Biostatistical Considerations: Biologics and Biomarkers in Oncology

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No Relationships to Disclose

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Outline

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Traditional Cytotoxic Development Paradigm

- Phase 1: Characterize Safety

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  - $3 + 3$

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$3 + 3$ Design for Dose Escalation on Toxicity

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- RP2D is highest dose with ≤ 1 DLT/6 patients

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Effective Use of $3 + 3$

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- Not choose between doses that are not extremely toxic

Possible Non-Cytotoxic Developmental Contexts

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- Biological therapy highly likely to be very low in toxicity
- Biological therapy unlikely to have increasing toxicity with increasing dose
- Addition of a component to a known therapy intended to reduce toxicity and, possibly, increase efficacy

Why Not Use $3 + 3$ in the Non-Cytotoxic Context?

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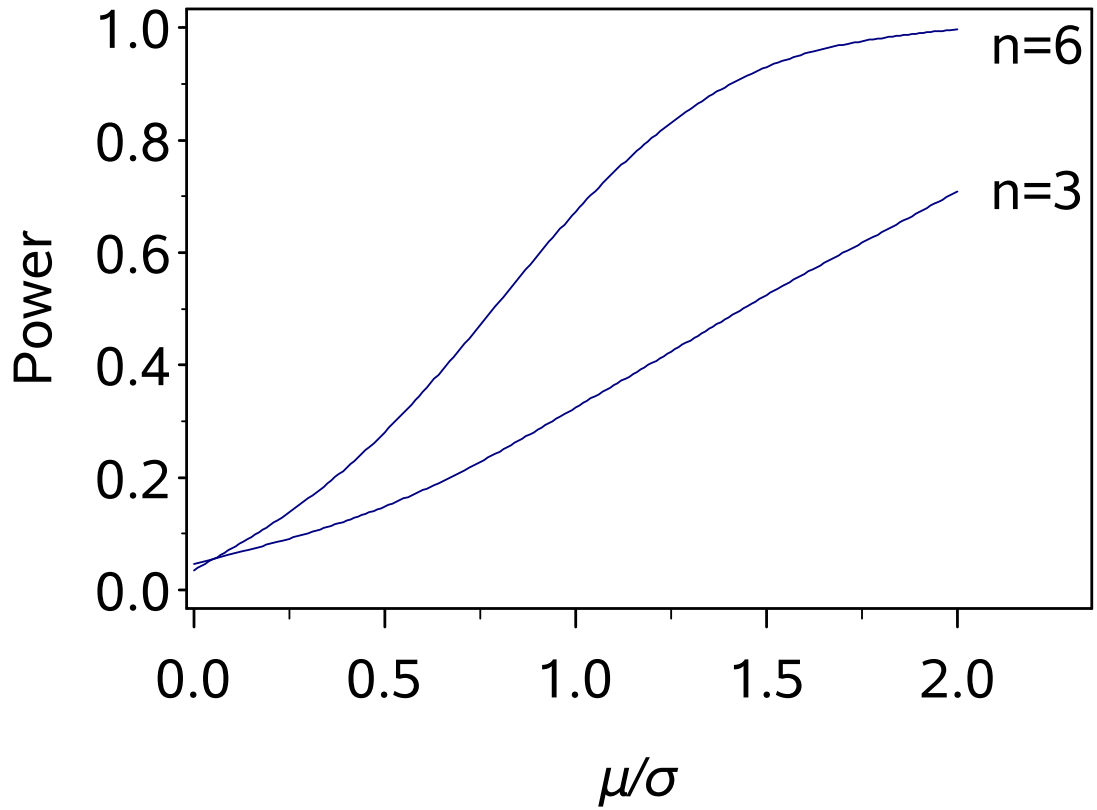
- Cohort sizes of 3 and 6 are often too small to be useful for the most relevant objectives

Testing Biomarker Endpoints Between $3+3$ Cohorts

- Test $H_o : \mu = 0$, one-sided, $\alpha = 0.05$



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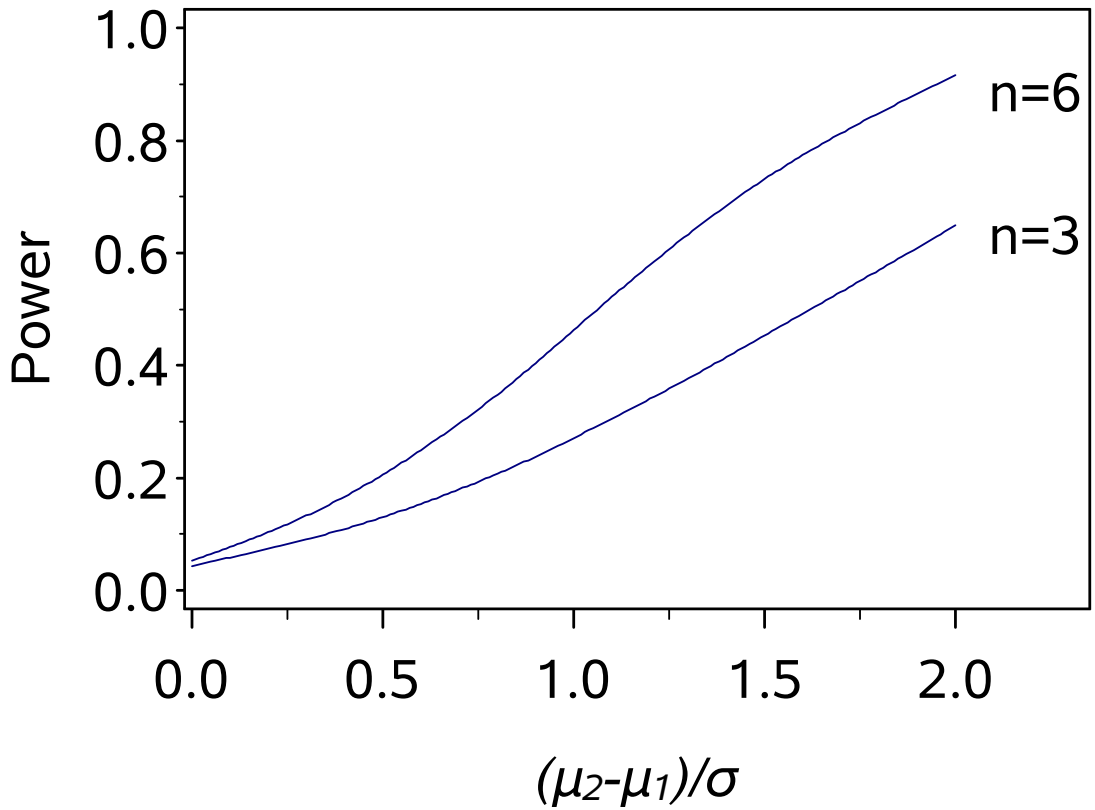

