Adaptive Platform Trial Scientific Meeting

September 28 – 29 • Toronto, Canada

CanTreatCOVID

Canadian Adaptive Platform Trial of Treatments for COVID in Community Settings

Bayesian Analysis in Adaptive Trials

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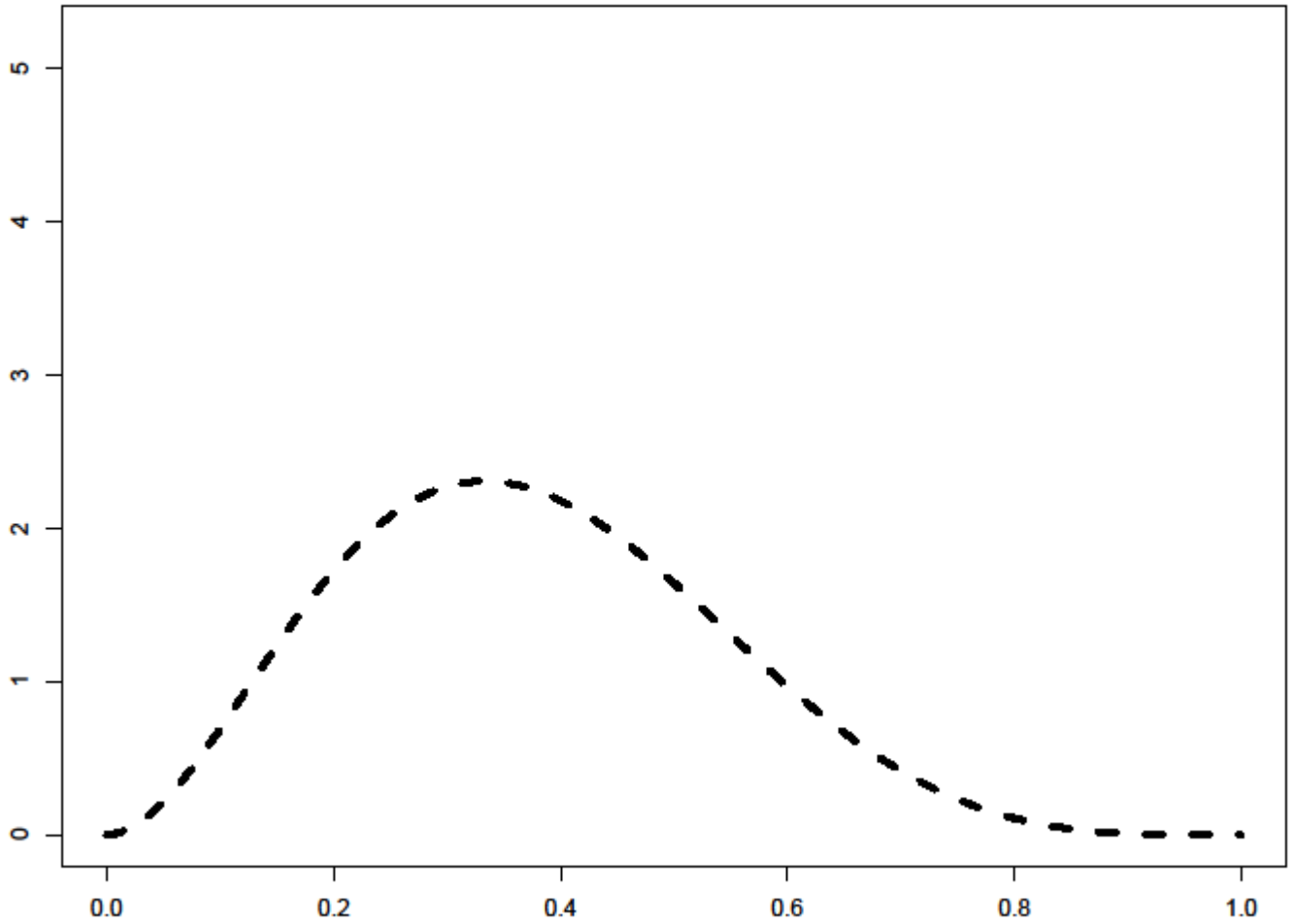
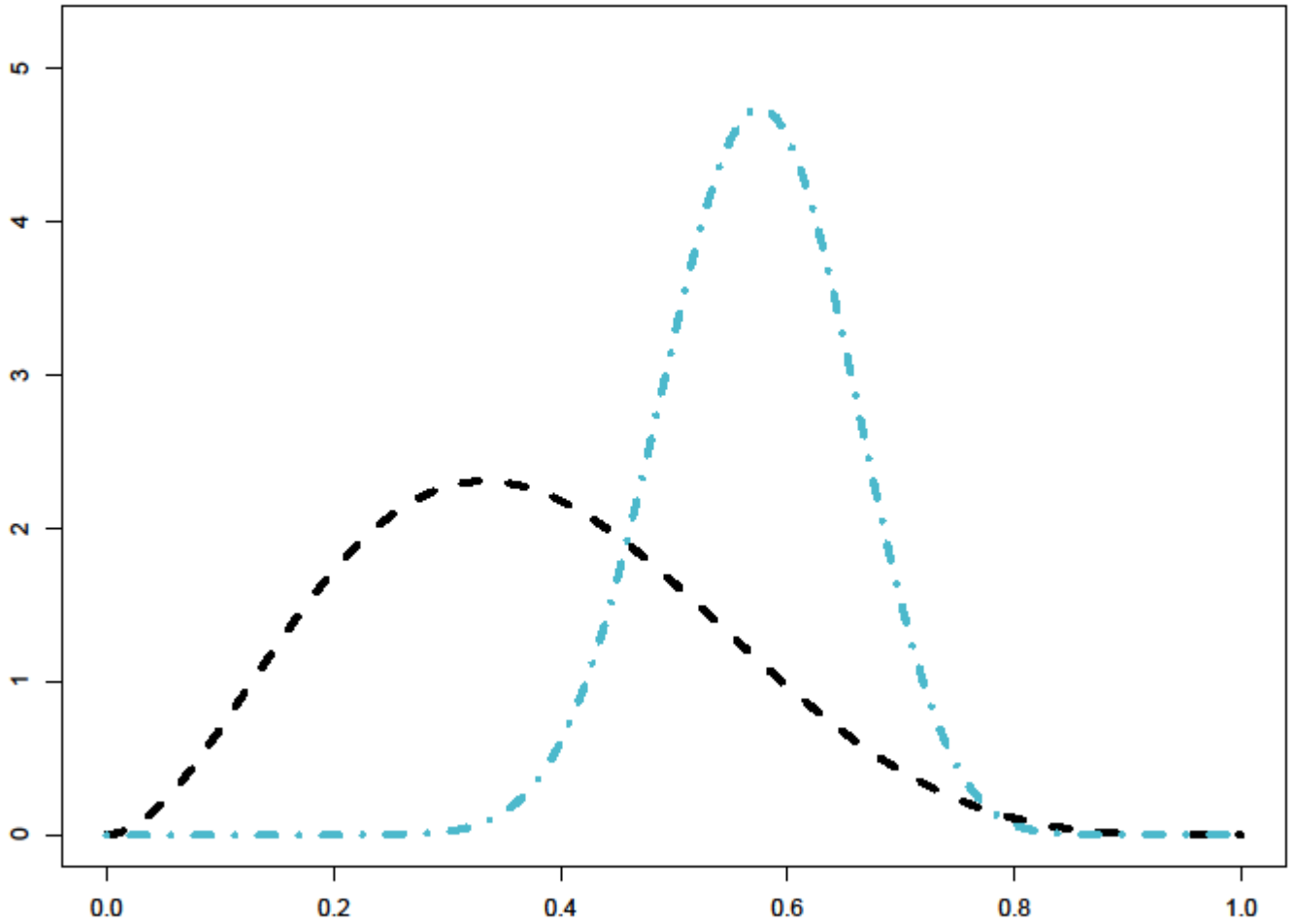
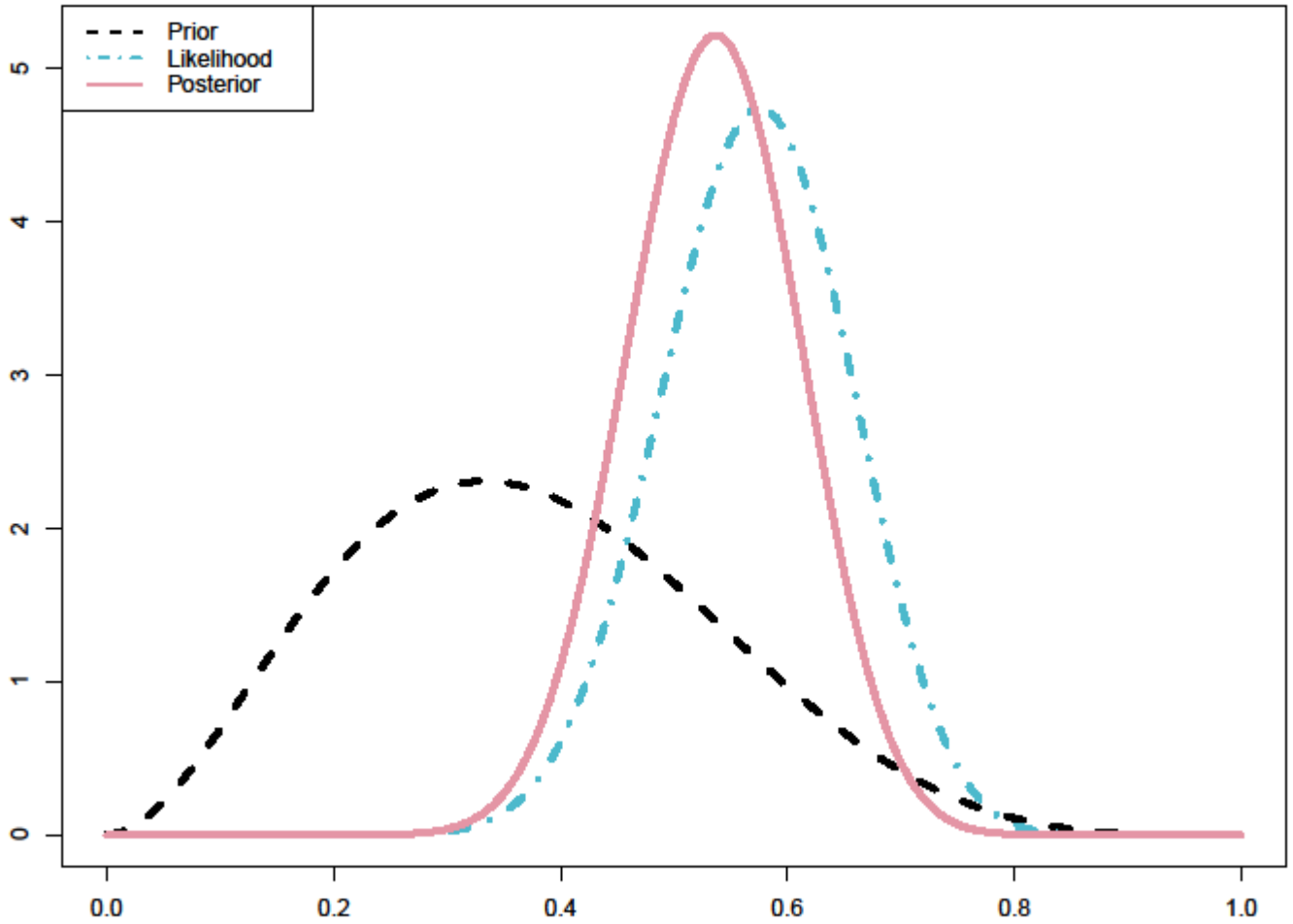
An Introduction to Bayesian Methods



