

Optimizing Power and Sample Size for Biomarker-Driven Basket Trials in Neurodegenerative Diseases

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Abstract
IR028

Running multiple indications simultaneously in a biomarker-driven basket trial dramatically reduces enrollment sample sizes, lowers R&D costs, and eliminates guesswork to rapidly transition winning indications into Phase 3.

INTRODUCTION

Shared Pathologies: Rare neurodegenerative diseases (like HD, PSP, and ALS) share underlying cellular pathologies.

Pan-Indication Potential: Therapies targeting these shared mechanisms are promising, but sequential drug development is too slow and costly.

The Sequential Dilemma: Predicting an indication's success without prior data makes sequential testing highly risky.

The Parallel Basket Solution: A master protocol tests multiple indications simultaneously with small cohorts, replacing guesswork with empirical data.

METHODS

Running the Basket Trial:

- **Single Master Protocol:** Evaluates one drug across multiple rare disease groups (HD, PSP, ALS, AD) at the same time under a unified study structure.
- **Small Parallel Groups:** Enrolls small initial cohorts to quickly compare proof-of-concept results side-by-side.
- **Objective Biomarkers:** Replaces noisy subjective scales with a 3-tier biomarker panel (blood, fluid, and imaging) to catch clear drug signals fast.

Power Calculations:

Historical Data Extraction: Sourced natural disease progression and placebo decline rates from ClinicalTrials.gov and published literature.

Sample Size Projections: Standardized endpoint noise using MSDR and Cohen's d to plot power curves across candidate diseases.

RESULTS

Biomarker Endpoint: Shared biomarkers may exhibit similar sensitivity to change across diseases.

Clinical Endpoint: High endpoint variability substantially increases the required sample size for an indication.

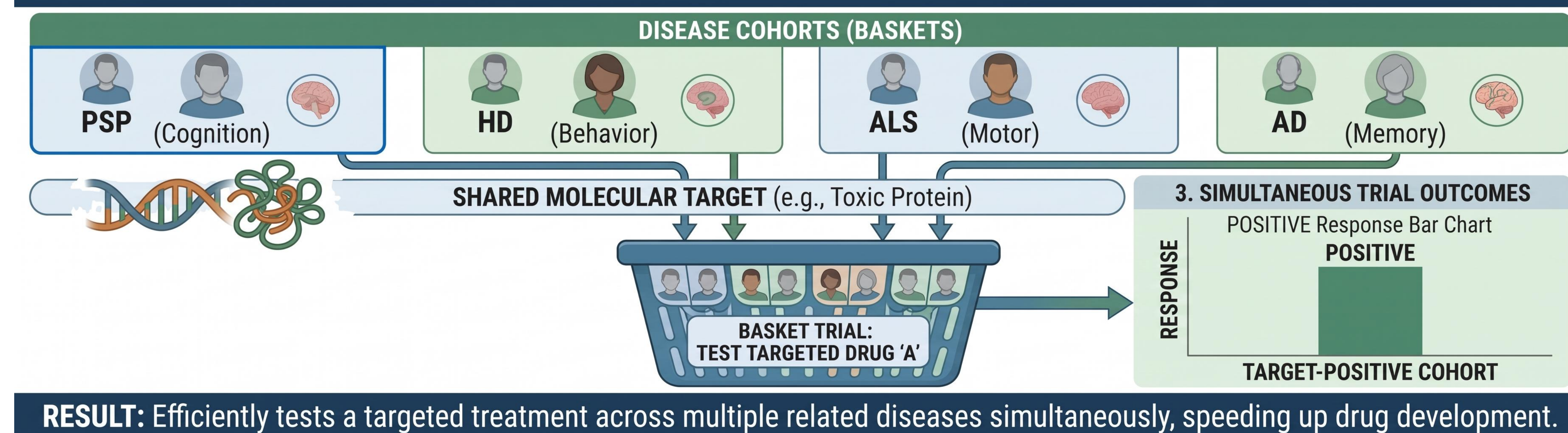
Reduce Risk: Choosing a single lead indication based on opinion is high-risk and requires massive enrollment.

The Basket Trial Advantage: Test multiple indications with small parallel arms under a master protocol to evaluate without massive upfront enrollment.