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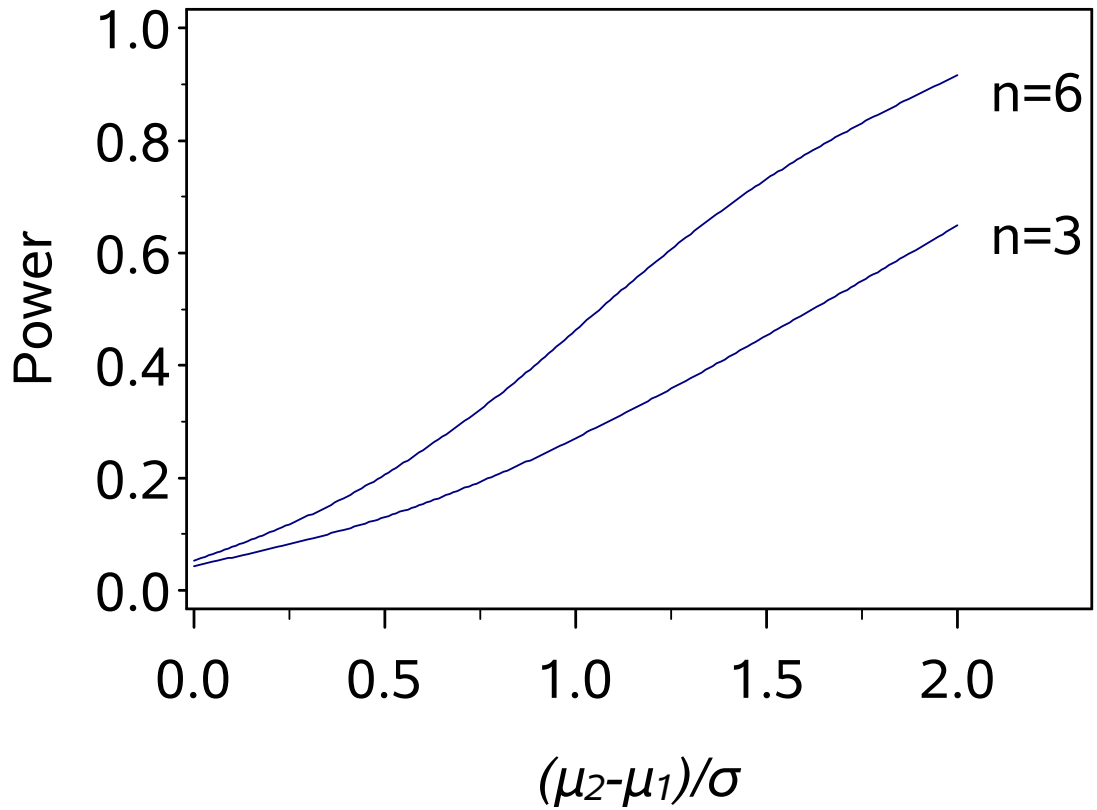

- Power for $\pi = 0.3$ versus $\pi = 0.05$ (1-sided, $\alpha = 0.05$) is 0.18

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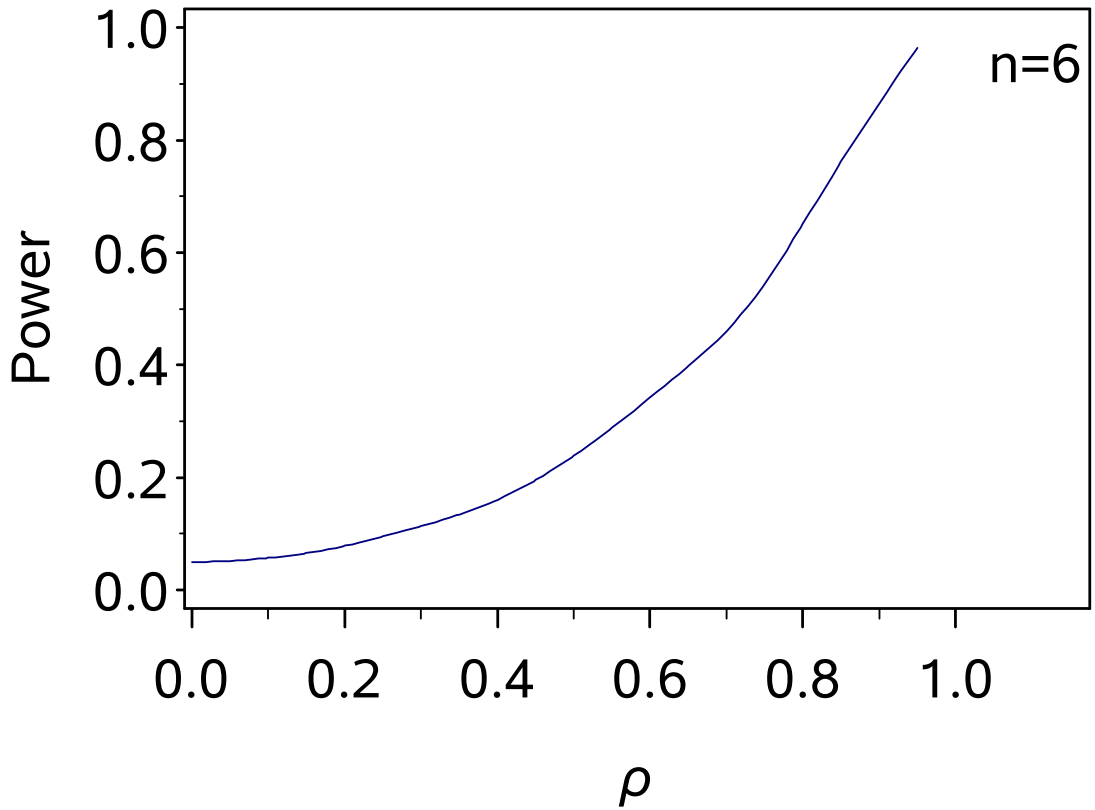

Expansion Cohort?

