Optimizing Dose Selection with Respect to Multiple Safety/Efficacy Endpoints Using Clinical Utility Concepts

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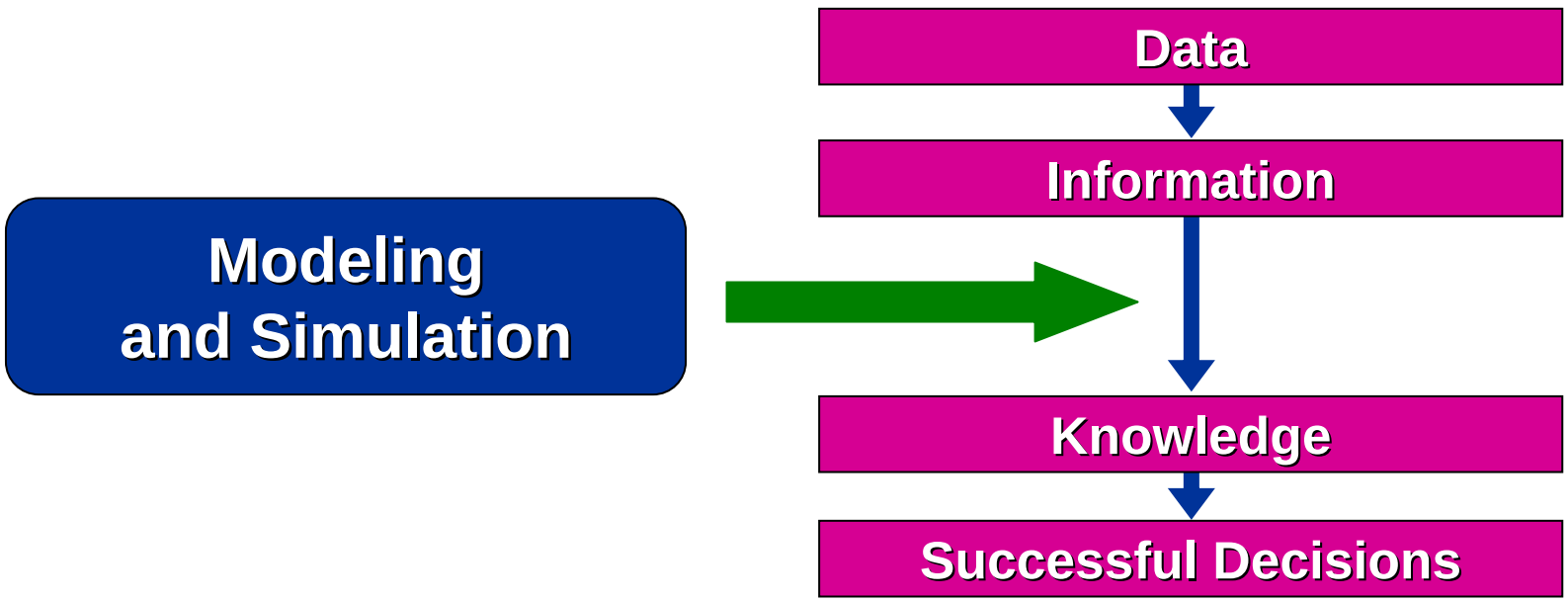
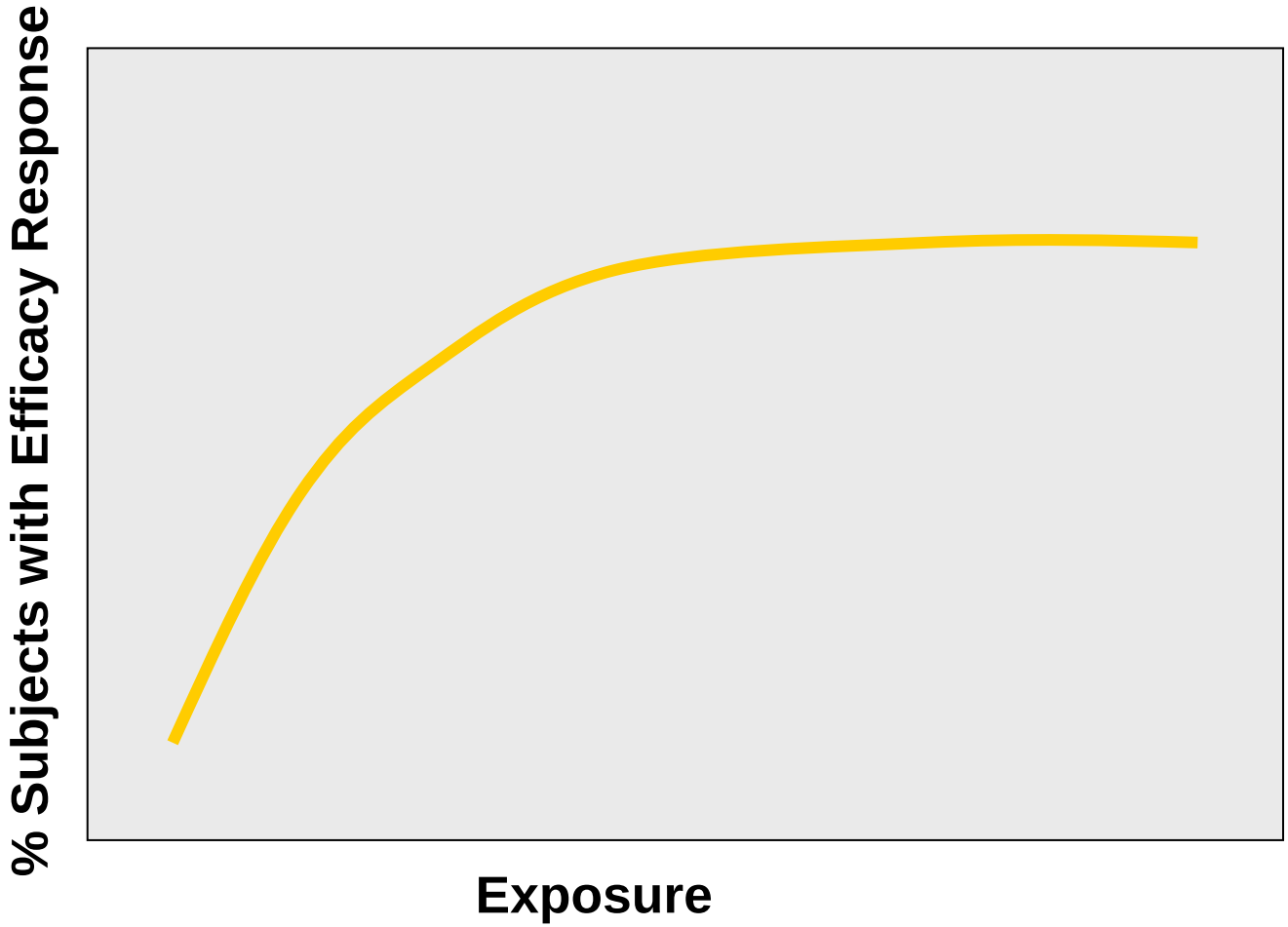
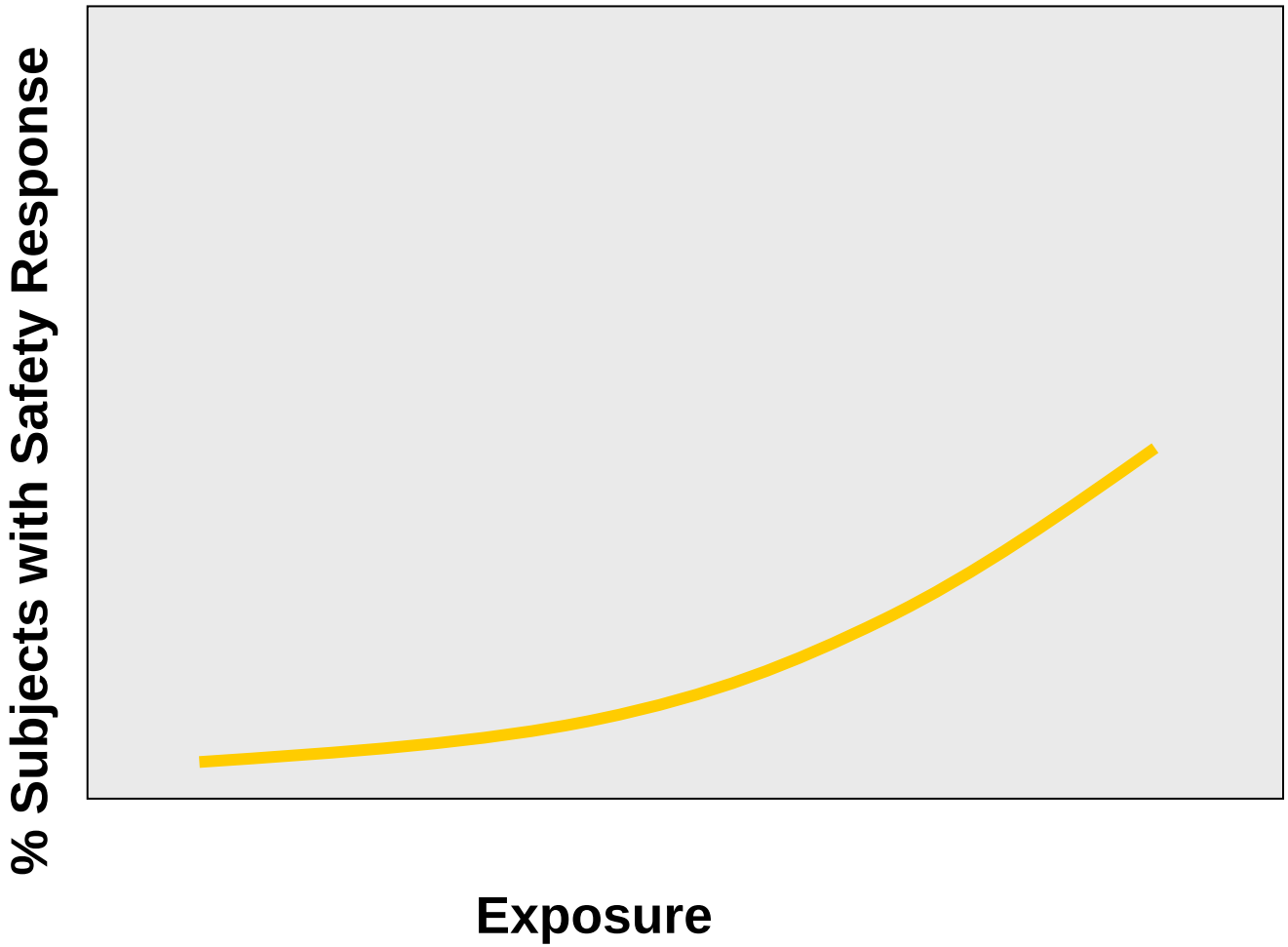
Transforming Information into Knowledge