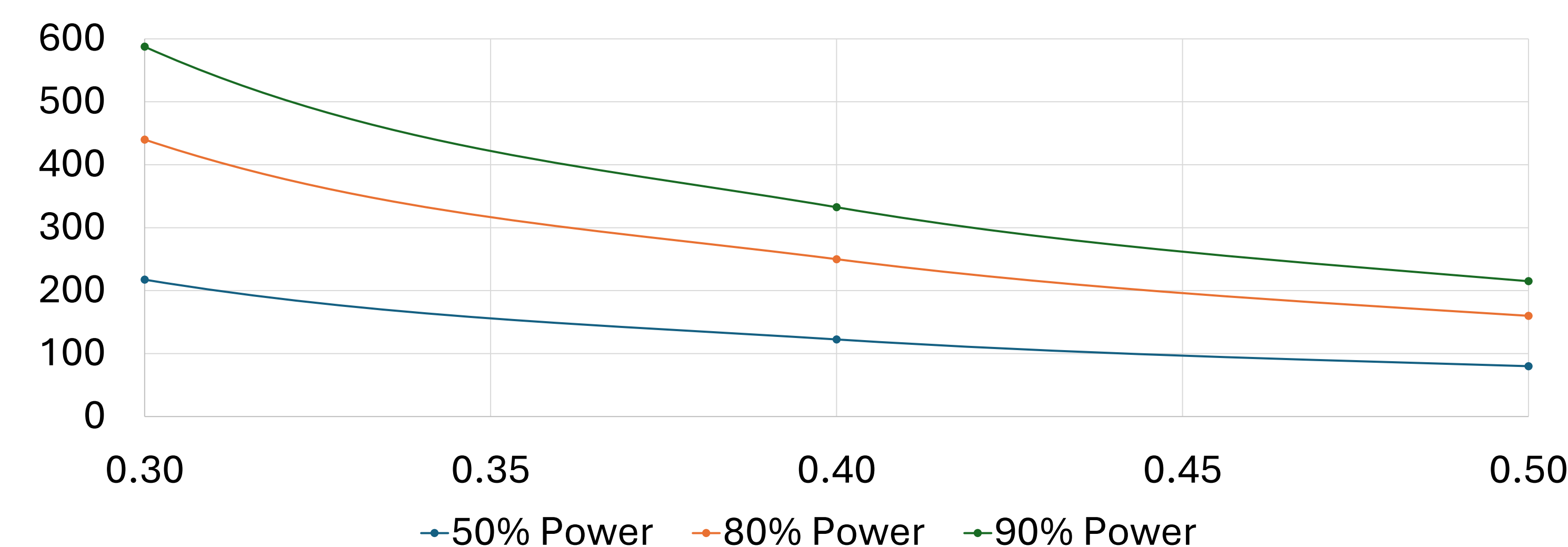
Rapid Phase 3 Transition: Simultaneous studies reveal the ideal indication to confidently advance to Phase 3.