- No provision for incorporation of expansion cohort safety responses into estimate of RP2D

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- High probability of expansion at suboptimal dose
- Maximal (at $p = 0.5$) 95% exact two-sided binomial confidence interval based on 12 patients: (0.21,0.79)

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- Three or six participants per arm is insufficient for decision making other than eliminating grossly toxic doses
- *Escalation* on toxicity produces poor operating characteristics when the probability of toxicity is very low or a monotonic dose-toxicity relationship is unlikely

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Criteria for Early Phase Trials of Non-Cytotoxics

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Alternative Objectives In Early Phase Combination Therapy Studies

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Alternative Objectives In Early Phase Combination Therapy Studies

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- Estimate biologically effective doses
- Eliminate biologically ineffective doses from further consideration
- Assess relationships between markers at biologically effective doses

Scenario 1: Autologous Tumor Cell Vaccine

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  - Establish immunological response at highest dose

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  - Determine if lower doses also induce response

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- Objectives
  - Characterize immunological response
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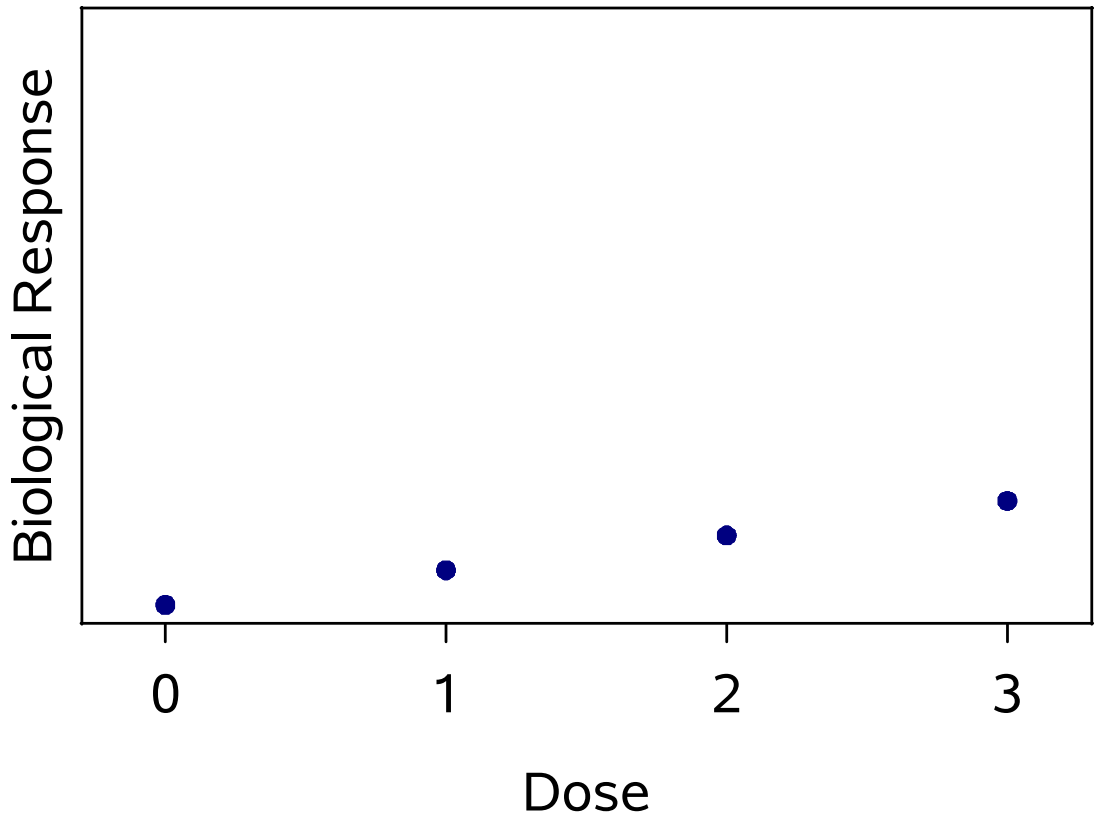
  - Determine if lower doses also induce response
  - Monitor toxicity

