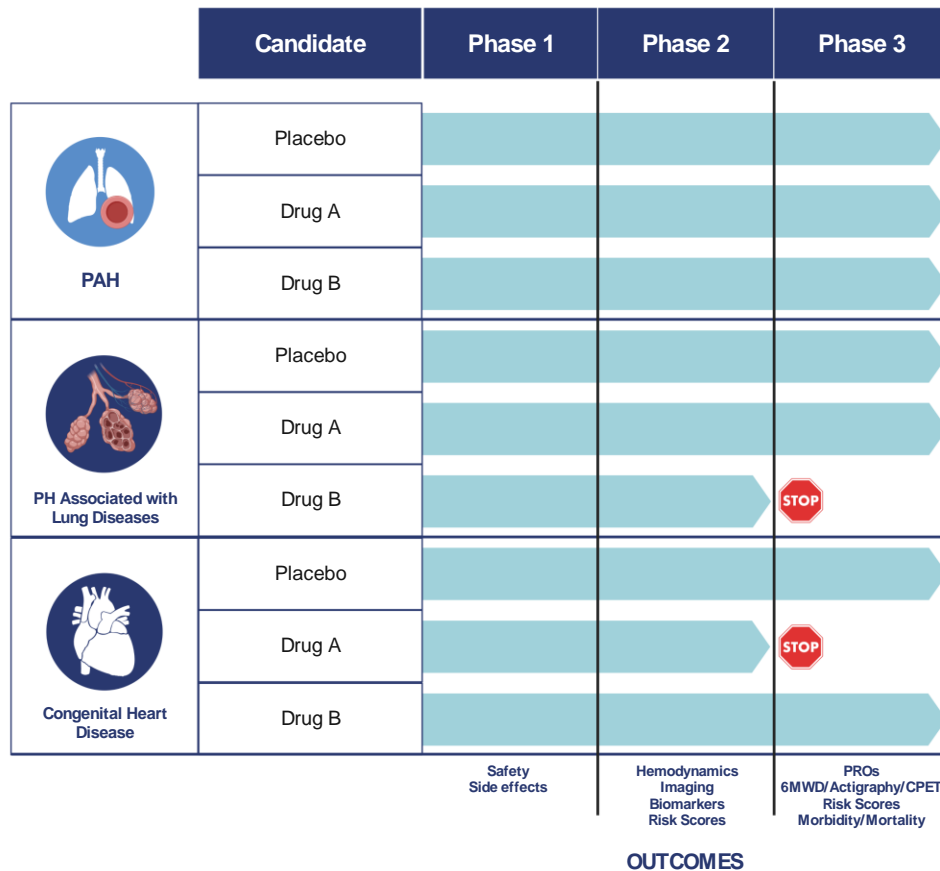
**e-Figure 2. Adaptive seamless phase 2/3 trial design.**

Participants are randomized to treatment A, treatment B or placebo. Assessment of the phase 2 outcome indicates that treatment B is unlikely to benefit or is harmful. Treatment B is discontinued, and the phase 3 study continues with treatment A compared to placebo. Created with BioRender.com



**e-Figure 3. Theoretical design for an adaptive basket platform trial for therapeutics targeting right ventricular failure due to pulmonary arterial hypertension and other conditions.**

Participants within each condition would be randomized to Drug A, Drug B, or placebo. After assessment of safety and side effects in Phase 1, candidate drugs are tested in Phase 2. Candidate treatments meeting the primary endpoints in Phase 2 can proceed into Phase 3 using a seamless phase 2/3 design. Candidate treatments that do not meet Phase 2 efficacy endpoints do not proceed to Phase 3, with efficacy that may vary between conditions. Created with BioRender.com.



**e-Table 1. Primary endpoint definitions and components in outcome-driven pulmonary arterial hypertension trials**

Trial	Primary Outcome Definition	Definition of Worsening PAH
COMPASS-2(1)	Time to the first morbidity/mortality event. Defined as time to death from any cause, hospitalization for worsening PAH or start of intravenous prostanoid therapy, atrial septostomy, lung transplant, or worsening PAH.	Worsening PAH, defined as either 1 or 2: <ol style="list-style-type: none"> <li>1) moderate or marked worsening of PAH symptoms on the patient global self-assessment together with the initiation of a subcutaneous or inhaled prostanoid or use of open-label bosentan;</li> <li>2) no change or mild worsening of PAH symptoms accompanied by a decrease in 6MWD by more than 20% from the previous visit or by more than 30% from the baseline visit, together with the initiation of a subcutaneous or inhaled prostanoid or use of open-label bosentan.</li> </ol>
SERAPHIN(2)	Time to the first event related to PAH, defined as worsening of PAH, initiation of treatment with intravenous or subcutaneous prostanoids, lung transplantation, atrial septostomy, or death from any cause up to the end of treatment	Worsening PAH, defined as the occurrence of all three of the following: <ol style="list-style-type: none"> <li>1) decrease in the 6MWD of at least 15% from baseline, confirmed by a second 6MWD performed on a different day within 2 weeks;</li> <li>2) worsening of symptoms of PAH;</li> <li>3) need for additional treatment for PAH</li> </ol>
GRIPHON(3)	Time to first event. Death or a complication related to PAH, whichever occurred first, up to the end of the treatment period.  Complications related to PAH were 1) disease progression or worsening of PAH that resulted in hospitalization, 2) initiation of parenteral prostanoid therapy or long-term oxygen therapy, 3) the need for lung transplantation, or 4) balloon atrial septostomy.	Disease progression, defined as a <ol style="list-style-type: none"> <li>1) decrease from baseline of at least 15% in the 6MWD (confirmed on a different day)</li> </ol> Plus <ol style="list-style-type: none"> <li>2) worsening in functional class (for the patients with functional class II or III at baseline) or the need for additional treatment of pulmonary arterial hypertension (for the patients with functional class III or IV at baseline)</li> </ol>
AMBITION(4)	Time to first occurrence of a composite end point of death, hospitalization for worsening pulmonary arterial hypertension, disease	Disease progression, defined as a decrease of more than 15% from baseline in the 6MWD combined with functional class III or IV

