

A Data-Driven Framework for Rare Disease Protocol Design: Integrating Real-World Evidence, Patient Perspectives, and Regulatory Guidance

PCR5



Craig McIllooney*, Bavaajan Devarapalli, Vatsal Chhaya, Shaurya Deep Bajwa, Kapil Khambholja
Catalyst Clinical Research, Wilmington, NC, USA

Presented at ISPOR Europe 2025: November 9-12, 2025; Glasgow, Scotland

INTRODUCTION



Problem

Global Burden

- 300M+ people, 7,000+ rare diseases — yet <10% have approved therapies.

Low Success Rates

- Only ~12% of rare disease drug candidates reach approval vs. ~20% for common diseases.

Small & Diverse Populations

- Tiny, heterogeneous cohorts hinder statistically sound study designs.

Evidence Challenge

Sparse Natural History Data

- Incomplete disease understanding limits endpoint validation.

Regulatory Readiness Gap

- Fragmented evidence weakens submission quality and slows review.

The Way Forward

- Adopt data-driven, fit-for-purpose protocol frameworks to enable future-ready rare disease research.

OBJECTIVES

To develop a conceptual, regulatory compliant framework for rare disease protocol design.

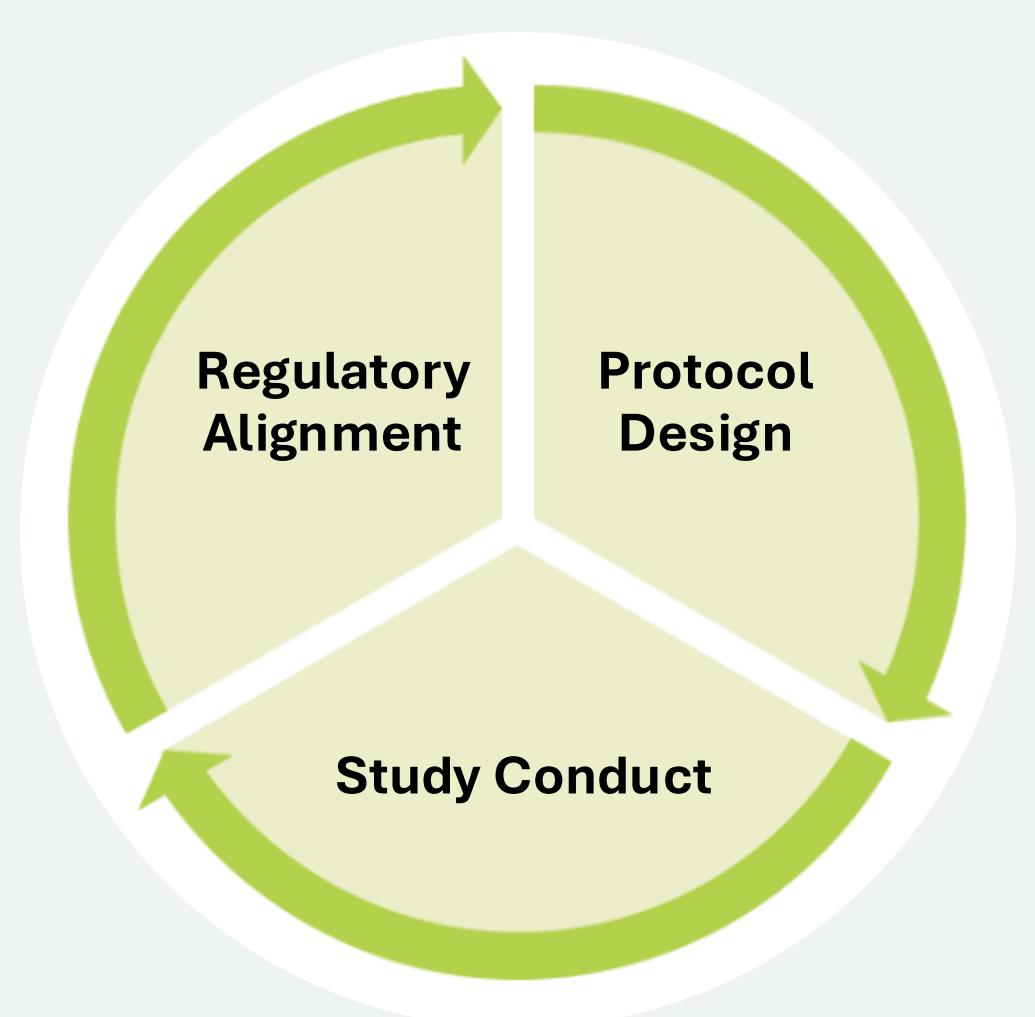
METHODS

Mixed-methods approach combining regulatory, clinical, and real-world evidence (RWE) sources.