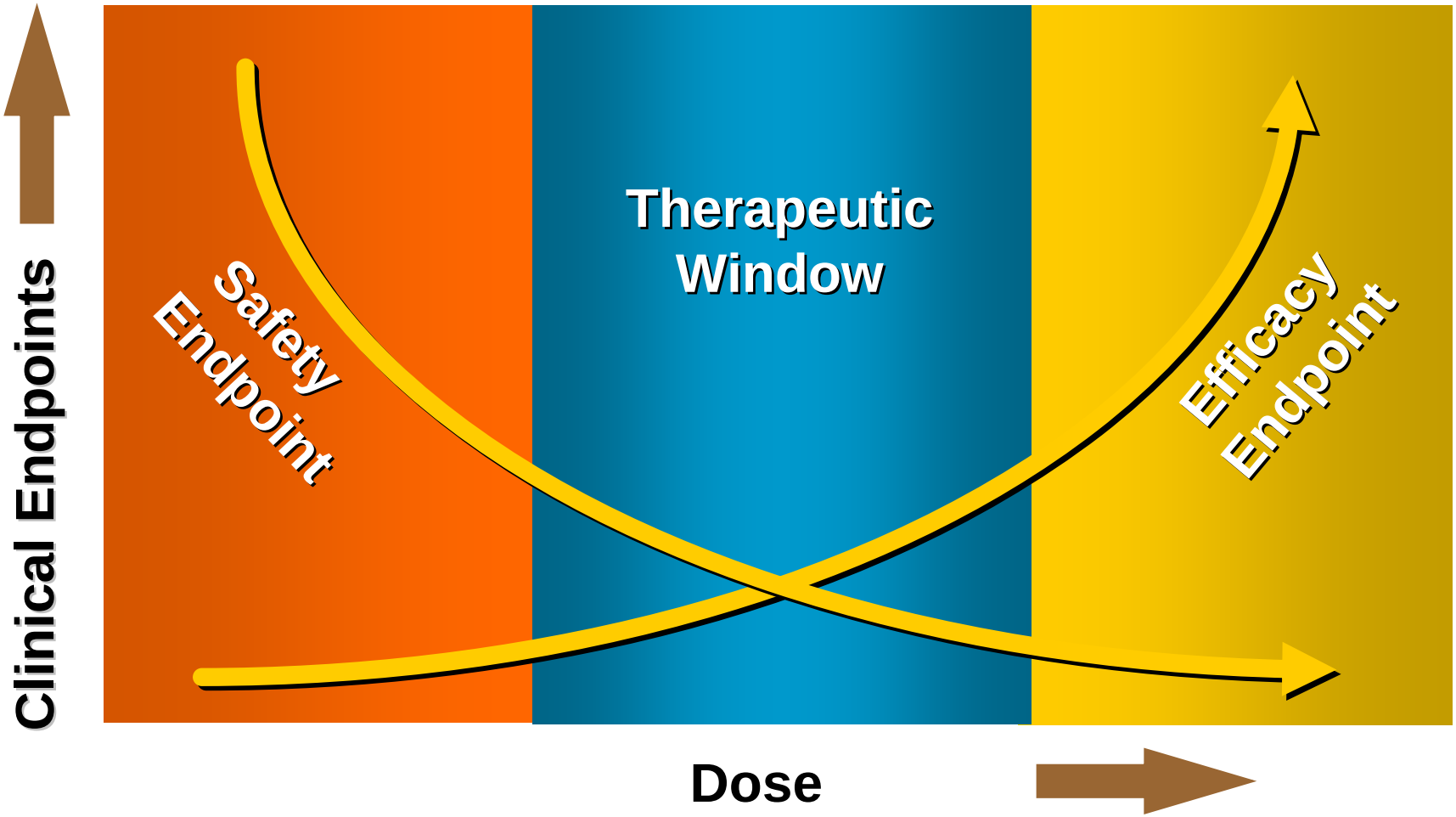
Exposure-Efficacy Response



Exposure-Safety Response



Select Optimal Dose Regimen



Need for Clinical Utility Measure

- Assessment of benefit/risk requires consideration of disparate factors (Efficacy/Safety)
- Implicitly subjective value judgments are made in assigning importance to efficacy/safety endpoints
- Reasons underlying differences in expert opinions are not always evident
- Facilitates a priori specification of Go/No Go criteria

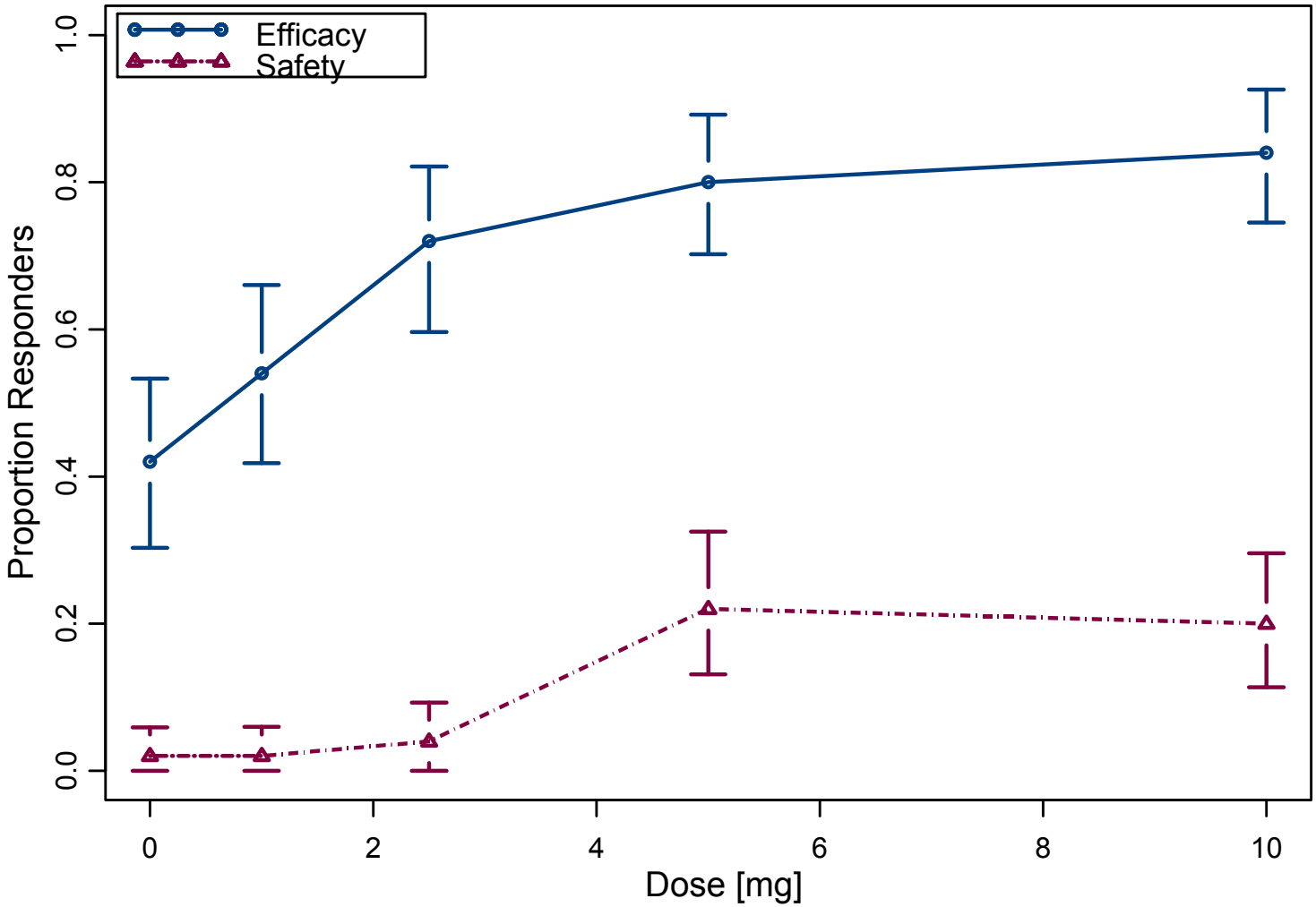
Desired Attributes of Clinical Utility Measure

- Quantitative scalar measure of benefit/risk
  - Facilitates comparison with reference treatment (placebo or active comparator)
  - Values greater than zero indicate benefit > risk
- Combines multiple measures of safety and efficacy
  - Binary
  - Ordered categorical
  - Continuous
- Subjective value judgments are explicitly stated