An Introduction to Bayesian Methods

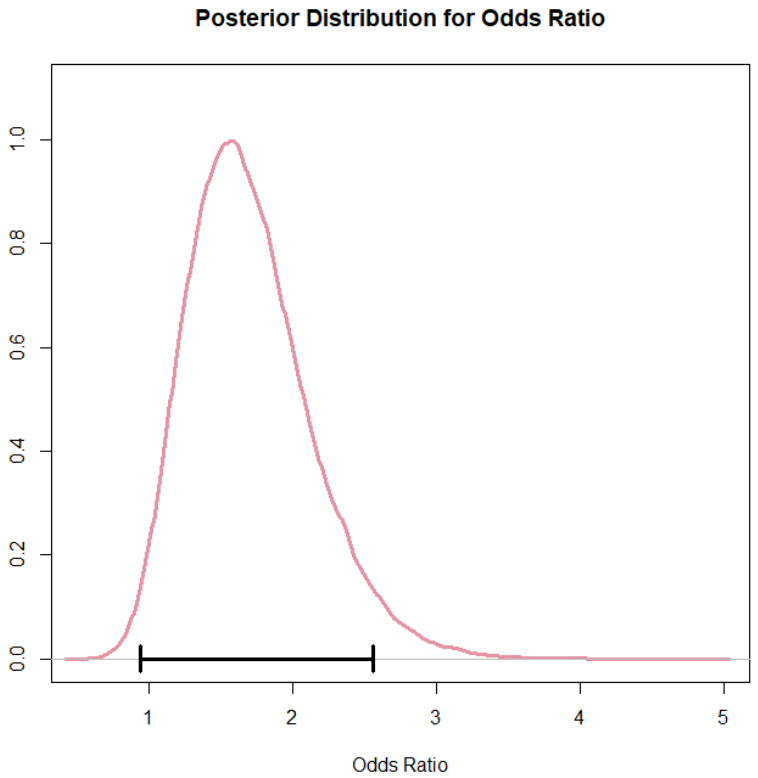


An Introduction to Bayesian Methods



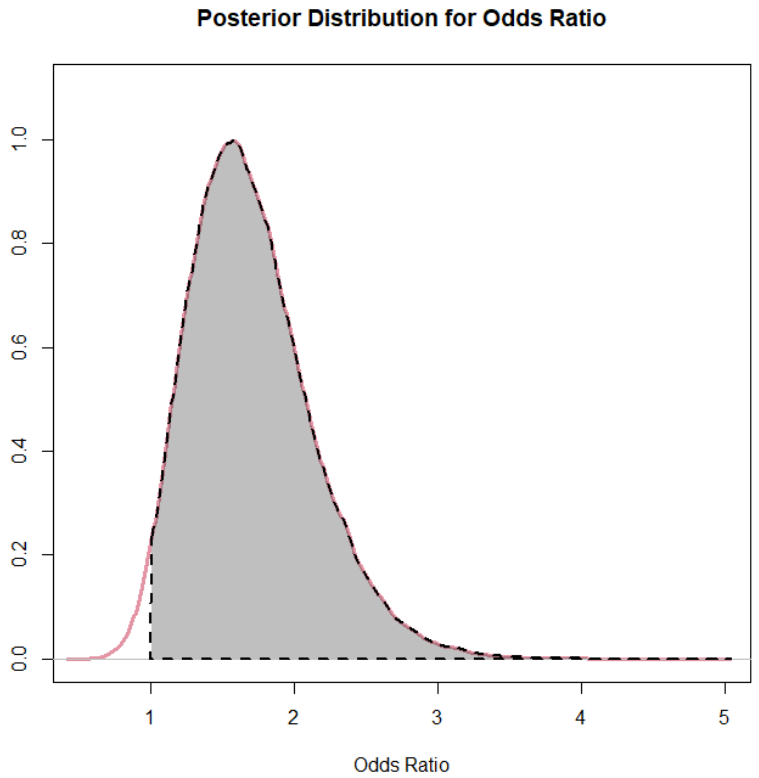
An Introduction to Bayesian Methods

- The posterior distribution contains all parameter information.
- Posterior summaries:
  - Mean: 1.7
  - Median: 1.6
  - Variance: 0.19
  - 95% Credible Interval: (0.94, 2.56)



