A biomarker-based adaptive two-stage randomized phase II study design

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Trial Design Setting

- Phase II
- Putative targeted therapy
- Limited historical data
  - No well-defined sensitive subgroup
  - Outcome within biomarker-defined subgroups
- Potential biomarker to identify sensitive pop
  - Sufficient frequency of biomarker +
- Randomization
  - Reference arm
  - Intermediate endpoint
- Include all patients, allows preliminary assessment of biomarker-treatment interaction on short-term outcome
- interim analysis

Phase II Trials-Targeted Therapy

Q: **How well do we know drug** and target?

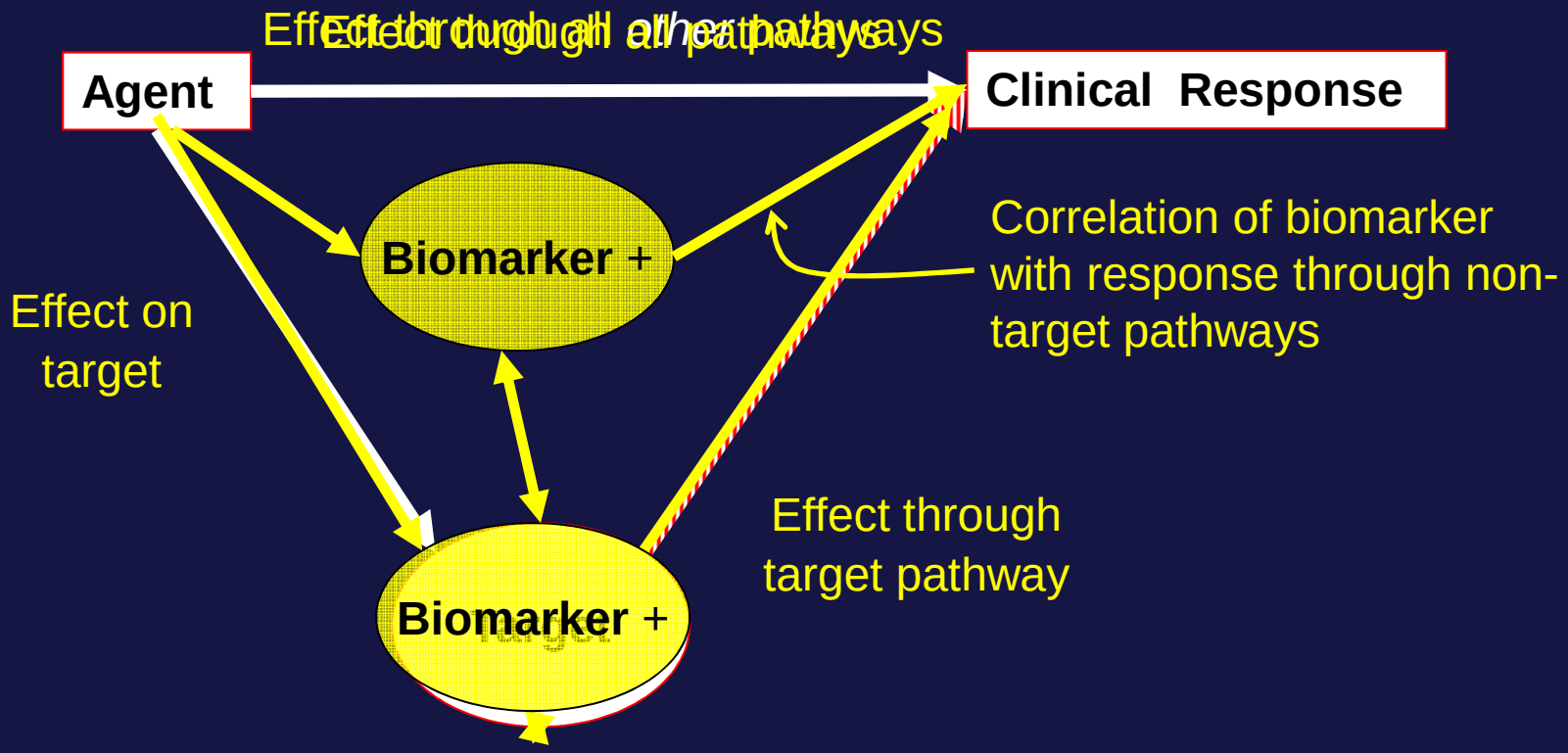
Q: **Is the drug active** AND do we have the correct biomarker to identify a sensitive population?