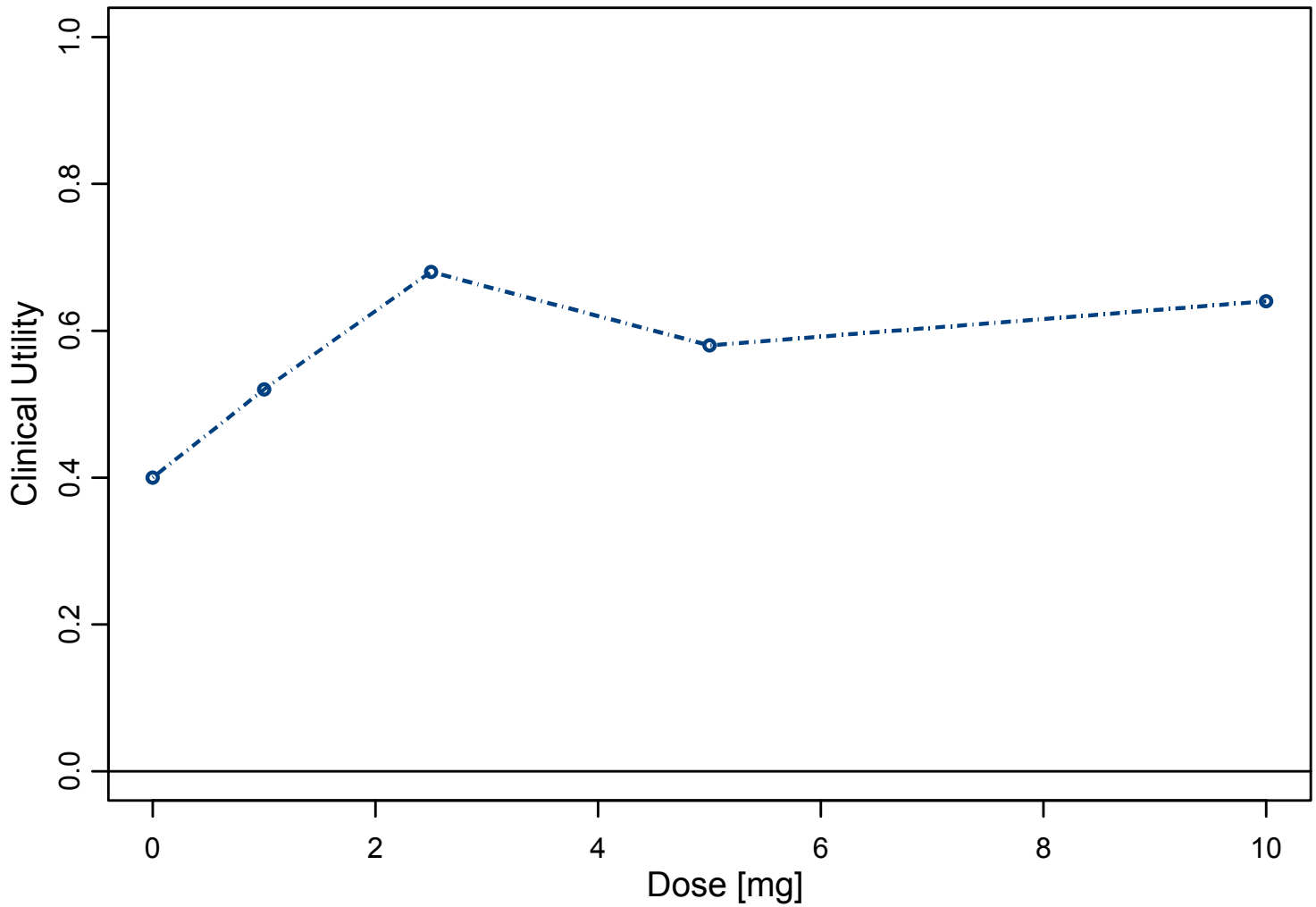
Case Study: Drug A

- Phase 2 Study:
  - Placebo controlled, parallel group
  - 4 active doses (1, 2, 5, and 10 mg)
  - Sample size = 250 (50 per dose group)
- Efficacy Endpoint: Binary
- Safety Endpoint: Binary

Drug A: Dose Response (Efficacy and Safety)



Clinical Utility (P[Efficacy] – P[Safety]) vs. Dose



Clinical Utility and Relative Clinical Utility

- Clinical Utility (CU):
  - Intuitively, CU for dose *d*:

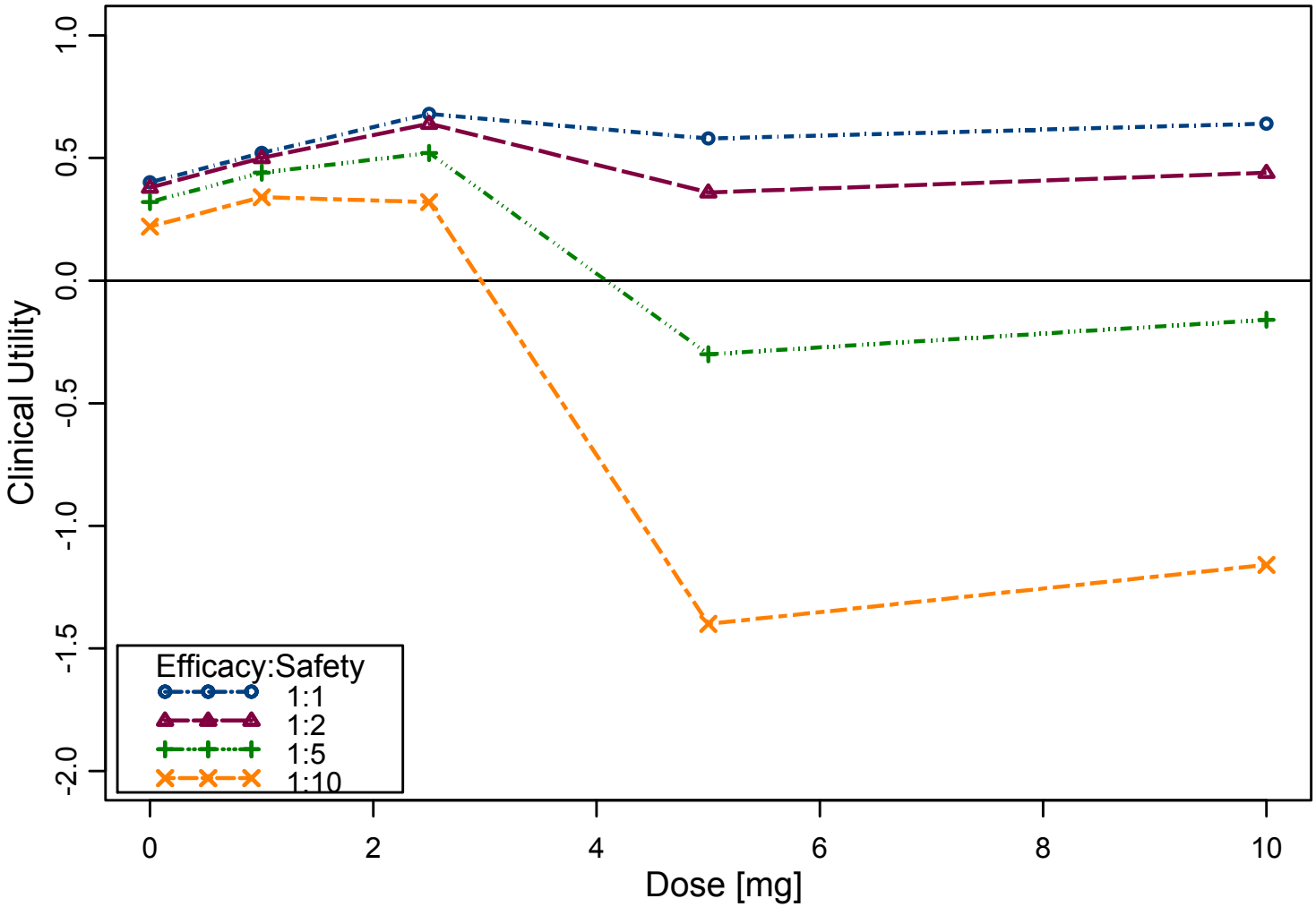
    $CU_d = P(Efficacy_d) - P(Safety_d)$
  - Account for relative importance of Efficacy:Safety

    $CU_d = P(Efficacy) - WT * P(Safety)$
- Relative Clinical Utility (RCU):
  - CU relative to reference treatment (placebo or active comparator)