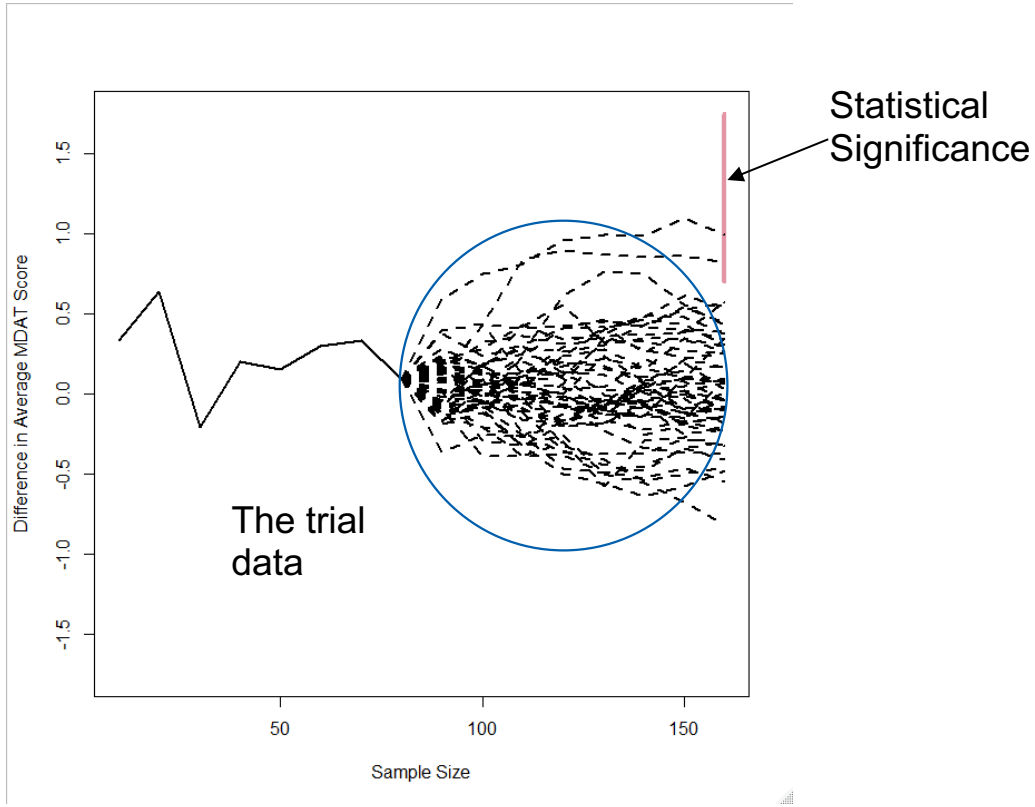
Summarizing a Bayesian analysis

- The posterior distribution contains all parameter information.
- Posterior summaries:
  - Mean: 1.7
  - Median: 1.6
  - Variance: 0.19
  - 95% Credible Interval: (0.94, 2.56)
  - Probability of positive treatment effect: 0.98



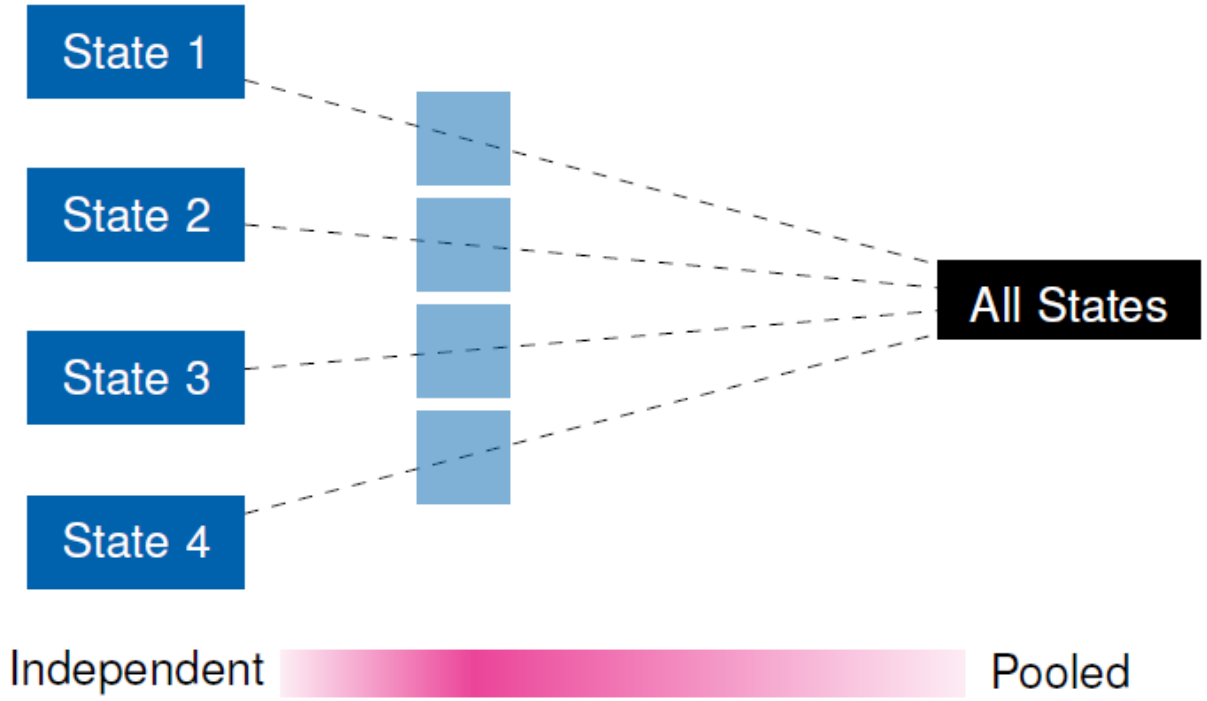
Predictive Probability

- Some Bayesian analyses also consider the *predictive* distribution.