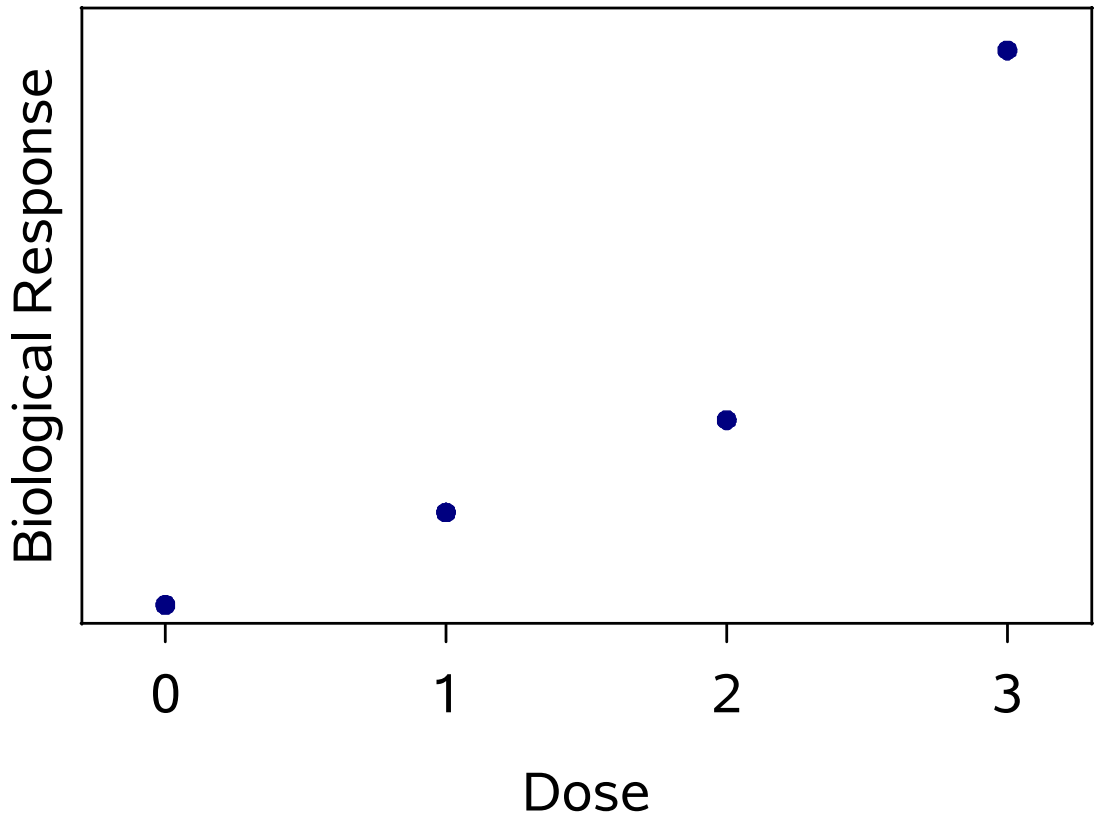
Dose Preference

- No dose is effective



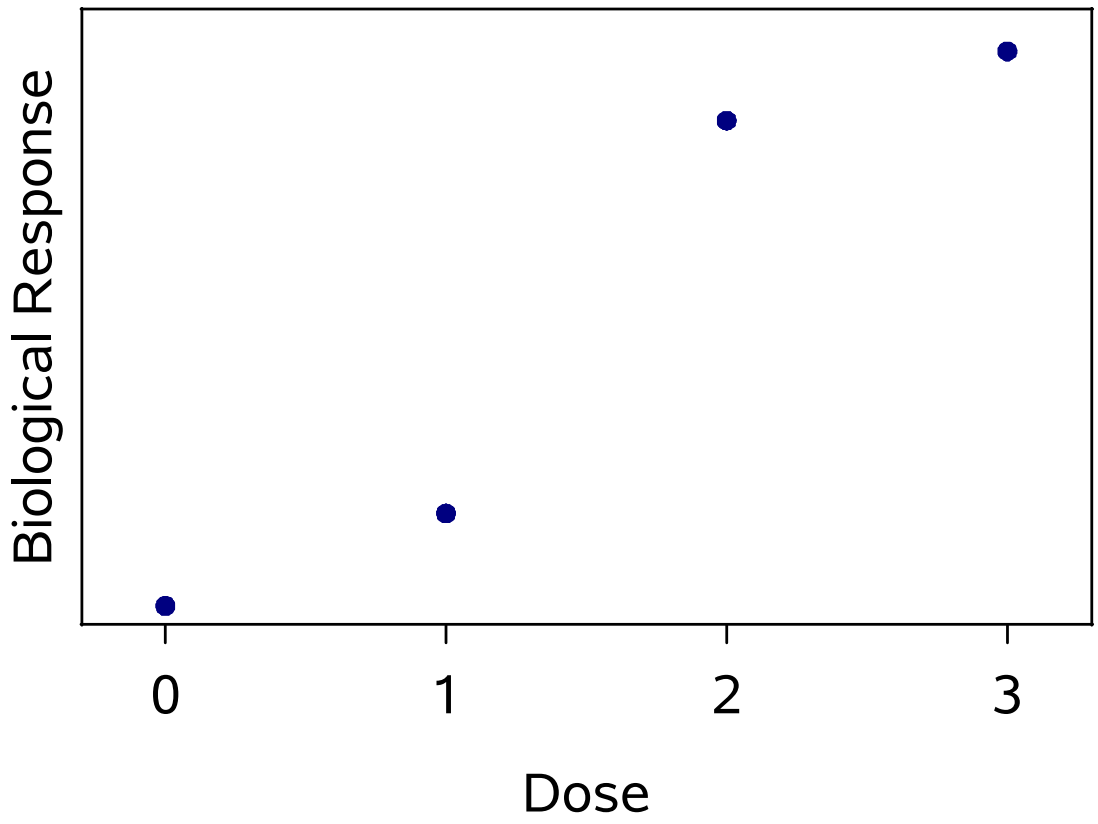
Dose Preference

- Prefer Dose 3



Dose Preference

- Prefer Dose 2



Goals

- Establish immunologic activity at highest dose

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- Determine if lower doses are as effective as highest dose

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- Avoid ineffective doses

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Simple Randomized Trial

- Global stopping rule for toxicity

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- Equal allocation of participants to dosing arms

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- Too many participants?

Two- (or Three-) Stage Randomized Trial with Continual Monitoring (Adapted from Su, 2010)

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- Once activity is established at highest dose, add randomization to lower dose
- Interim analysis (frequentist), or continual assessment (Bayesian) comparing doses
- If lower dose is not as effective, stop, otherwise, choose lower dose as minimal biologically effective or lower the dose further and repeat

Two-Stage Design, Example 1

- Two doses

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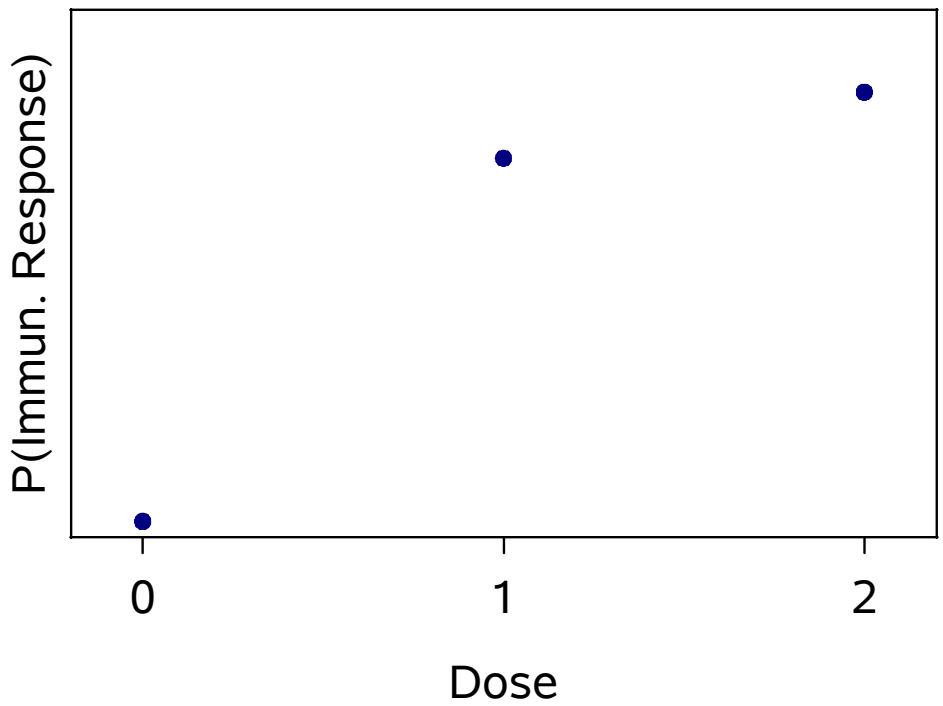

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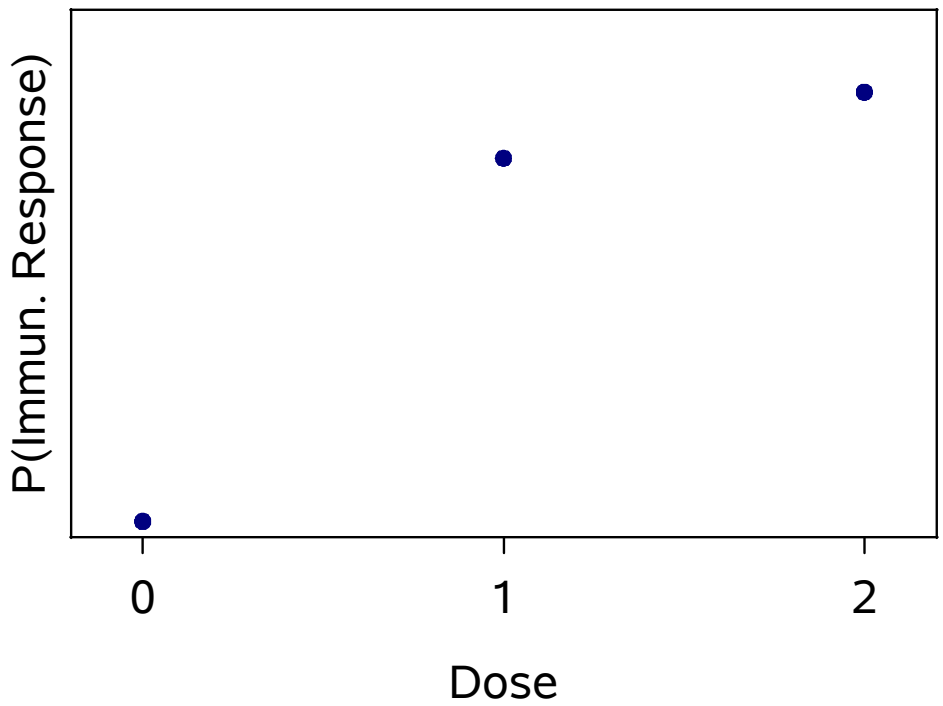