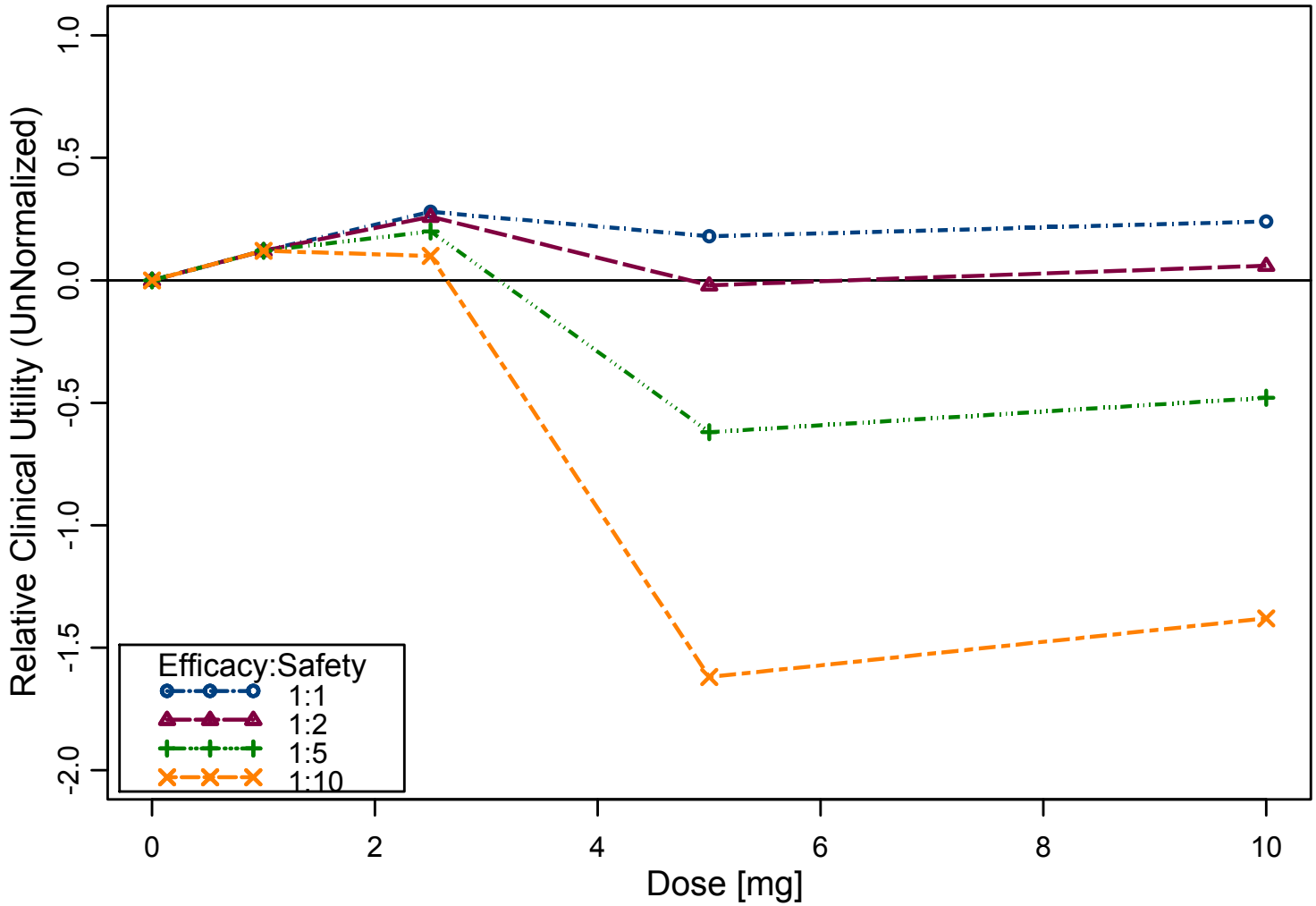
    $RCU_{d,UN} = CU_d - CU_{ref}$
  - Normalize so scale is independent of arbitrary WT