Dynamic Borrowing

- Bayesian methods can consider *dynamic borrowing*



Types of Bayesian Adaptive Trials

- Dose finding Studies
  - Bayesian Continual Reassessment Method
  - Utility Driven Designs
- Response-Adaptive Randomization
- Sequential Monitoring
  - Futility
  - Efficacy
- Enrichment Designs
- Seamless Designs

Simulations in Clinical Trial Design

FDA: An adaptive design is defined as a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial.

- Statistical trial design determines:
  - Which adaptations should be made
  - The impact of these adaptations
- Decision rules for the trial adaptations are needed
  - We must state the "trigger" for each adaption.
- Simulations are usually required.

Designing a Simulation

1. Specify the research question:
   a) PICO
   b) Goal of adaptive designs
2. Develop model for data analysis and simulation
3. Design the trial decision rules
4. Determine key scenarios for simulation
5. Run simulation
6. Evaluate results and present to key stakeholders.

Example: 1) Research Question

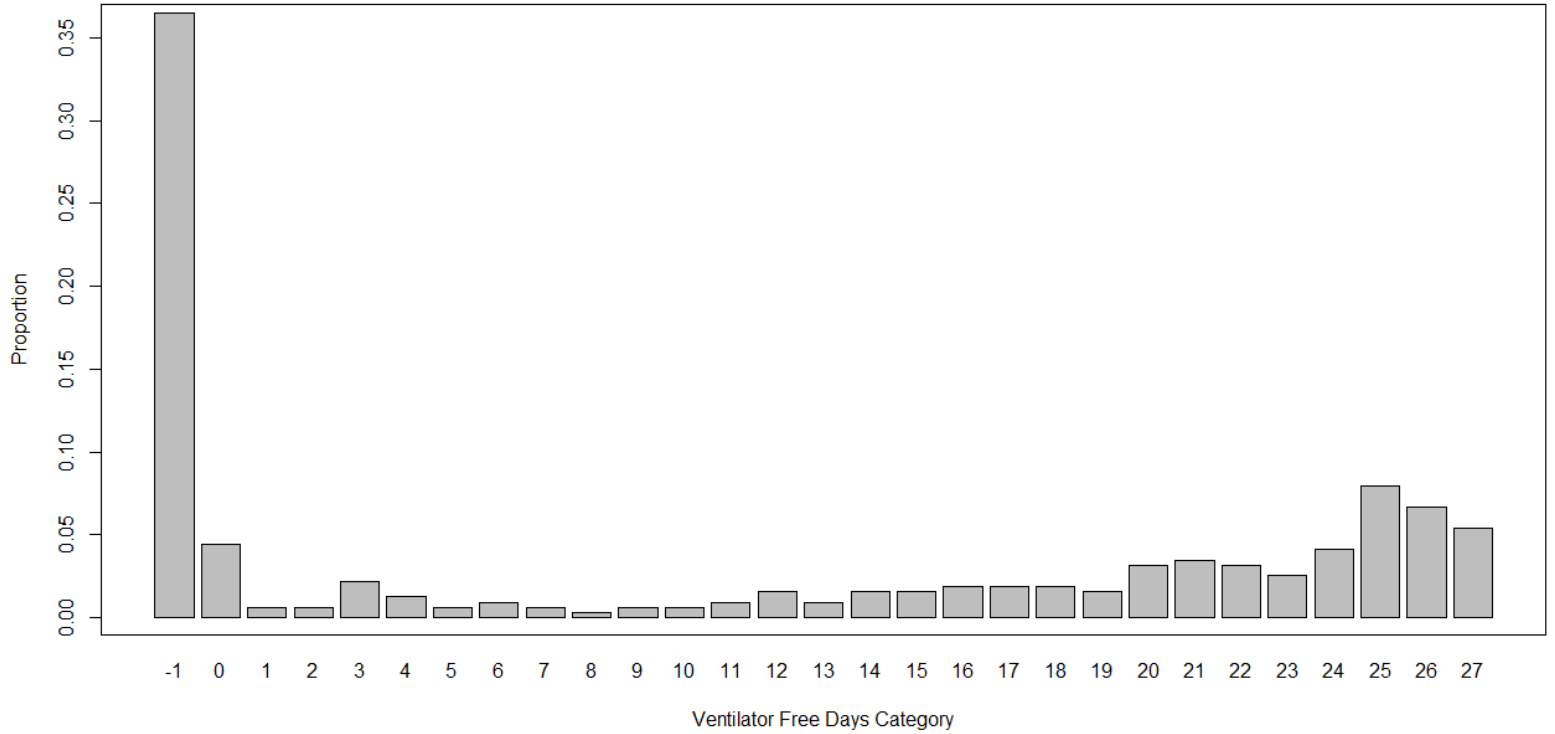
- **P**opulation: Patients with acute hypoxemic respiratory failure.
- **I**ntervention: Novel ventilation strategy
- **C**omparator: Standard Care
- **O**utcome: Ventilator Free Days