Reviewed:

- Global regulatory and scientific publications.
- Data from open-access registry: www.clinicaltrials.gov.
- Expert opinion.

Insights synthesized into a three-pillar framework:

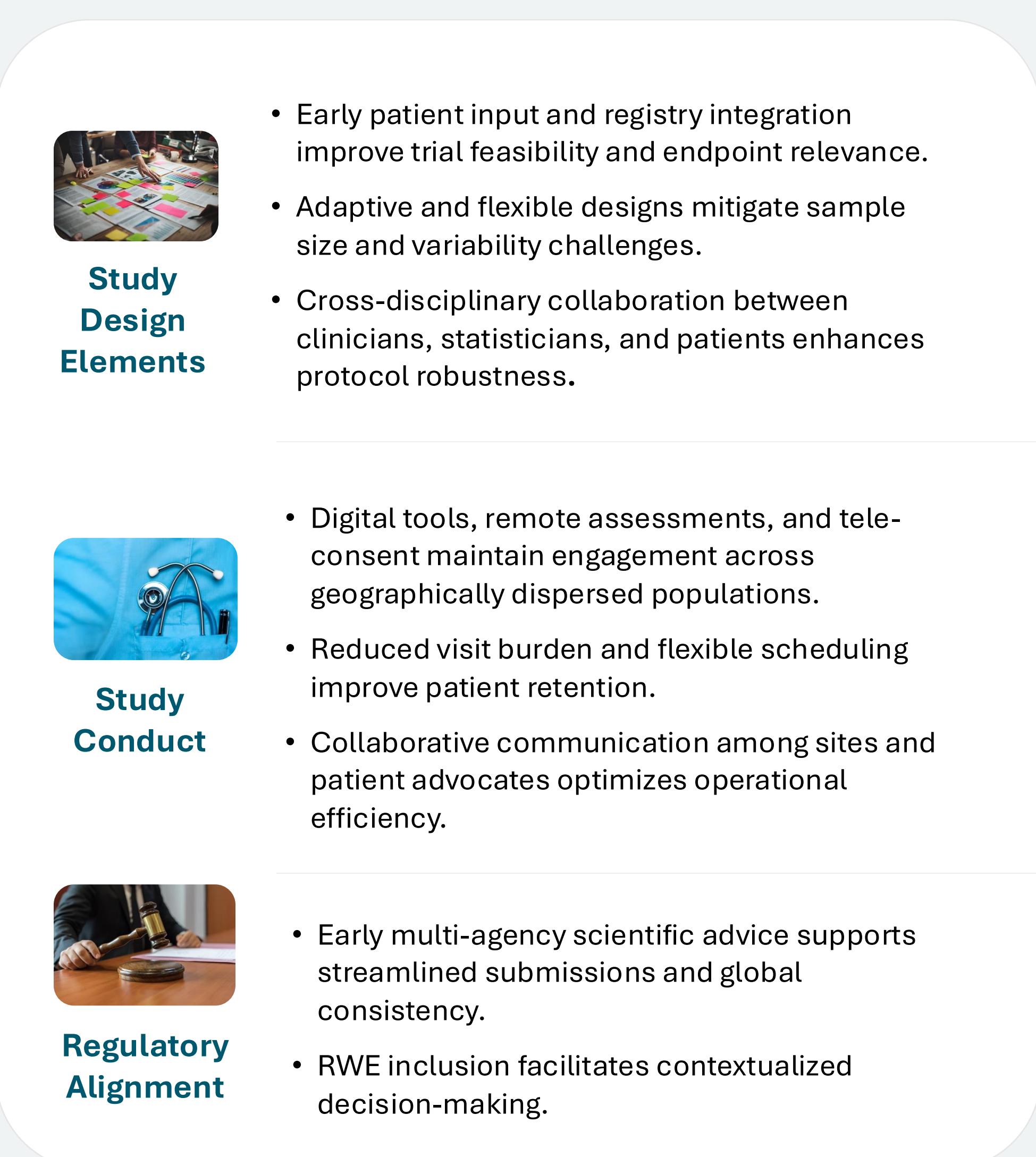
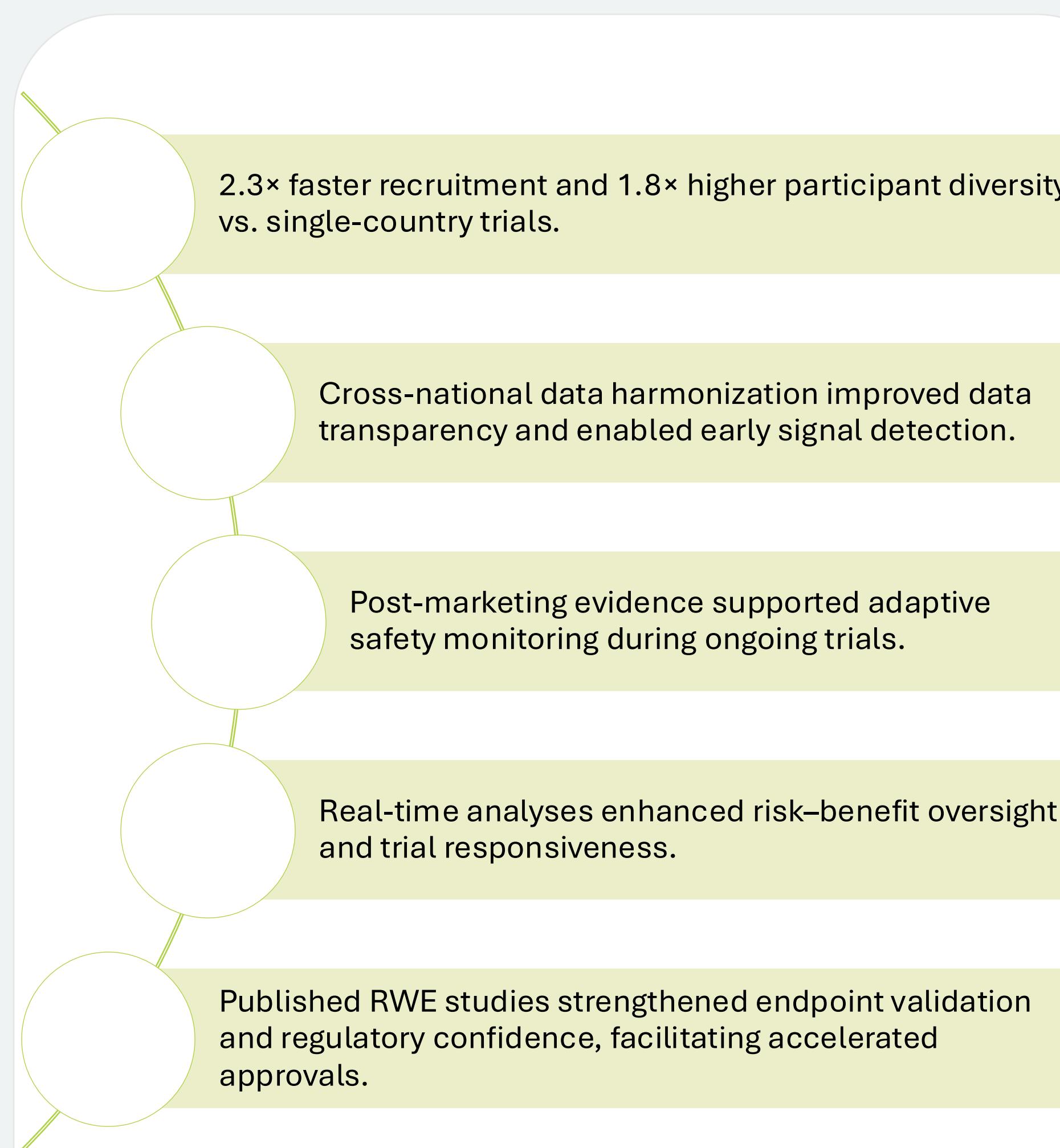
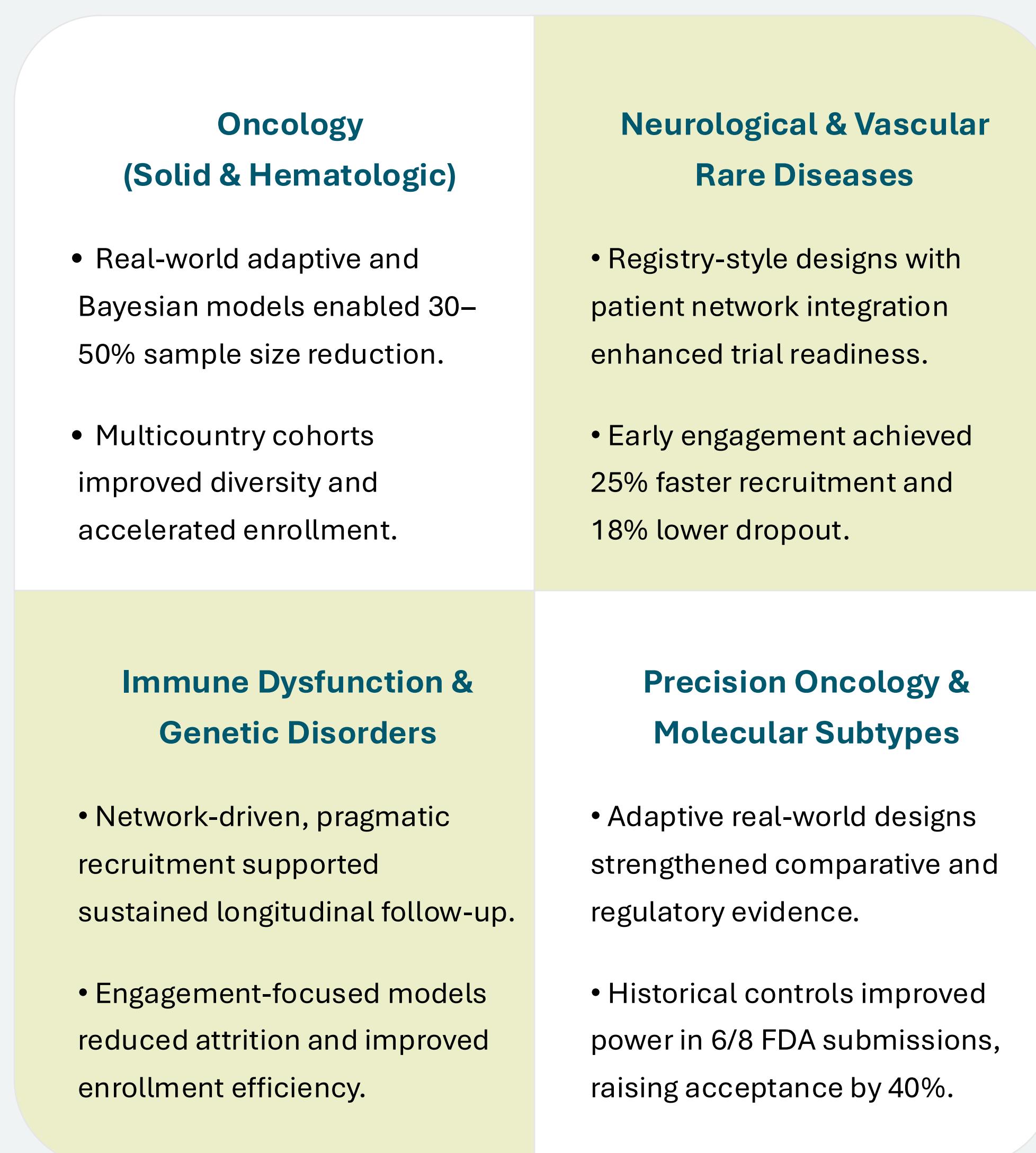