Goal of trial:

1. **Assess Intervention's activity** AND
2. Assess Biomarker's predictive ability AND
3. Inform Phase III trial design, eligibility

Phase II Evaluation of Biomarker & Agent

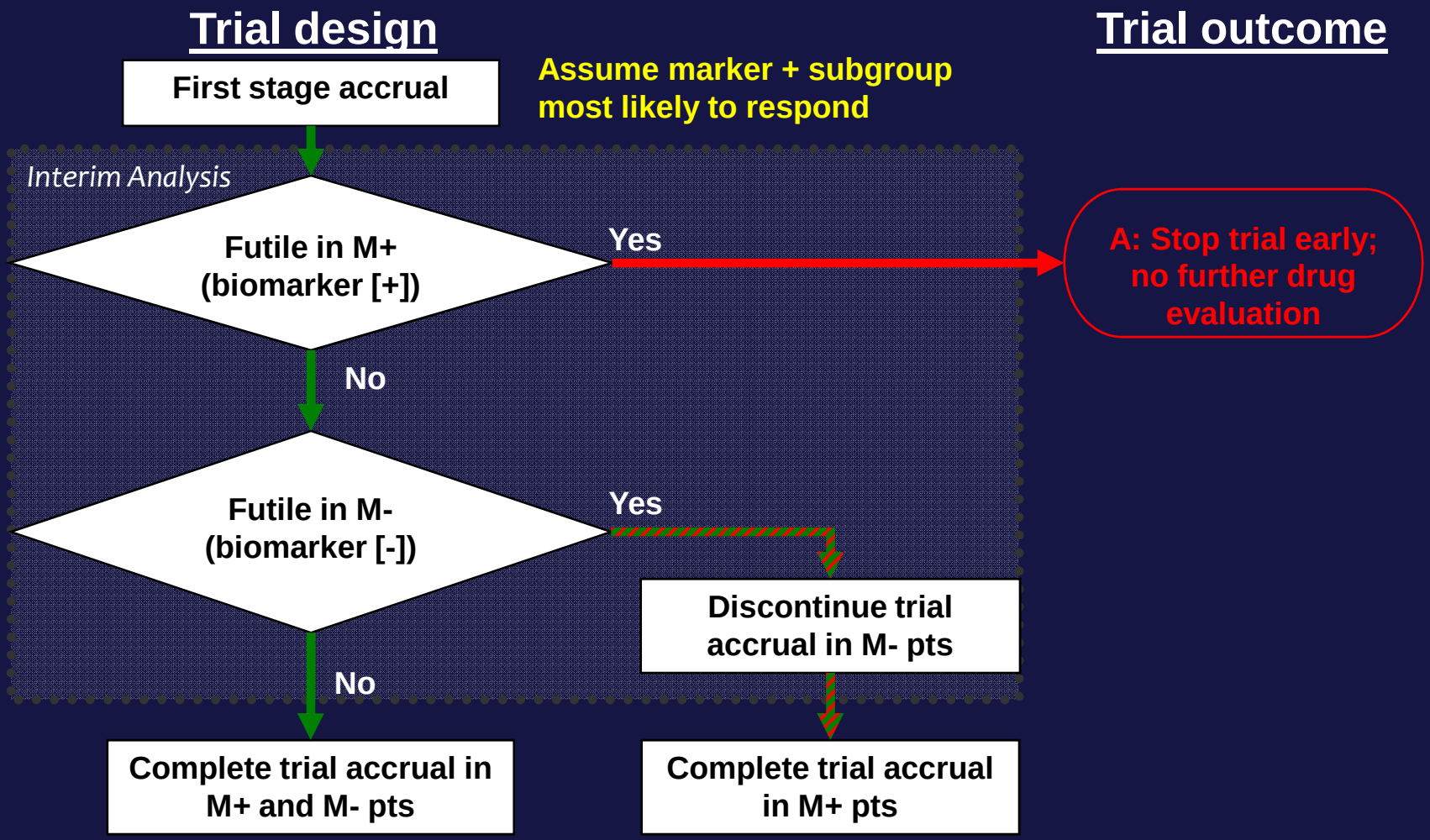
- **Mechanistic diagram**



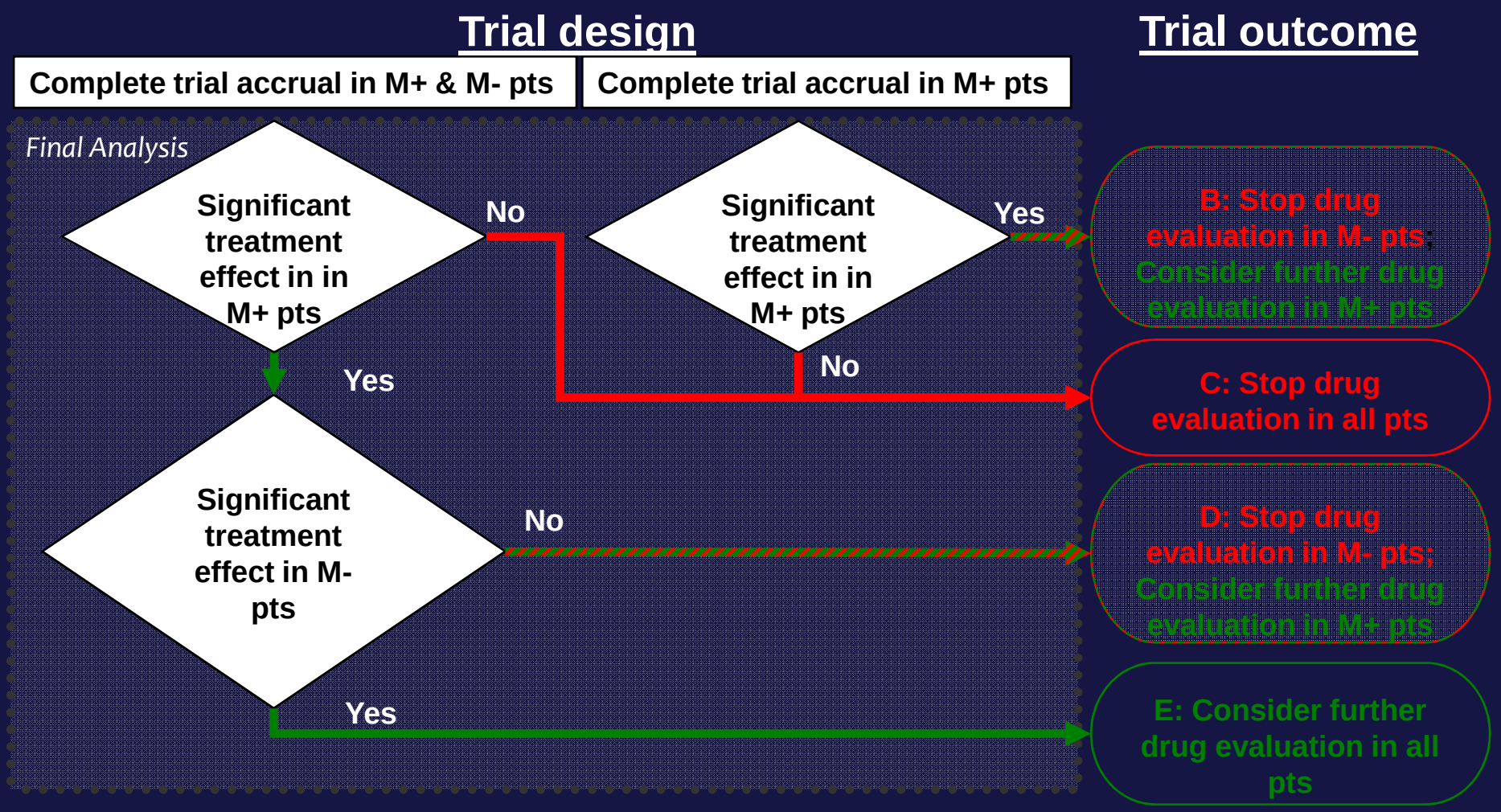
Trial Designs Using Biomarkers

1. Single Arm Phase II
   a. with selection, stratification or parallel studies
   b. multi-stage
   c. adaptive
2. Randomized Phase III
   a. Target marker positive
   b. Randomized Treatment Strategy
   c. “Randomize-All”
   d. Adaptive (Interim analysis: futility, negative interaction, efficacy)
3. Phase II/III

Trial Design & Outcomes Stage I



Trial Design & Outcomes Stage II



Simple Example

Marker +

- **65% of population**
- **30% response**
- **Assumed most likely to be sensitive**