- **Adaptions**
  - Futility
  - Efficacy
  - Treatment Effect Heterogeneity

PRACTICAL
Platform Randomized Trial

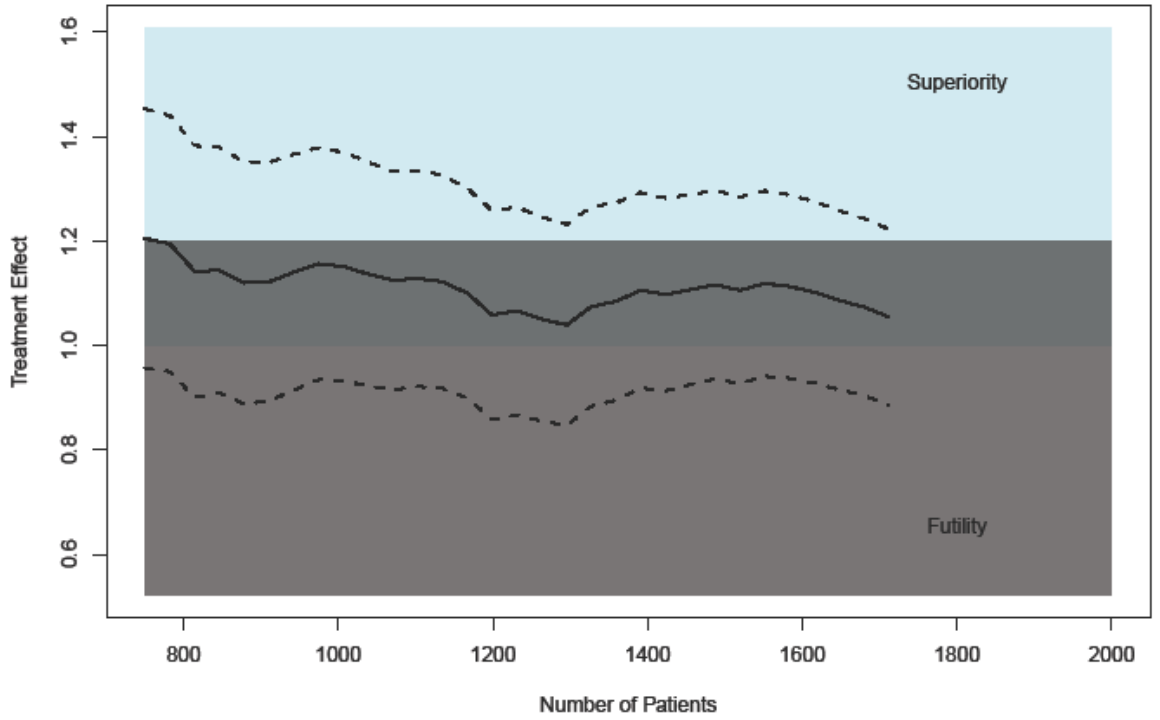
Example: 2) Model for the Data

- Simulate proportion in each category with a *Multinomial distribution*
- Treatment effects evaluated with a *proportional odds model*.
- To account for heterogeneity across groups, use *dynamic borrowing*.



Example: 3) Trial Decision Rules

- Only evaluate after an initial recruitment.
- Stop for either *futility* or *superiority*
- Two severity states will be evaluated separately.
- Analyses every three months.