- Dose 1 is preferred

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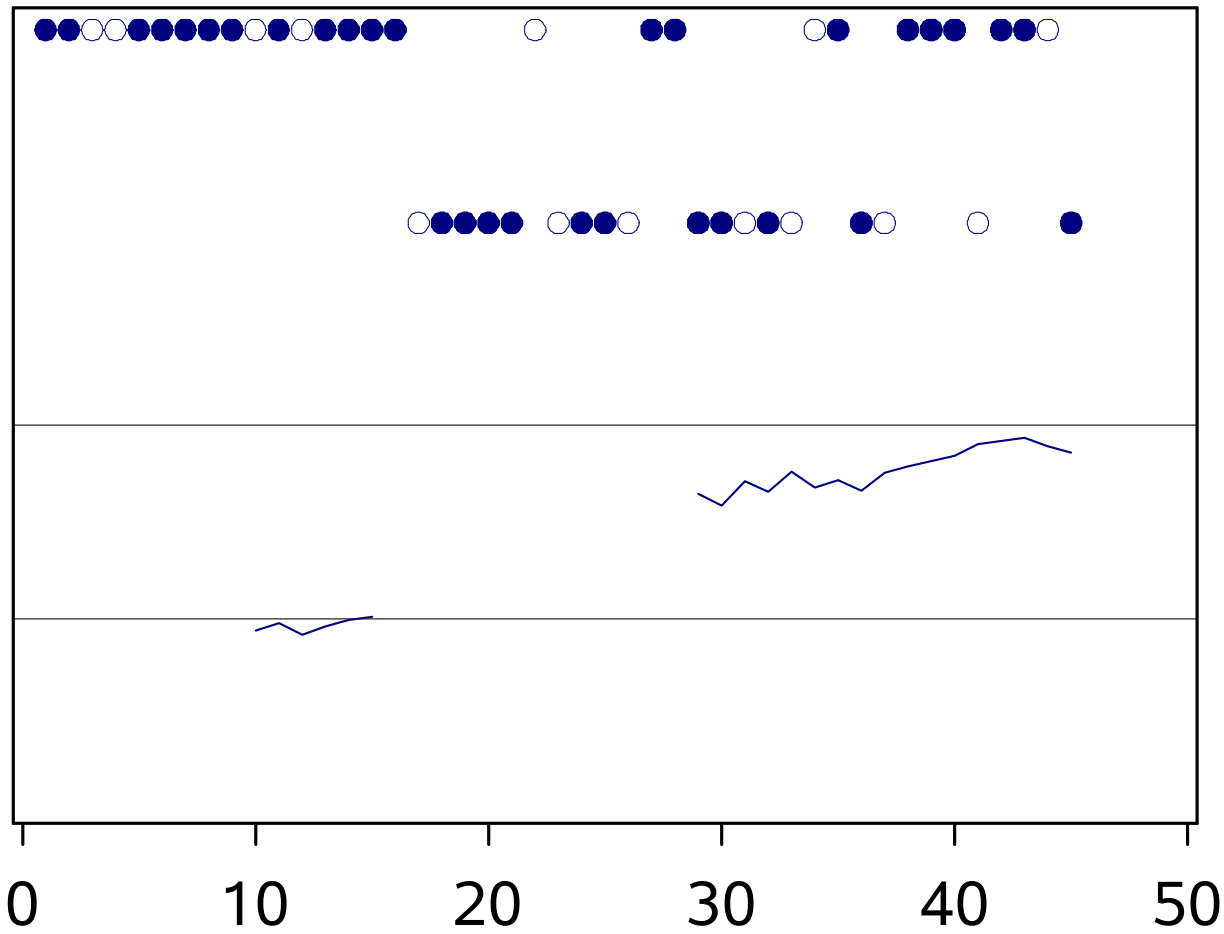

Two-Stage Design, Example 1

	# Resp / # Trt	$\hat{p}$	90% CI
High	20/27	0.74	(0.57,0.87)
Low	11/17	0.65	(0.42,0.83)

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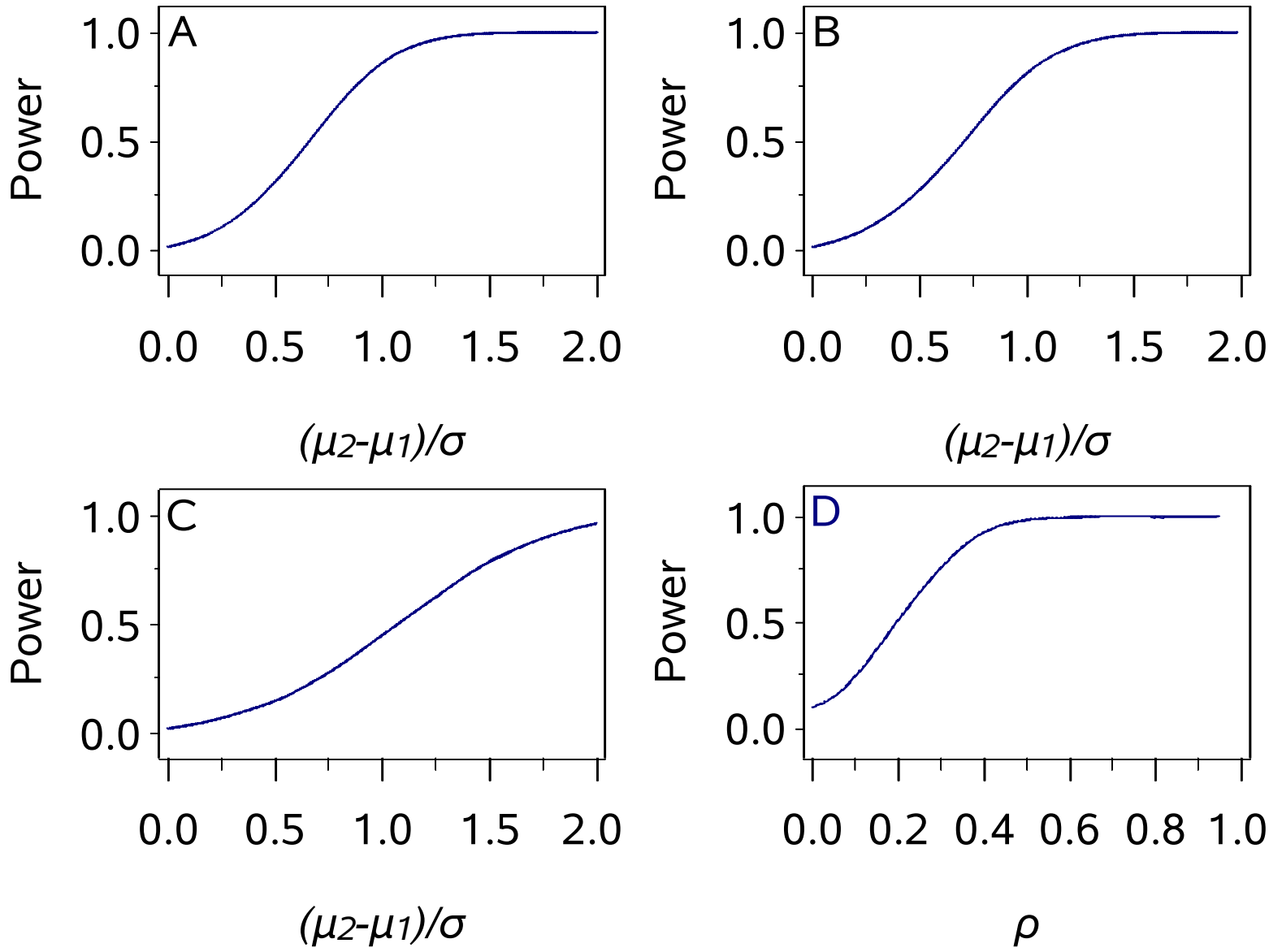