RESULTS

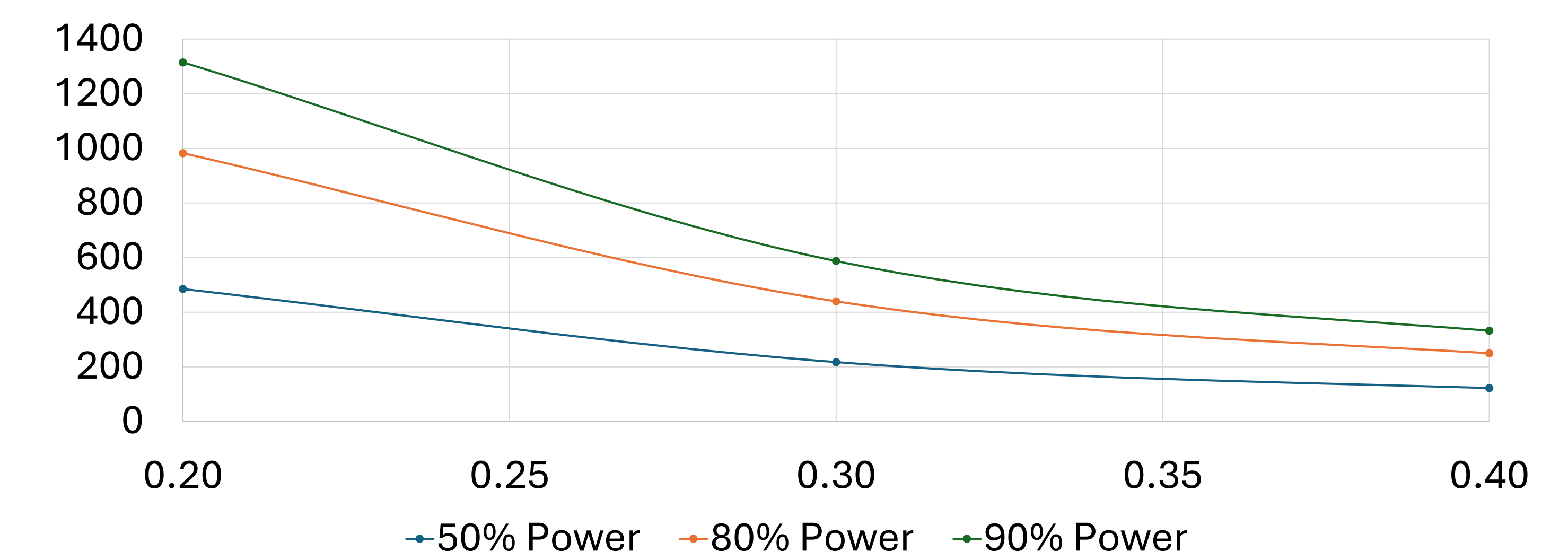
BASKET TRIAL: A SIMPLIFIED VIEW FOR NEURODEGENERATIVE DISEASES



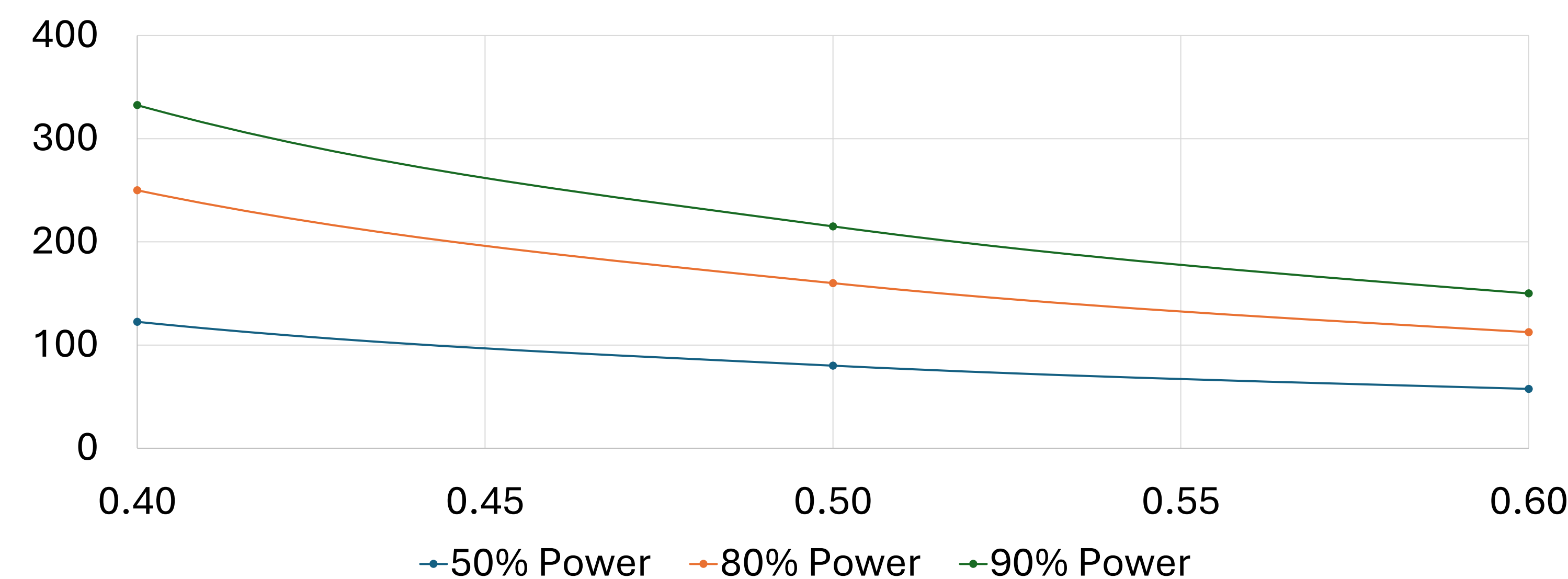
Huntington's Disease Total Sample Size – 30% effect (20% dropout)