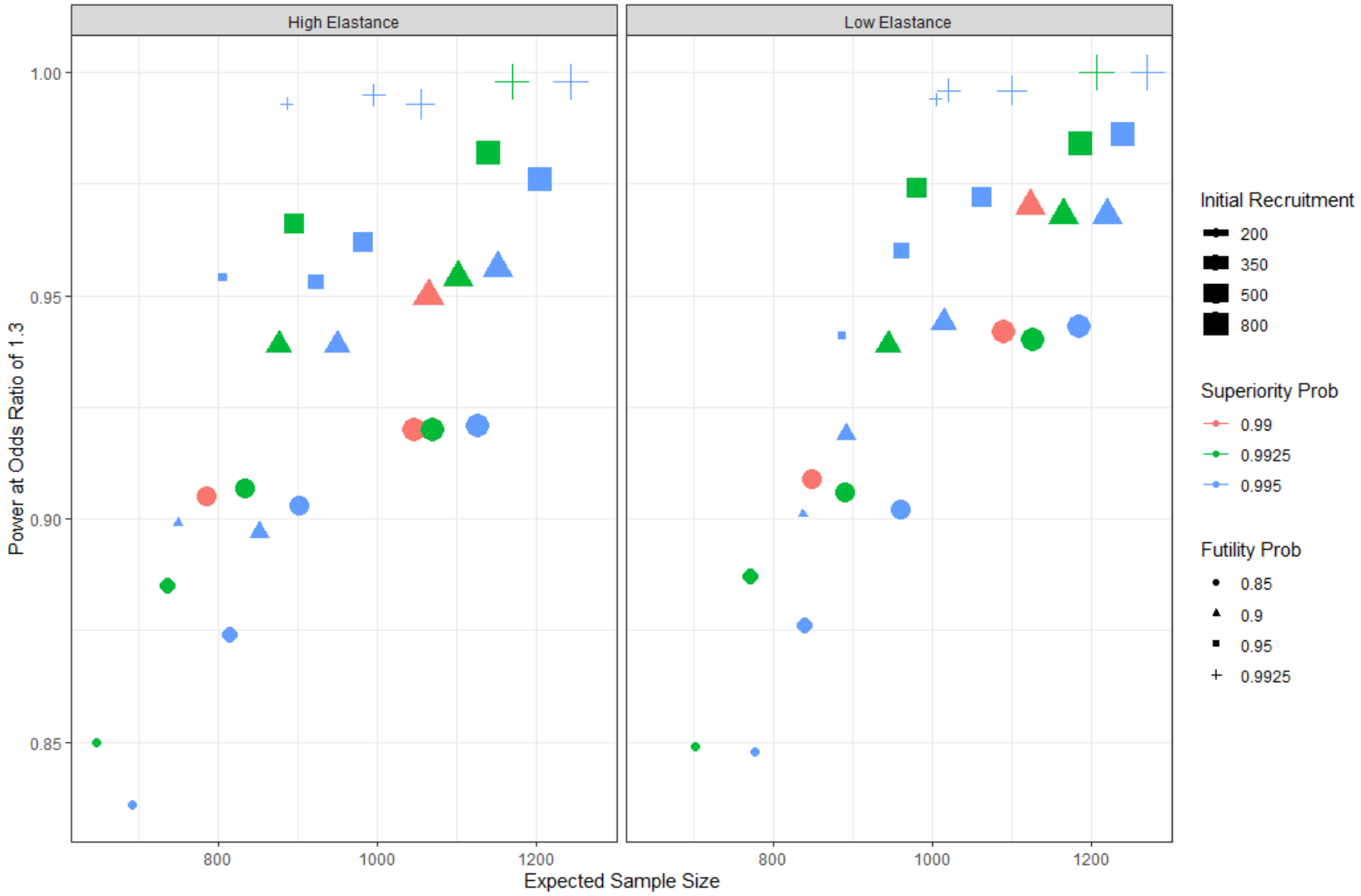


Example: 4) Simulation Scenarios

1. Determine decision thresholds by varying (128 scenarios):
   a) Probability to stop for *superiority*: 0.975, 0.99, 0.9925, 0.995
   b) Probability to stop for *futility*: 0.85, 0.9, 0.95, 0.9925
   c) Initial recruitment: 200, 350, 500, 800
   d) Proportional odds ratio: 1, 1.3
2. Evaluate power of the chosen design (34 scenarios):
   a) Same proportional odds ratios: 0.8, 1, 1.1, 1.2, 1.25, 1.3, 1.5
   b) Different proportional odds ratios:

Severity State A	0.8	1.1	1.2	1.25	1.3	1.5	1.1	1.2
Severity State B	1	1	1	1	1	1	1.3	1.3

Example: 6) Present Results



Example: 6) Present Results