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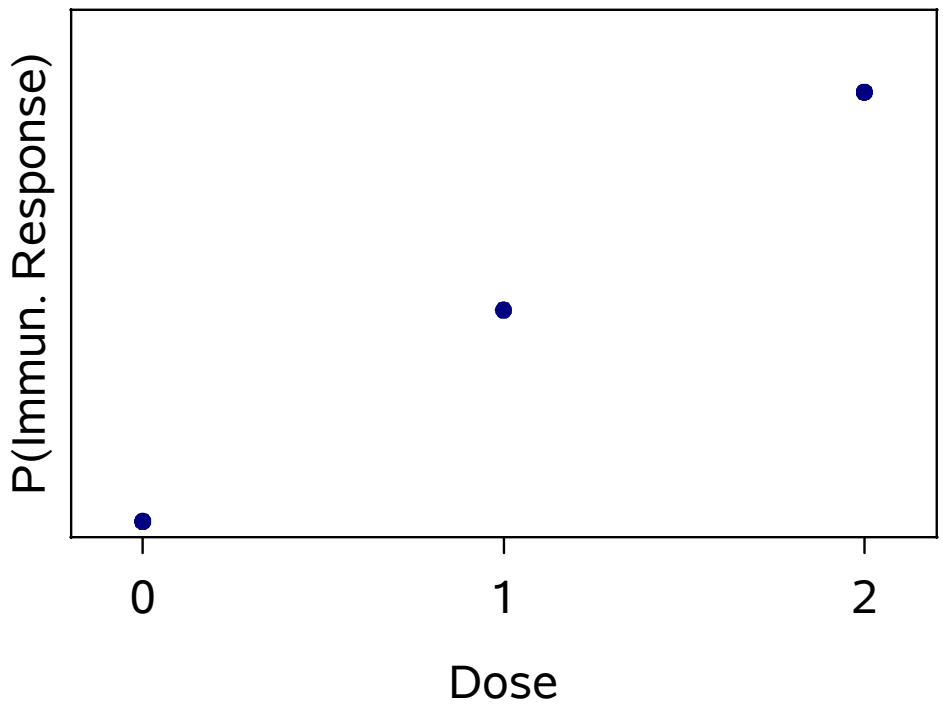

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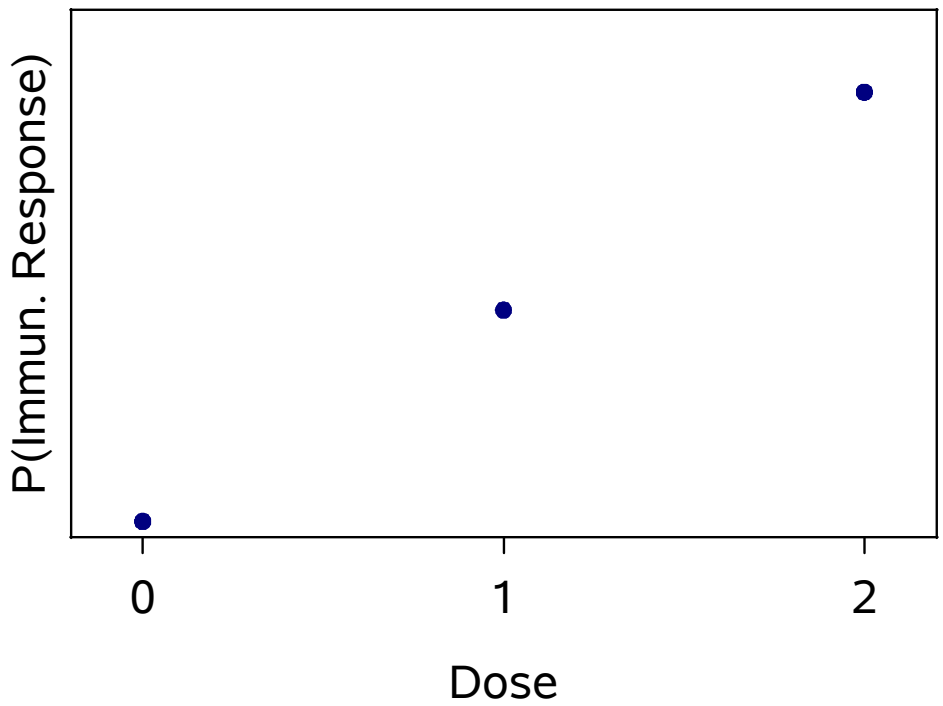