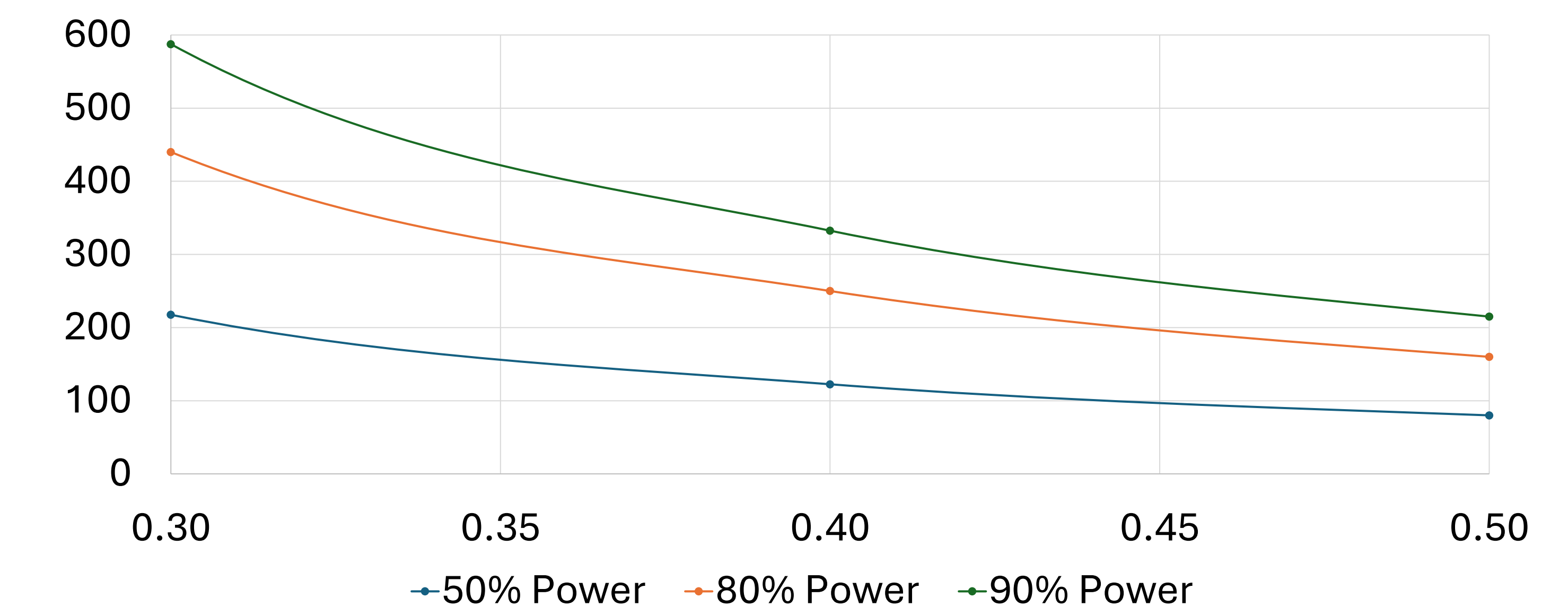
Mild/Moderate AD Total Sample Size – 30% effect (20% dropout)



PSP Total Sample Size – 50% effect (20% dropout)



ALS Total Sample Size – 30% effect (20% dropout)



REFERENCES

1. **U.S. Food and Drug Administration. (2023).** *Rare Diseases: Considerations for the Development of Drugs and Biological Products Guidance for Industry*. U.S. Department of Health and Human Services, CDER/CBER.
2. **Woodcock, J., & LaVange, L. M. (2017).** Master protocols to study multiple therapies, multiple diseases, or both. *New England Journal of Medicine*, 377(1), 62–70
3. **ClinicalTrials.gov.** U.S. National Library of Medicine. Database of publicly and privately conducted clinical studies (Historical placebo cohort data extraction).

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