

Making it Happen: Enrollment Strategies & Adaptive Designs in PAH

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The authors would like to acknowledge the contribution of [Peyton Sandroni, PhD](#), in the preparation of this poster.



Background

Why Operational Strategy Matters

Pulmonary Arterial Hypertension (PAH) remains a rare and heterogenous disease area associated with significant clinical trial complexity.

Key development challenges include:

- Limited patient populations and specialist centers
- Complex diagnostic confirmation requirements
- High screen failure rates
- Geographic recruitment variability
- Increasing protocol complexity

To improve development efficiency, sponsors are increasingly adaptive Phase II/III designs capable of supporting:

- Earlier dose selection
- Interim decision-making
- Seamless development strategies
- Reduced exposure to ineffective therapy

These strategies depend heavily on surrogate endpoints capable of demonstrating treatment effects within shorter timelines

Methods

Review of Operational Benchmarks & Endpoint Utilization

Operational benchmarks across recent PAH studies were reviewed, including:

- Enrollment timelines
- Site startup performance
- Screen failure trends
- Geographic variability in recruitment

Common surrogate and clinical endpoints were assessed for:

- Sensitivity to early treatment effects
- Operational feasibility
- Utility in adaptive interim analyses

Endpoints evaluated include:

- Pulmonary vascular resistance (PVR)
- NT-proBNP
- Exercise capacity requirements
- Clinical worsening outcomes

Enrollment Realities in PAH

Persistent Challenges Across Global Studiess

Operational Factor	Impact on Execution
Limited specialist centers	Reduced enrollment velocity
Complex eligibility	Elevated screen failure
Hemodynamic confirmation requirements	Delayed randomization
Competing studies	Recruitment variability
Global site heterogeneity	Inconsistent startup timelines

- Enrollment rates remain modest across global PAH programs
- Site productivity varies substantially
- Initial feasibility projections may overestimate recruitable populations
- Centralized review processes improve consistency but require operational coordination

Adaptive Trial Designs

Increasing Use of Flexible Development Strategies

Increasingly implemented to:

- Small patient populations
- Pressure to accelerate timelines
- Need for efficient dose optimization
- Ability to leverage early biologic signals

Execution depends on:

- Timely data cleaning and reconciliation
- Near real-time data availability
- Centralized endpoint review
- Coordinated interim analysis planning
- Cross-functional communication and collaboration between sponsors, CROs, and vendors

Execution Strategies

Operational Approaches to Improve Efficiency

Best Practices

- Prioritize experienced PAH centers
- Conduct realistic enrollment forecasting
- Utilized centralized eligibility review
- Implement proactive recruitment strategies
- Engage with Patient Advocacy Groups
- Ensure interim analysis readiness early
- Align biomarker and imaging vendors before “first patient in”

Success Factors

- Strong data management infrastructure
- Consistent site communication
- Rapid issue escalation pathways
- Integrated oversight across functional teams

Surrogate Endpoints

Operational and Scientific Considerations

Purpose: Early Hemodynamic Response Signal

Key Considerations

- Standardized right heart catheterization (RHC) across sites
- High inter-site variability in waveform acquisition and interpretation
- Dependence on experienced catheterization labs and PAH specialists
- Scheduling challenges may delay baseline and interim assessments

Solutions

- Central adjudication of RHC tracings
- Mandatory site qualification and reader training
- Window restrictions around interim analysis timepoints
- Real-time query resolution for waveform quality issues

NT-proBNP | Purpose: Rapid Biomarker Responsiveness

Key Considerations

- High biologic variability across patients
- Sensitivity to renal function, fluid status, and comorbidities
- Importance of consistent sample collection timing
- Risk of inter-laboratory variability without central processing

Solutions

- Same-time-of-day collection at each visit
- Standardized plasma processing with defined timelines in protocol
- Central lab integration directly into interim analysis datasets
- Automated flagging of outlier values requiring reconciliation

Exercise Testing (i.e., 6-Minute Walking Test, Cardiopulmonary Exercise Testing) Purpose: Functional Assessment Of Treatment Effect

Key Considerations

- Site-to-site variability in coaching and encouragement

Solutions

- Learning effects across repeated assessments
- Environmental variability affecting patient performance
- Requirement for strict procedural consistency (i.e., oxygen supplementation, calibration/retraining requirements)
- Video-based training and certification for assessors
- Central review of selected assessments
- Repeat baseline assessments to reduce learning effect
- Environmental controls for temperature and traffic

Clinical Worsening (i.e., Composite Endpoint with Adjudication Burden) Purpose: Long-term Outcome Measure, Healthcare Utilization

Common components include PAH-related hospitalization, disease progression, initiation of parenteral prostacyclin, lung transplantation, and death.

Key Considerations

- Event-driven endpoints mature slowly in rare disease population
- Variability in hospitalization practices across countries
- Dependence on rapid event reporting and documentation
- Requirement for blinded independent adjudication committees

Solutions

- Independent Clinical Event Committee (CEC)
- Centralized hospitalization review
- Real-time notification workflows
- Integrated medical monitoring and adjudication tracking

