

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

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CATALYST FLEX

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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.

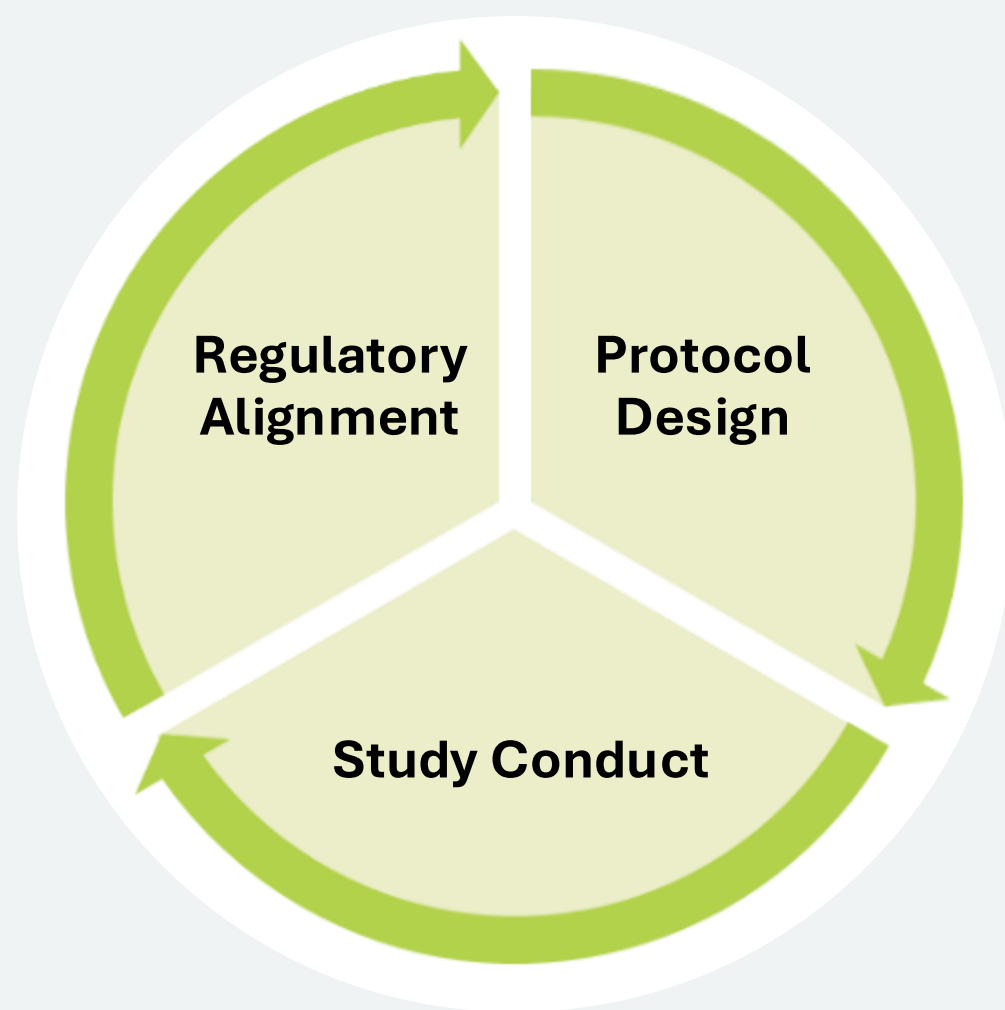


Data from open-access registry: www.clinicaltrials.gov.



Expert opinion.

Insights synthesized into a **three-pillar framework**:



RESULTS AND DISCUSSION

Insights from ClinicalTrials.gov Clinical Study Protocols

Oncology (Solid & Hematologic)

- Real-world adaptive and Bayesian models enabled 30–50% sample size reduction.
- Multicountry cohorts improved diversity and accelerated enrollment.

Immune Dysfunction & Genetic Disorders

- Network-driven, pragmatic recruitment supported sustained longitudinal follow-up.
- Engagement-focused models reduced attrition and improved enrollment efficiency.