- Dose 2 is preferred

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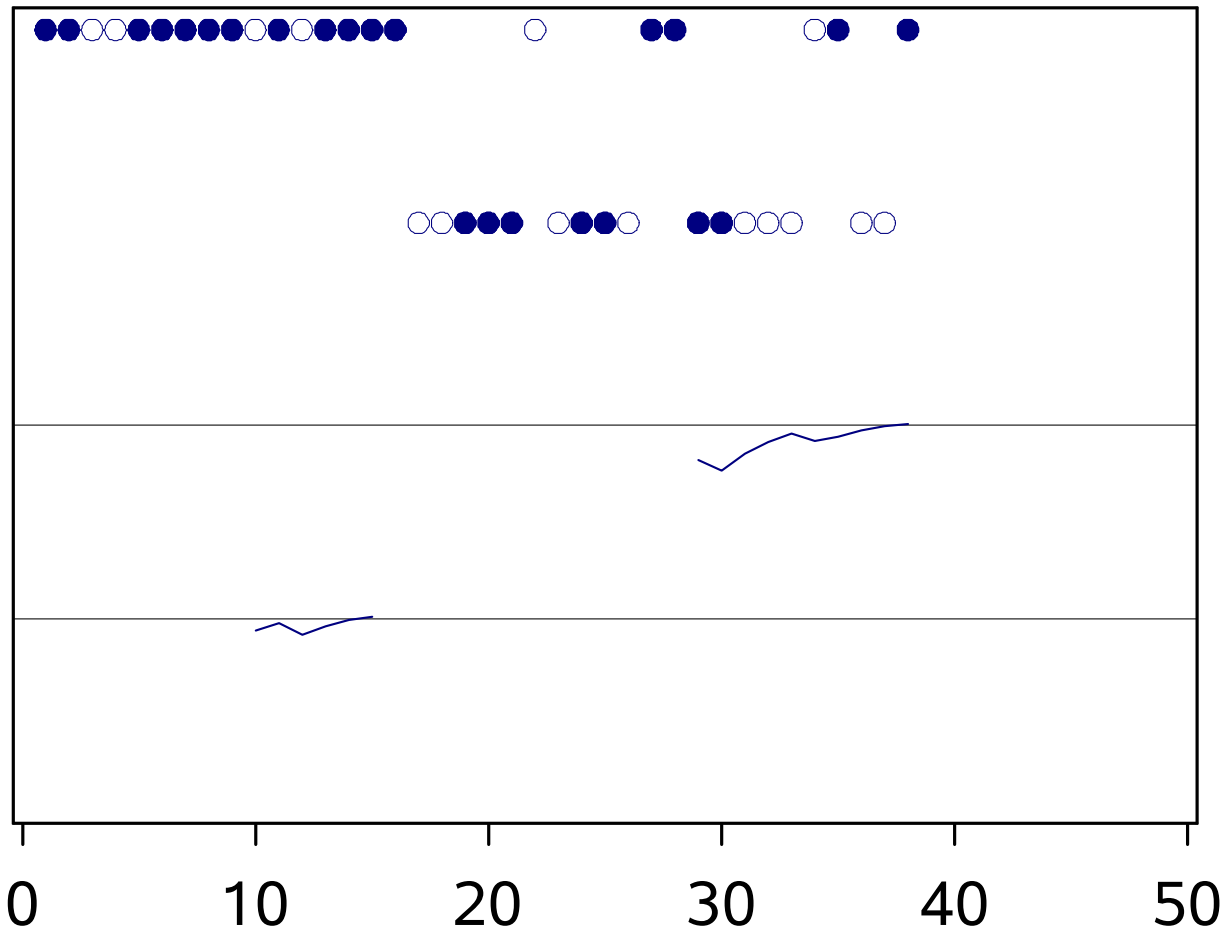
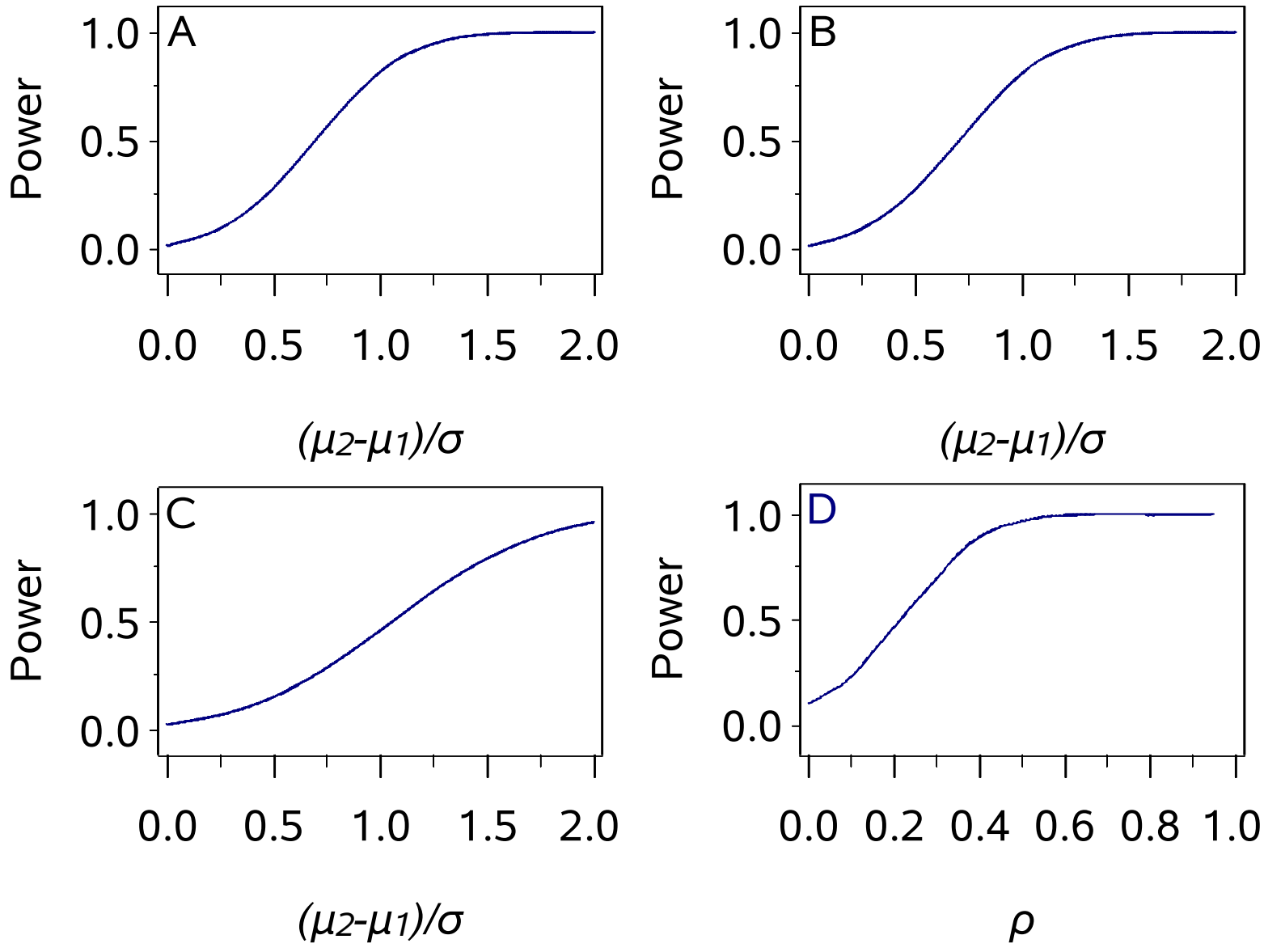


Two-Stage Design, Example 2

	# Resp / # Trt	$\hat{p}$	90% CI
High	16/22	0.73	(0.53,0.87)
Low	7/16	0.44	(0.23,0.67)

Two-Stage Design, Example 2



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- Accrual goal: 50 participants randomized to four doses (including control)

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Why Do We Persist In Undersizing Studies?

