ASK THE EXPERTS

What's on Your Pulmonary Embolism Trial Wishlist?

Insights on what's needed to advance diagnosis, treatment decision-making, and outcomes.

With Pavan K. Kavali, MD; Mona Ranade, MD; and Amir Darki, MD, MSc

Pavan K. Kavali, MD
Associate Professor of Radiology and Surgery
Mallinckrodt Institute of Radiology
Washington University School of Medicine
St. Louis, Missouri
Disclosures: Consultant to Penumbra, AngioDynamics, and Surmodics; safety review board for Nanobiotix and Advarra.

The landscape of pulmonary embolism (PE) management has evolved dramatically, progressing from simple anticoagulation (AC) toward more nuanced risk stratification and advanced therapies such as mechanical thrombectomy (MT) and catheter-directed lytic therapy (CDT). Despite this progress, significant clinical equipoise remains, particularly regarding which intermediate-risk patients truly benefit from intervention. For too long we have relied on an alphabet soup of registries, single-arm studies, and subgroup analyses. What is missing is a definitive, patient-centered trial that tells us not just whether we can treat, but who should be treated, when, and why.

My ideal PE trial would begin by defining who genuinely benefits from advanced therapy. Intermediate-risk PE remains a broad category that groups together a wide range of physiologic presentations. Although guidelines subdivide patients into intermediate-high and intermediate-low risk, these labels still mask substantial heterogeneity. Some intermediate-high patients recover beautifully with AC alone, while others progress rapidly to right ventricular (RV) failure, shock, and death. A trial that incorporates multimodal risk stratification using imaging scores, biomarkers, RV strain, NT-proBNP (N-terminal pro–B-type natriuretic peptide), troponin, and pulmonary artery (PA) pressures could substantially identify the group with reversible RV dysfunction who stand to benefit most from reperfusion therapy.

The next priority is redefining trial endpoints. Mortality has often been dismissed as too rare to serve as a meaningful primary endpoint in PE research; yet, excluding it entirely prevents us from identifying the patients who experience a true survival benefit. Rather than avoiding mortality endpoints, we need trials that meaningfully evaluate both all-cause and PE-related mortality. This requires enrolling patients who are at legitimate risk of clinical deterioration, including those with evolving RV failure, elevated cardiopulmonary demand, limited physiologic reserve, or disproportionate clinical stress compared to their clot burden. When these patients are selected using imaging, biomarkers, and artificial intelligence (AI)–driven CT analysis, a contemporary trial is more likely to accumulate enough events to assess 30- and 90-day mortality. This matters because deaths after PE may stem from the embolism itself, comorbid conditions, or complications of therapy.

At the same time, PE-related mortality must be adjudicated carefully. Distinguishing deaths directly caused by PE from those due to unrelated factors will clarify whether advanced therapies change the natural history of the disease or merely improve early hemodynamic or imaging findings without altering survival. When mortality outcomes are linked to physiologic, perfusion, and imaging data, we can better understand why some patients with similar initial clot burdens and similar 48-hour clot resolution have very different trajectories. This approach also helps identify the biological and cardiopulmonary characteristics that separate survivors from nonsurvivors.

Beyond mortality, we need endpoints that matter to the majority of patients who survive intermediate-risk PE. These include functional recovery, freedom from exertional dyspnea, and overall quality of life. Metrics such as

the 6-minute walk test, cardiopulmonary exercise testing, patient-reported outcomes like PEmb-QoL, and RV recovery on follow-up imaging should be central. Importantly, follow-up must extend beyond discharge or 7 days. The clinical story of PE unfolds over months and sometimes years. A game-changing trial would track recovery trajectories and identify who returns to normal life, who does not, and why.

A critical component of this vision is the integration of AI-based imaging analytics. Modern tools can extract quantitative insights from CT PE protocols by measuring RV volumes, assessing perfusion deficits, characterizing clot morphology, and tracking postintervention changes. In a next-generation trial, AI would compare baseline and 48-hour imaging to determine which patients demonstrate true physiologic recovery versus those who show radiographic improvement yet remain limited. These analyses could uncover the biological and physiologic factors that drive divergent outcomes in patients who appear similar at presentation.

Finally, each of the above parameters should be encompassed in a pragmatic, multicenter, device-agnostic trial that compares standardized catheter-based therapy to optimized AC in clearly defined intermediate-risk patients. Embedding the study within existing PE response team (PERT) networks would enhance feasibility and reflect real-world practice with few exclusion criteria. The goal is a trial that remains broad enough for real-world applicability while maintaining the rigor required for reproducible results.

The future of PE research is not about doing more interventions. It is about doing smarter interventions for the right patients and measuring outcomes that matter. That is the PE trial I am wishing for.

Mona Ranade, MD
Clinical Associate Professor, Radiology
Stanford University
Los Angeles, California
Disclosures: Consultant to Penumbra, Inari/Stryker, Boston Scientific Corporation, Akura Medical, and Medtronic.

Despite major strides in acute PE management, many of our current trials remain narrowly focused—often excluding the very populations that reflect real-world complexity. My PE trial wishlist centers on addressing these clinically meaningful, yet underexplored intersections in PE care: cancer, infection/inflammation, device mechanics, time to intervention, extracorporeal mechanical oxygenation (ECMO) timing, and health care economics.