Marker –

- **35% of population**
- **10% response**

Power to detect a 20% increase in response

Maximum Type I Error: 10%

Maximum Type II error: 20%

Marker + subgroup drives the trial outcome

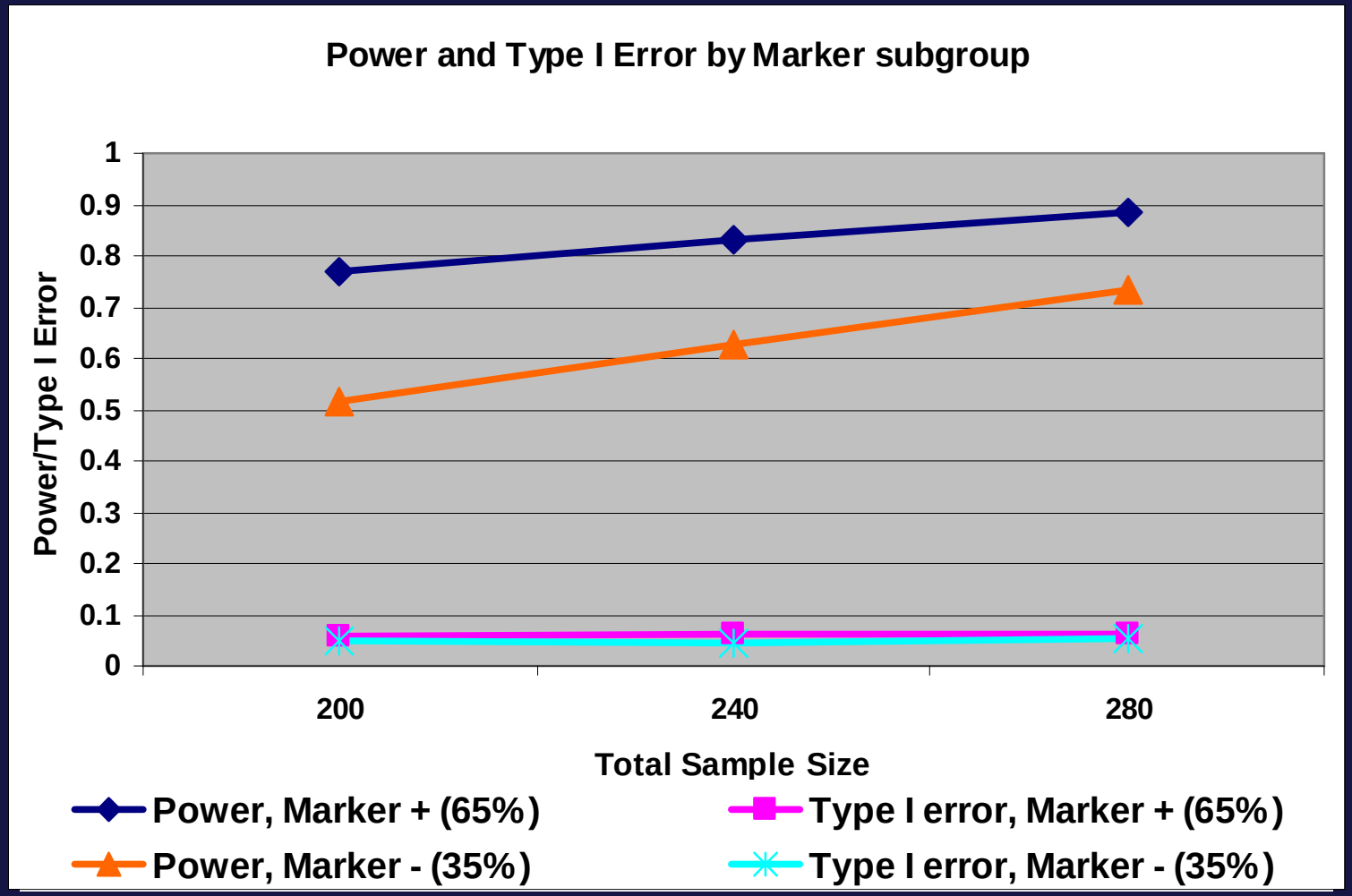
Simple Example

Two stage design

Interim analysis based on futility: response rate in reference arm is greater than that in experimental arm