	<p>progression, or unsatisfactory long-term clinical response.</p>	<p>symptoms at two consecutive visits separated by at least 14 days</p> <p>Unsatisfactory long-term clinical response, defined as any decrease from baseline in 6MWD at two consecutive clinic visits after baseline separated by at least 14 days, and functional class III symptoms assessed at two clinic visits separated by at least 6 months (for those in the study at least 6 months)</p>
<p>FREEDOM-EV(5)</p>	<p>Time to first adjudicated clinical worsening event, which was defined as death from any cause, hospitalization for worsening PAH, disease progression, initiation of inhaled or infused prostacyclin therapy, or unsatisfactory long-term clinical response</p>	<p>Disease progression, defined as a decrease in 6MWD at least 15% from baseline or too ill to walk directly related to PAH progression, confirmed by two 6MWD tests on different days, and worsening functional class or appearance of symptoms of right heart failure</p> <p>Unsatisfactory long-term clinical response, defined as decrease in 6MWD at week 24 or beyond at 2 consecutive visits on different days and sustained functional class III or IV symptoms for at least 24 consecutive weeks.</p>

Abbreviations: 6MWD – 6-minute walking distance; PAH – Pulmonary arterial hypertension



**e-Table 2. Comparison of risk assessment tools in pulmonary arterial hypertension**

	<b>French invasive</b>	<b>French Non-invasive</b>	<b>SPAHR/ COMPERA</b>	<b>COMPERA 2.0</b>	<b>REVEAL 2.0</b>	<b>REVEAL Lite 2</b>
Variables	NYHA FC I or II 6MWD > 440 m RAP < 8 mmHg CI $\geq 2.5 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$	NYHA FC I or II 6MWD > 440 m NT-proBNP < 300 ng/L or BNP < 100 ng/L	NYHA FC 6MWD RAA (SPAHR only) Pericardial effusion (SPAHR only) NT-proBNP or BNP RAP CI SvO2	NYHA FC 6MWD NT-proBNP or BNP	WHO Group 1 subgroup Demographics (age & male sex) NYHA FC SBP HR 6MWD NT-proBNP or BNP DLCO RAP PVR	NYHA FC SBP HR 6MWD NT-proBNP or BNP
Risk Strata	5 (number of low risk criteria present 0-4)	4 (number of non-invasive low-risk criteria present 0-3)	3	4	8	3
C-Index at baseline	0.61-0.62(15,16)	..	..	0.67(17)	0.70-0.74(15,18)	0.71(19)
C-index at follow-up	0.64-0.72(15,16)	0.74(16)	0.62(15)	0.73(17)	0.74-0.76(15,18)	0.70(19)

Abbreviations: 6MWD – 6-minute walking distance, BNP – brain natriuretic peptide, COMPERA – Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension, CI – cardiac index, DLCO – diffusion capacity for carbon monoxide, HR – heart rate, NT-proBNP – N-terminal pro-brain natriuretic peptide, NYHA FC – New York Heart Association Functional Class, PVR – pulmonary vascular resistance, RAA – right atrial area, RAP – right atrial pressure, REVEAL - Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management, SBP – systolic

blood pressure, SPAHR – Swedish Pulmonary Arterial Hypertension Registry, SvO<sub>2</sub> – mixed venous oxygen saturation, WHO – World Health Organization

**e-Table 3. Quality of life measurement tools in pulmonary arterial hypertension**

<b>Instrument</b>	<b>Domains</b>	<b>Number of Items</b>	<b>References</b>
<b>Generic</b>			
SF-36	8	36	(6)
EQ-5D	5	5 + VAS	(7)
<b>PH-Specific</b>			
CAMPHOR	3	65	(8,9)
Living with Pulmonary Hypertension	2	21	(10,11)
EmPHasis-10	1	10	(12)
PAH-SYMPACT	2	11	(13,14)

Abbreviations: CAMPHOR – Cambridge Pulmonary Hypertension Outcome Review, PAH-SYMPACT – Pulmonary arterial hypertension symptoms and impact, SF-36 – Short Form-36, VAS – visual analogue scale

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