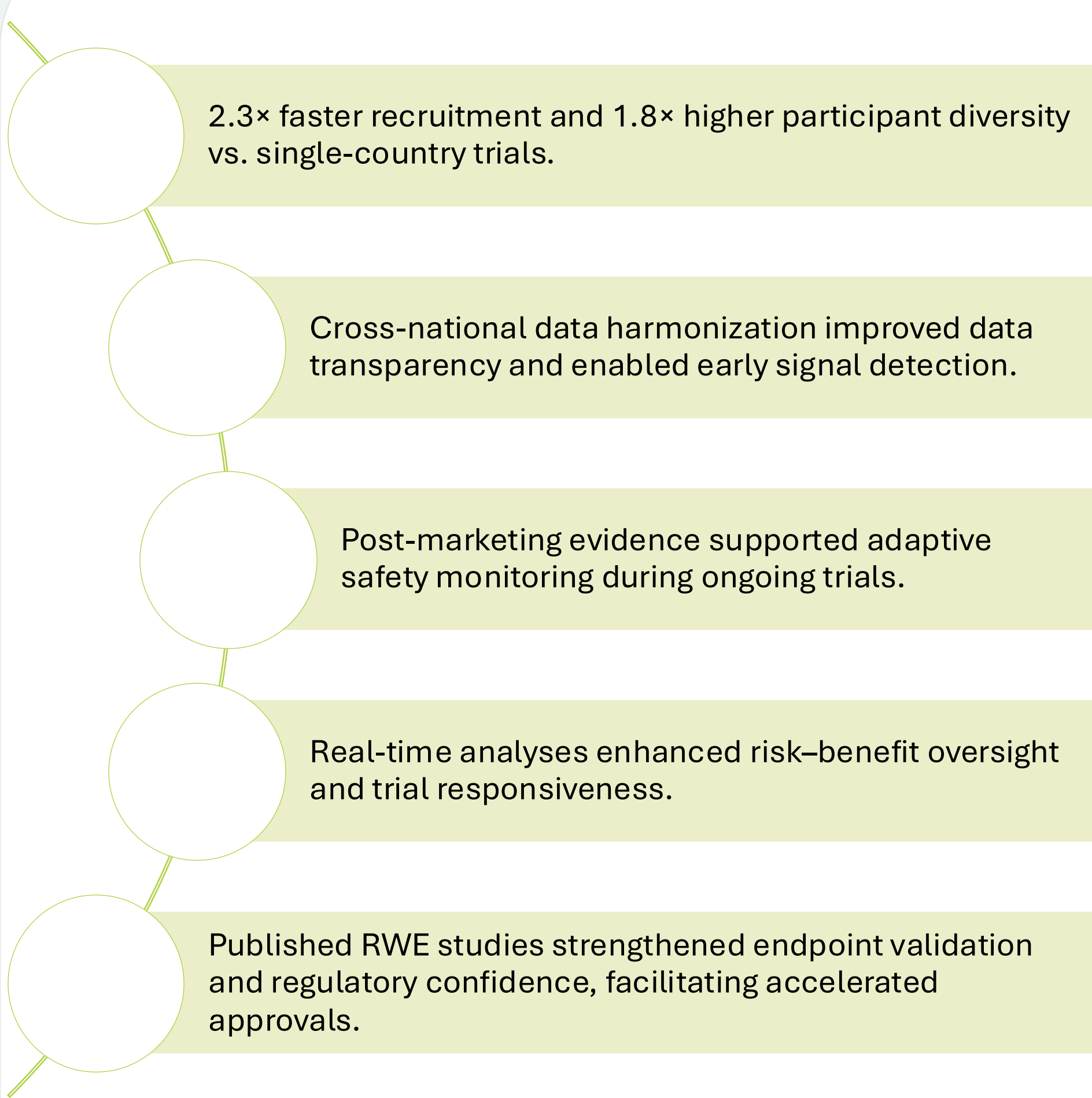
Neurological & Vascular Rare Diseases

- Registry-style designs with patient network integration enhanced trial readiness.
- Early engagement achieved 25% faster recruitment and 18% lower dropout.

Precision Oncology & Molecular Subtypes

- Adaptive real-world designs strengthened comparative and regulatory evidence.
- Historical controls improved power in 6/8 FDA submissions, raising acceptance by 40%.

Insights from Global Regulatory Guidance and Publications



Insights from Experts Interviews



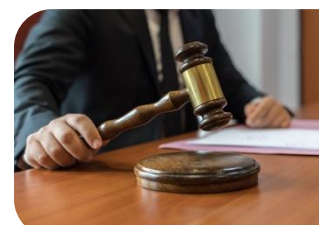
Study Design Elements

- Early patient input and registry integration improve trial feasibility and endpoint relevance.
- Adaptive and flexible designs mitigate sample size and variability challenges.
- Cross-disciplinary collaboration between clinicians, statisticians, and patients enhances protocol robustness.



Study Conduct

- Digital tools, remote assessments, and tele-consent maintain engagement across geographically dispersed populations.
- Reduced visit burden and flexible scheduling improve patient retention.
- Collaborative communication among sites and patient advocates optimizes operational efficiency.



Regulatory Alignment

- Early multi-agency scientific advice supports streamlined submissions and global consistency.
- RWE inclusion facilitates contextualized decision-making.

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 - ERDERA
- Rare Diseases - HTAi
- Rare therapies and UK regulatory considerations - GOV.UK

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