    $RCU_d = RCU_{d,UN}/(sup(|RCU_d|, d \in Doses)$

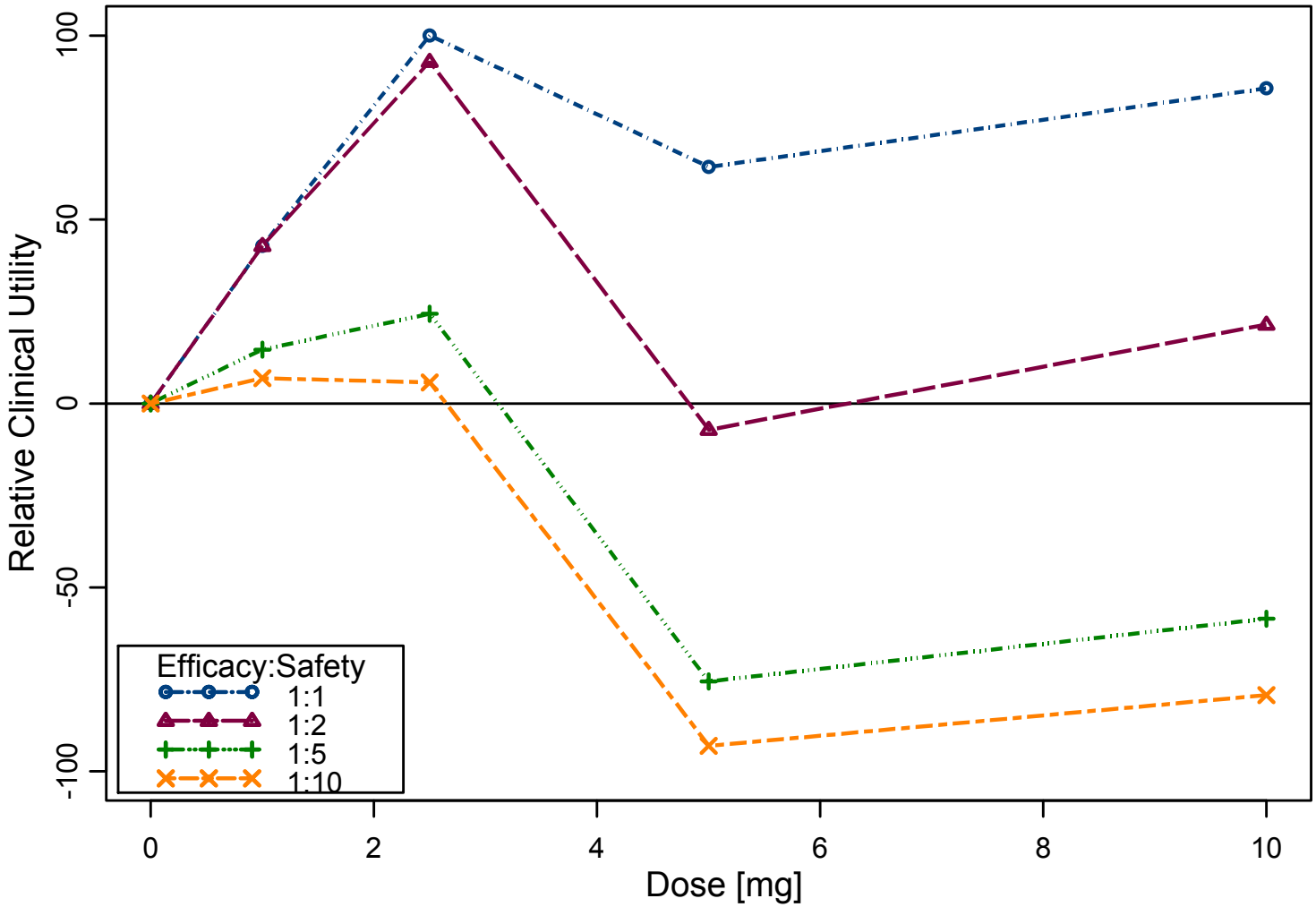
Clinical Utility vs. Dose



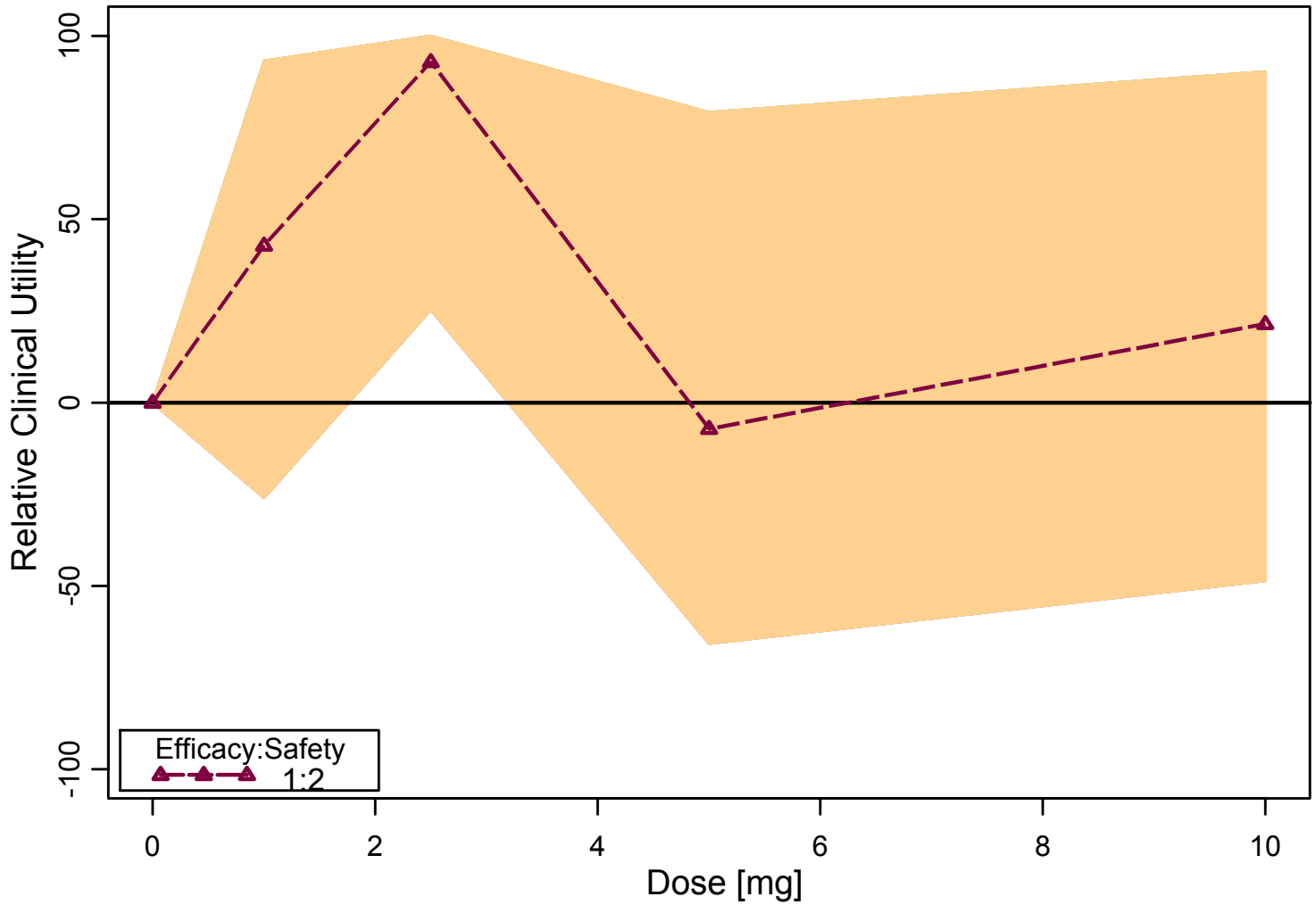