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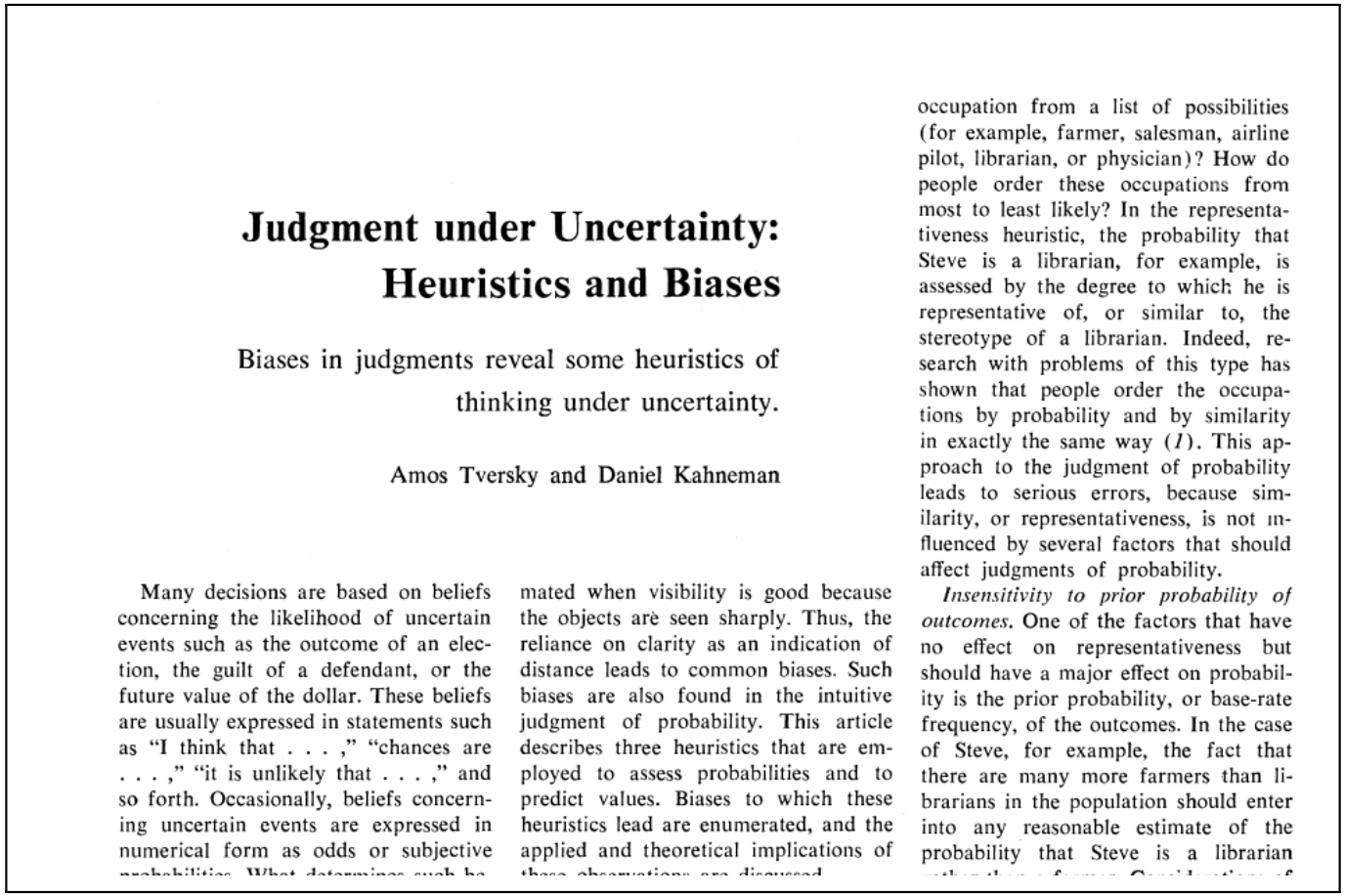

Judgment under Uncertainty: Heuristics and Biases

Biases in judgments reveal some heuristics of thinking under uncertainty.

Amos Tversky and Daniel Kahneman

Many decisions are based on beliefs concerning the likelihood of uncertain events such as the outcome of an election, the guilt of a defendant, or the future value of the dollar. These beliefs are usually expressed in statements such as "I think that . . . ," "chances are . . . ," "it is unlikely that . . . ," and so forth. Occasionally, beliefs concerning uncertain events are expressed in numerical form as odds or subjective

mated when visibility is good because the objects are seen sharply. Thus, the reliance on clarity as an indication of distance leads to common biases. Such biases are also found in the intuitive judgment of probability. This article describes three heuristics that are employed to assess probabilities and to predict values. Biases to which these heuristics lead are enumerated, and the applied and theoretical implications of

occupation from a list of possibilities (for example, farmer, salesman, airline pilot, librarian, or physician)? How do people order these occupations from most to least likely? In the representativeness heuristic, the probability that Steve is a librarian, for example, is assessed by the degree to which he is representative of, or similar to, the stereotype of a librarian. Indeed, research with problems of this type has shown that people order the occupations by probability and by similarity in exactly the same way (*1*). This approach to the judgment of probability leads to serious errors, because similarity, or representativeness, is not influenced by several factors that should affect judgments of probability.

Insensitivity to prior probability of outcomes. One of the factors that have no effect on representativeness but should have a major effect on probability is the prior probability, or base-rate frequency, of the outcomes. In the case of Steve, for example, the fact that there are many more farmers than librarians in the population should enter into any reasonable estimate of the probability that Steve is a librarian

- Tversky & Kahneman, *Science* 1974
- We use heuristics that tend to overweight the evidence from the first few data points in a series

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- Larger trials are difficult for young investigators

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- Comparisons of results from trials with different designs is challenging

Can't We All Just Get Along?

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- Realistically power the study to achieve primary objective

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- Assess all the relevant operating characteristics of a given design
- Employ novel designs if we really think they will help

Can't We All Just Get Along?

- Use development process to determine the primary objective
- Realistically power the study to achieve primary objective
- Assess all the relevant operating characteristics of a given design
- Employ novel designs if we really think they will help
- Mutually engage bench scientists, trialists and statisticians during design, implementation and analysis

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