Active cancer: the biggest blind spot in MT research. One major unmet need is the management of massive and submassive PE in patients with active malignancy. These individuals are routinely excluded from MT studies due to concerns about bleeding risk or limited prognosis, yet they comprise a substantial high-risk cohort frequently presenting with PE. A dedicated prospective, multicenter trial comparing (1) MT plus AC versus MT alone versus AC alone in cancer-associated PE and (2) outcomes in nonanticoagulated MT patients with absolute contraindications (eg, intracranial hemorrhage) would directly inform the management of populations we currently treat empirically.

Inflammation, infection, and the RV: disentangling physiology. Another critical frontier is understanding how proinflammatory states, such as sepsis, pneumonia, or other infections, interact with RV strain in submassive PE. Distinguishing inflammatory cardiopulmonary compromise from true obstructive shock could dramatically improve selection for advanced intervention. Future trials should incorporate biomarkers (C-reactive protein, IL-6), advanced echocardiographic metrics (strain, TAPSE/systolic PA pressure, RV free wall mechanics), and phenotypic stratification to separate inflammatory shock from clot-driven hemodynamic collapse to refine our hemodynamic decision-making.

Procedural mechanics: does device size matter? It's time to interrogate the procedural side of MT more rigorously. We lack data on whether catheter caliber, aspiration mechanics, and clot volume extracted truly influence RV/LV ratio recovery, pulmonary vascular resistance, gas exchange at the alveolar level, and rates of rebound or persistent pulmonary hypertension. Correlating device characteristics with measurable cardiopulmonary outcomes could shift the field from a one-size-fits-all approach to genuine procedural optimization.

Time to intervention: the most understudied variable. Perhaps the least understood but most impactful variable is time to intervention. Delays in diagnosis, transfer, triage, or team activation may blunt the physiologic benefit of MT, particularly in intermediate-risk PE where early RV unloading may matter most. We urgently need trials that examine early versus delayed MT, RV recovery trajectories based on intervention timing, and system-level factors (emergency department workflow, PERT activation, community-to-tertiary transfer delays) to determine whether "faster is better" and, if so, how fast is fast enough.

ECMO timing and adjunctive therapy sequencing. Understanding timing of ECMO relative to CDT/MT—

before, during, or after intervention—is another critical gap. A trial that randomizes patients with cardiogenic shock to defined ECMO intervention sequences could generate urgently needed guidance for catastrophic PE.

Health care economics and systems-level reality. A transformative trial would incorporate economic and systems-level data, addressing resource utilization across diverse hospital environments; cost-effectiveness of MT, CDT, ECMO, and hybrid approaches; and barriers to timely access in community versus academic settings. This information is essential for shaping policy, reimbursement, and equitable national care models.

A platform trial that brings it all together. The ultimate "dream trial" is a pragmatic, registry-embedded, randomized platform trial that integrates all of these domains. Patients would be stratified by: (1) Clinical phenotype: Cancer, inflammatory state, shock type; (2) procedural variables: Catheter size, clot morphology, ECMO timing; (3) resource context: cademic versus community centers. The goal wouldn't simply be to compare devices—it would be to generate a unified, phenotype-driven, system-aware framework for PE management.

STORM-PE: a landmark step forward. Any wishlist for future trials must acknowledge the STORM-PE trial—now a landmark study demonstrating that MT is superior to systemic AC alone in intermediate-risk PE, particularly in improving RV function with a strong safety profile.[1] STORM-PE represents a pivotal step in validating MT, but it also raises deeper questions about which patients benefit most and when the intervention should occur—questions only a broader, phenotypically enriched research agenda can answer.

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Amir Darki, MD, MSc
Associate Professor of Medicine–Cardiology
Loyola University Medical Center
Chicago, Illinois
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Acute PE remains a leading cause of morbidity and mortality, with approximately 60,000 to 100,000 deaths annually in the United States.[1] The clinical presentation of acute PE is heterogeneous, ranging from incidental and asymptomatic to profound hemodynamic collapse and sudden death. Despite advances in diagnostic capabilities and therapeutic strategies, it is estimated that approximately 25% to 30% of all PE cases first present as sudden death, underscoring the urgent need for improved early recognition and treatment strategies.[1]

Accurate risk stratification plays a central role in guiding management of acute PE. Current prognostic tools such as the PE Severity Index, its simplified version, and the composite PE shock score are widely used in clinical practice. Their greatest strength lies in identifying low-risk patients, but they unfortunately have low positive predictive value, reflecting limited ability to differentiate clinically meaningful risk among intermediate- and high-risk patients.[2,3]

Beyond early mortality, it is increasingly recognized that risk assessment must also incorporate the potential for long-term morbidity. Up to 30% to 50% of patients may experience persistent dyspnea, reduced quality of life, and exercise impairment after acute PE.[4,5] Identifying patients at risk for both acute decompensation and chronic physiologic impairment remains an unmet need.

The field has rapidly advanced through multiple clinical trials evaluating catheter-directed therapies under investigational device exemption pathways. These studies have largely focused on the safety and efficacy of individual devices or comparison of endovascular devices. However, they have not adequately addressed the key clinical dilemma: determining which specific patients derive the greatest benefit from interventional therapy versus AC alone.

An ideal future trial would define which high-risk patients warrant early escalation of care while maintaining a low risk of bleeding. Additionally, it would identify subgroups at risk for developed chronic PE-related syndromes, including chronic thromboembolic pulmonary hypertension and chronic thromboembolic disease. A game changer would be the validation of a biomarker-integrated risk score with strong positive predictive value to guide advanced therapies, personalize treatment decisions, and ultimately improve both short- and long-term outcomes. ■

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