Relative Clinical Utility (Unnormalized) vs. Dose



Relative Clinical Utility vs. Dose



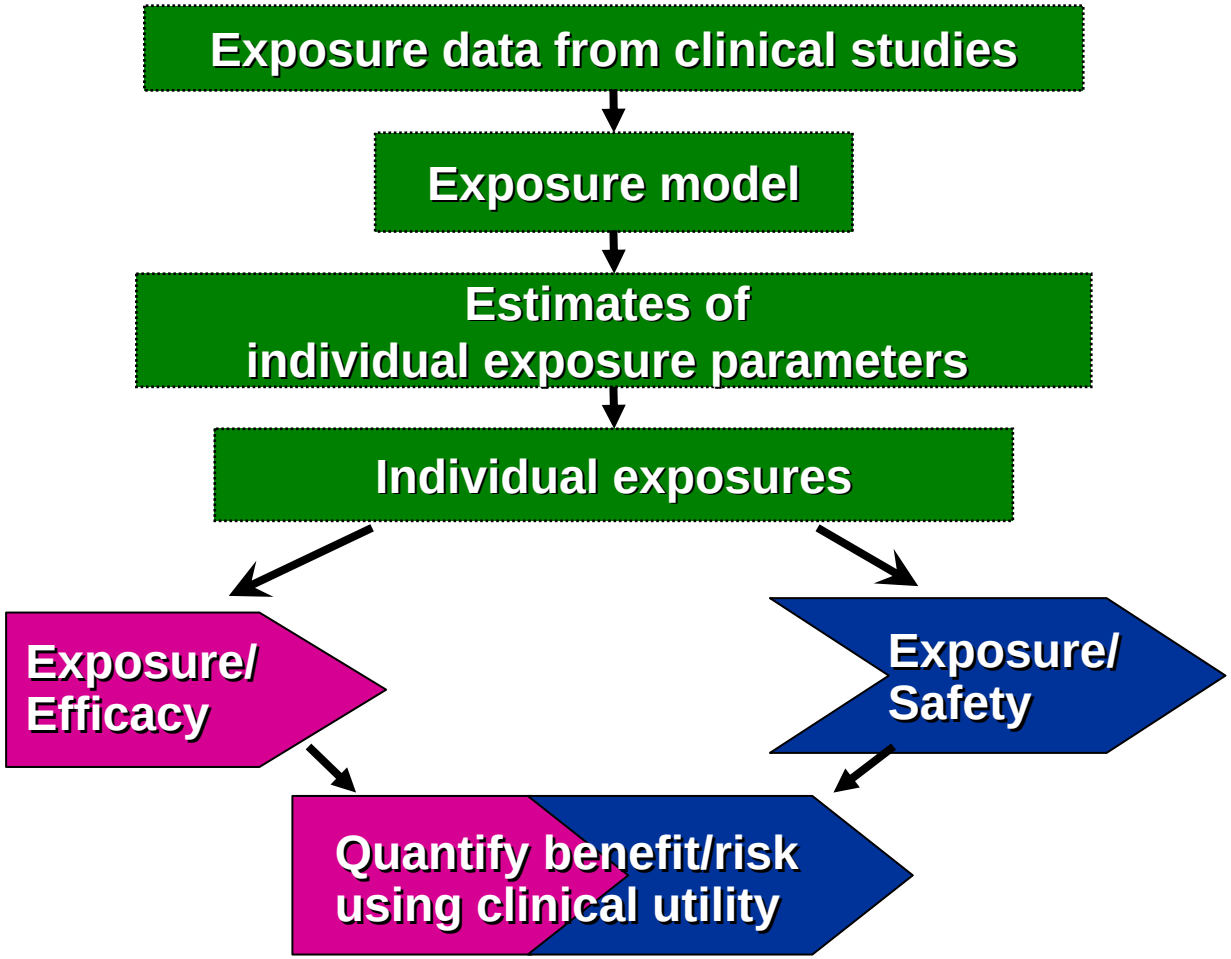
Uncertainty in Relative Clinical Utility