RESULTS AND DISCUSSION

Insights from ClinicalTrials.gov Clinical Study Protocols

Insights from Global Regulatory Guidance and Publications

Insights from Experts Interviews



STRENGTHS AND LIMITATIONS

Strengths:

- Integration of regulatory, clinical, and real-world evidence provides a comprehensive, pragmatic framework for rare disease trial design.
- Inclusion of clinical trials data ensures global applicability and real-world relevance.
- Evidence derived from clinical protocols, regulatory guidance, and expert perspectives offers robust multidimensional insights.
- Framework is aligned with FDA, EMA, and ICH M11 guidance, enhancing regulatory credibility.

Limitations:

- Dependent on secondary literature and published interviews; no primary data validation conducted.
- Registry access limitations may impact reproducibility of findings.
- Improvements in recruitment and feasibility are disease-specific and may not generalize across all indications.

CONCLUSION AND FUTURE RECOMMENDATIONS

- Early patient involvement and registry linkage enhance trial feasibility, recruitment, and relevance.
- Adaptive, hybrid, and decentralized designs effectively overcome limited population and endpoint variability challenges.
- Digital and remote trial tools optimize engagement and reduce patient burden in dispersed cohorts.
- Proactive, multi-agency regulatory engagement integrating RWE and data harmonization strengthens global approvals and safety oversight.
- Registry-informed multinational studies demonstrate faster recruitment, greater diversity, and enhanced pharmacovigilance.
- Future directions:** Expand AI-enabled simulations, registry data interoperability, and global harmonization of rare disease protocols to accelerate therapeutic access and regulatory readiness.

Redefining Rare Disease Trials

REFERENCES

- Guidance Documents for Rare Disease Drug Development | FDA
- ICH M11 guideline, clinical study protocol template and technical specifications - Scientific guideline | European Medicines Agency (EMA)
- European Policy - EURORDIS - Rare Diseases Europe
- Homepage - EDRDA
- Rare Diseases - HTAi
- Rare therapies and UK regulatory considerations - GOV.UK

CONTACT INFORMATION

Craig McIllooney

SVP, Catalyst Flex

Catalyst Clinical Research

Email: Craig.McIllooney@catalystcr.com
www.CatalystCR.com

Copyright ©2025 Catalyst Clinical Research.



SCAN HERE
TO LEARN MORE