Final analysis utilizes Fisher's Exact Test

Trial Design Characteristics



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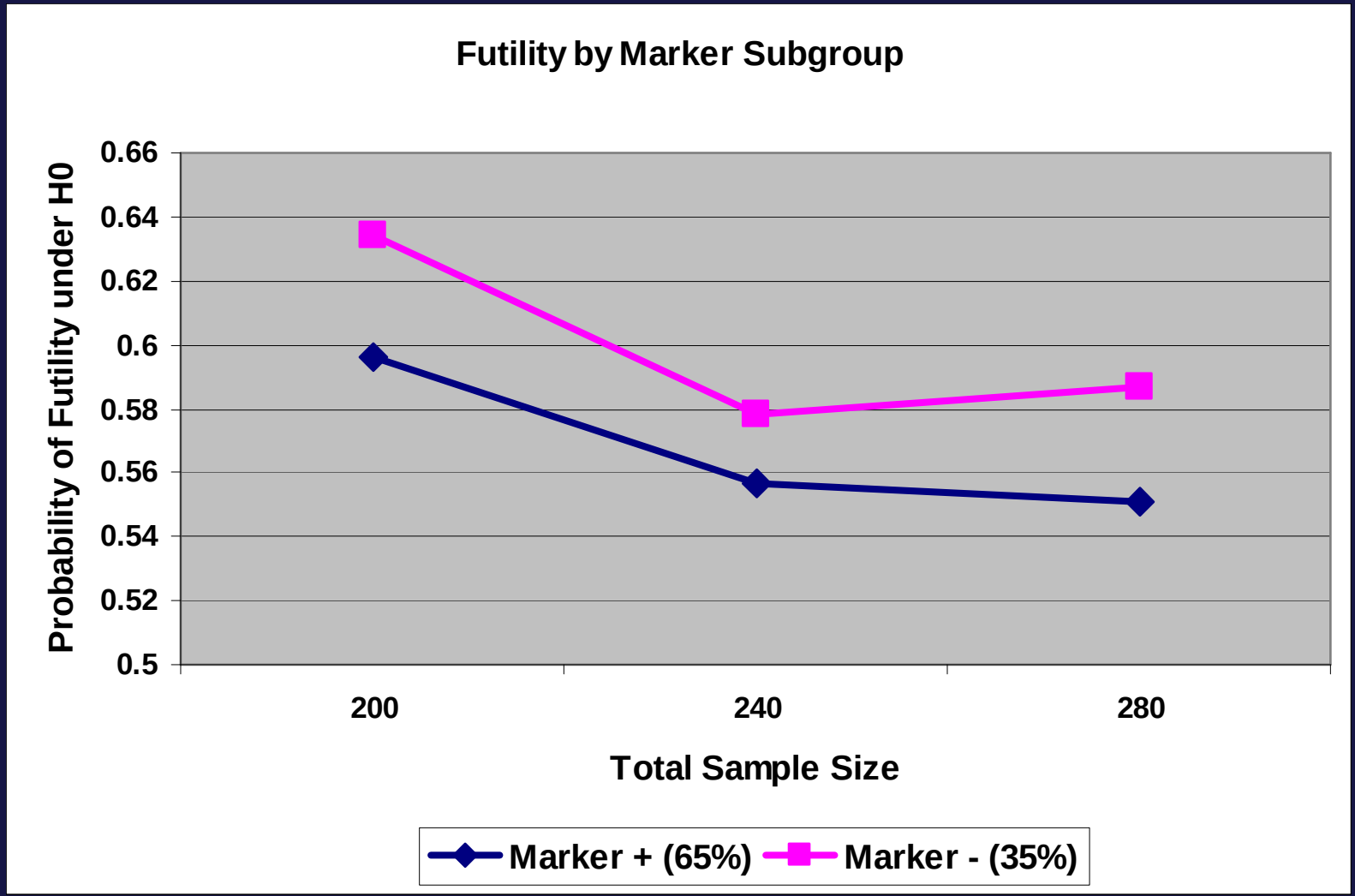
Trial Design Characteristics



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Summary

- Trial design is not general phase II design
- Requires consideration of the following:
  - Appropriate reference arm
  - Ratio of marker + (likely sensitive) to marker –
  - Sensitive population not well-defined
  - Lack of robust historical data
  - Can tolerate less precision for marker –
  - Aggressiveness of interim monitoring
  - Tolerable error rates for each subgroup
  - Can be generalized to other endpoints

Summary

- Enrolling all patients allows investigation of other biomarkers if biospecimens are collected
- Can generalize to likelihood approach
- In this setting a single arm trial can likely fail due to the failure of the biomarker
- Weigh the amount of time to screen for a single arm trial in selected population against the time to accrue the first stage of the randomized trial in unselected patients

Acknowledgements

Mark Brady, PhD

Thank you for your attention!