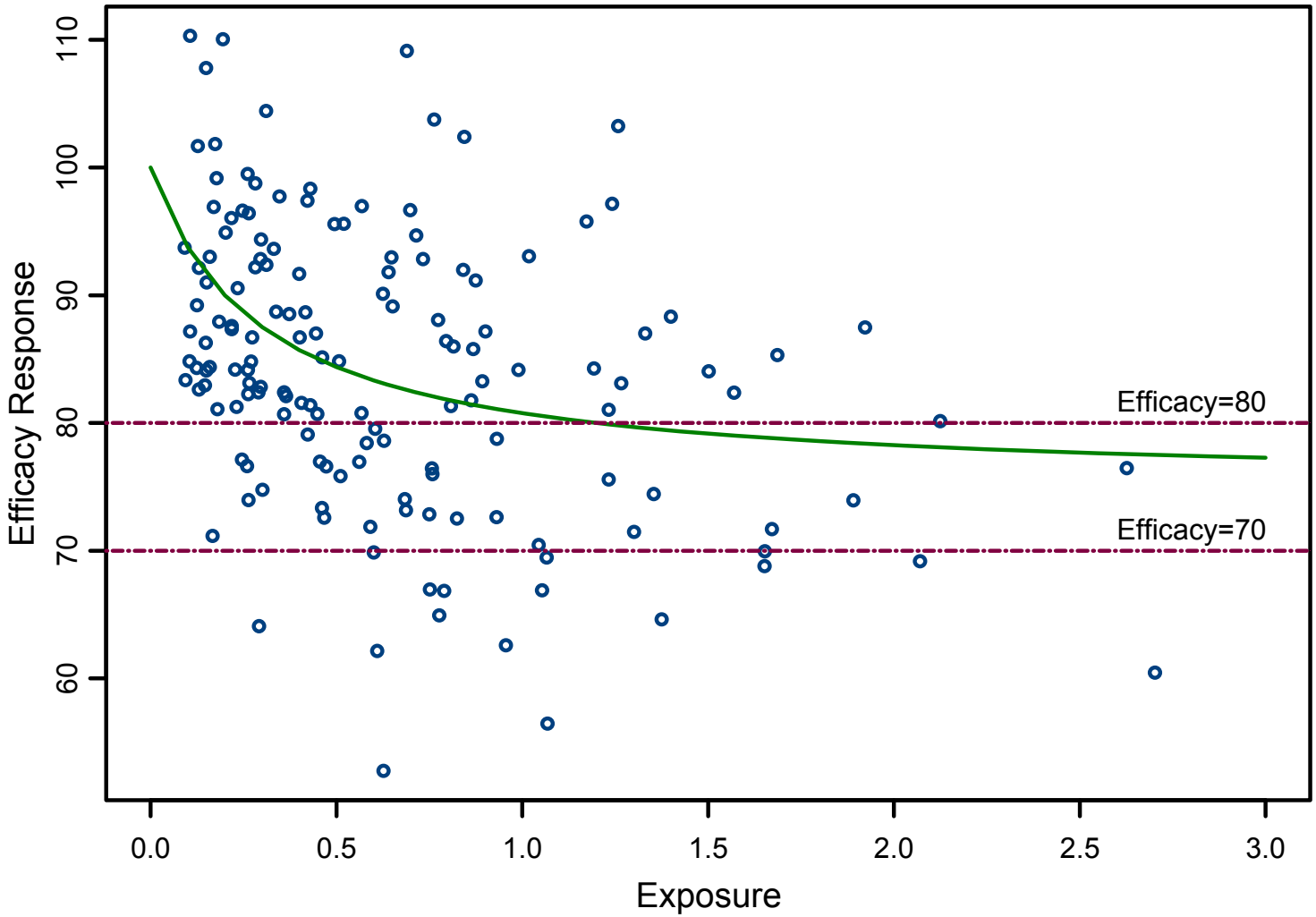
Case Study: Drug B

- Phase 2 Study:
  - Active comparator, parallel group
  - 4 doses (2.5, 5, and 10 mg)
  - Sample size = 200 (50 per dose group)
- Efficacy Endpoints (Categorize Continuous Response):
  - EFF.1: Efficacy ≤ 70
  - EFF.2: Efficacy ≤ 80 & Efficacy > 70
- Safety Endpoints (Ordered Categorical Response):
  - SAF.1: AE.Grade = 2
  - SAF.2: AE.Grade ≥ 3

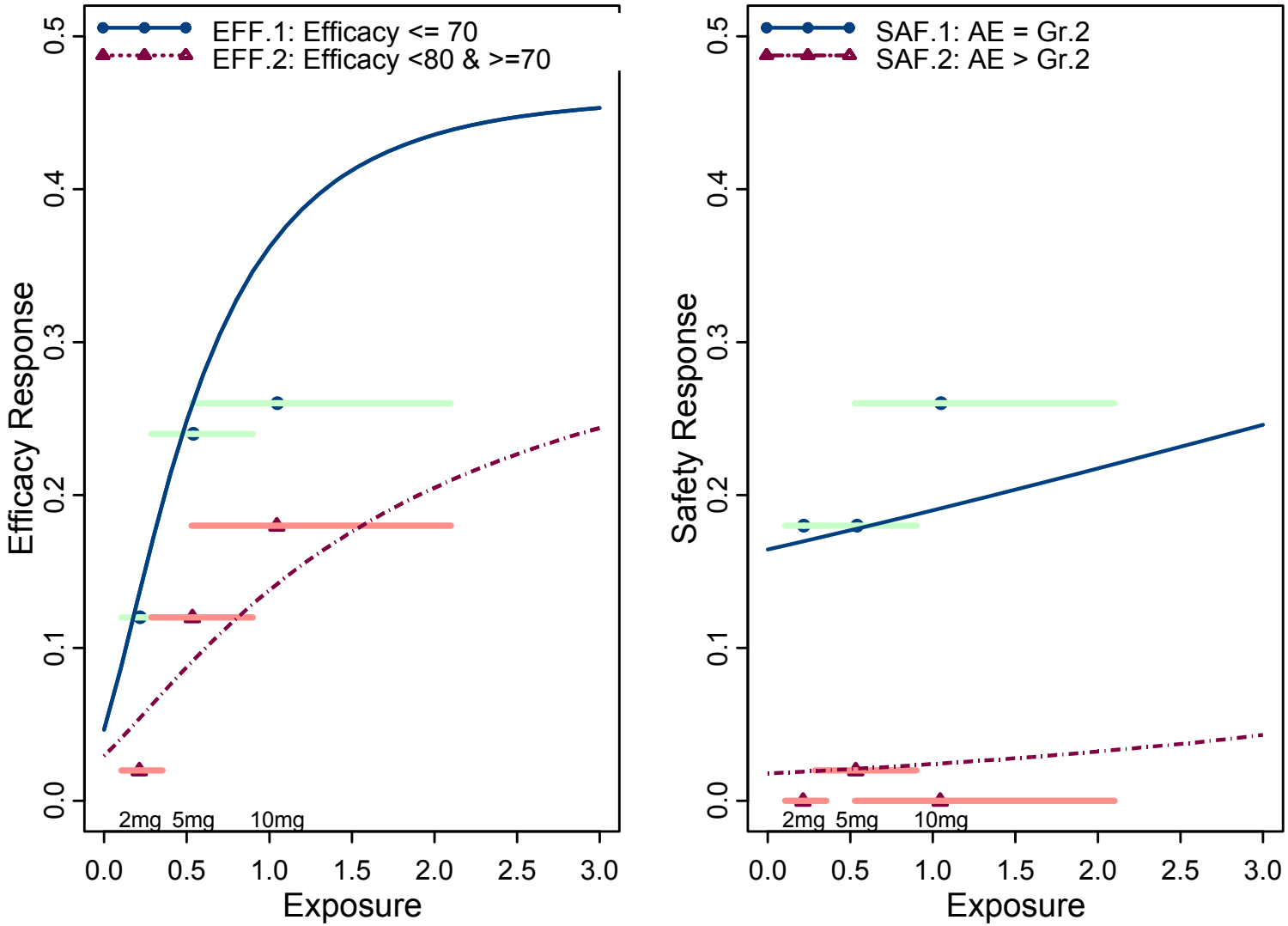
Modeling and Simulation Approach



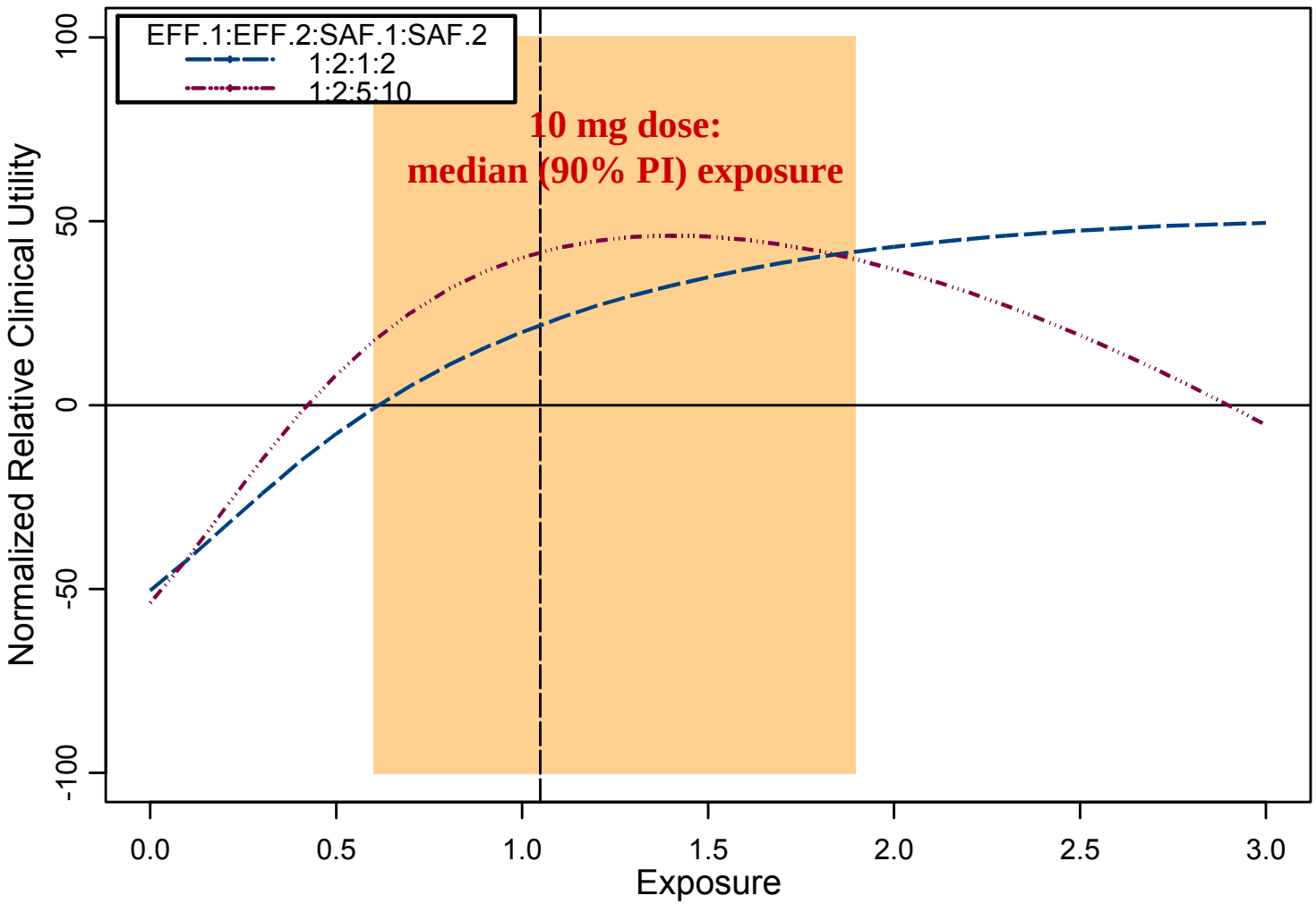
Exposure-Response (Efficacy)



Exposure-Response (2 Efficacy and 2 Safety)



Drug B: Relative Clinical Utility



Conclusions

- Clinical utility to determine optimal dose was applied to dose-response, as well as exposure-response data
- Clinical utility provides a means to explicitly state value judgments on the relative importance of efficacy and safety endpoints
- Clinical utility can be applied to binary, as well as categorical and continuous endpoints (by expressing the latter as multiple binary endpoints)
- Clinical utility can account for uncertainty
- Clinical utility facilitates decision making