# Basics of Simulation for Study Planning

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# Study Planning

- What would happen if the study were replicated many times?
- If we could do this, then we could summarize what happened.
- This type of is called an “operating characteristic”
- Common examples:
  - Power - how often did we reject the null?
  - Precision - how often did my 95% CI have width < X?

# Adaptive studies

- Adaptive studies often have “stopping rules” that allow the study to stop enrolling patients before the maximum sample size has been reached, either for efficacy or futility:
  - Efficacy: Already sufficient information; no need to continue
  - Futility: Insufficient information, even at the max sample size
- There are other types of adaptation too:
  - adjusting the max sample size
  - abandoning inferior or unsafe treatments
  - altering the allocation (randomization) ratio

# Adaptive studies

- Additional operating characteristics:
  - How often stopped early for futility?
  - How often stopped early for efficacy?
  - What was the typical (e.g., mean) sample size?

# Simulation

- A tool to mimic the process of replicating a study many times
- Implemented using a computer program with two main parts:
  a. Generating samples from a population
  b. Applying the statistical procedures

# Simple simulation example

- Estimate power of one sample study
  - Simulation step:
    - Draw sample of size n
    - Generate response using normal distribution
  - Analysis step:
    - Apply one-sided test (H0: mean = 0)
    - Compare p-value with 0.05 threshold

# Simple simulation example

See R Code example

# Note on number of simulations

- Number of sims affects precision of estimate of power
- Power estimate is like a sample proportion
- Can use standard precision methods to decide how many sims
- For example, if we want a specific margin of error, use:

$$n_\infty = \left( \frac{z^2_{\alpha/2} \hat{p}(1-\hat{p})}{\text{MOE}^2} \right)$$

- Need about 10000 sims to guarantee MOE of 0.01, with 95% conf.

# Simple adaptive trial example

- One-arm study (like before)
- One-sided test (H0: mean = 0)
- Enroll up to 500
- Interim analysis every 100
- At each analysis, stop for efficacy if p-value < 0.05
- Consider following operating characteristics:
  - Type-I error rate
  - Power
  - Sample size distribution

# Simple adaptive trial example

- At each analysis, stop for efficacy if p-value < 0.05
- Multiple opportunities to reject null
- May need to adjust threshold to preserve 5% type-I error

# Simple adaptive trial example

See R Code example

# Dealing with uncertainty

- Simulating study requires specification of all unknowns
- For example: the “true” effect size, variability in the outcome
- Often need to gauge sensitivity of power to unknowns
- For each unknown parameter, postulate a “high” and “low” value
- Redo simulation under all combinations

# Dealing with uncertainty

See R Code example

# Other issues

- Evaluate sensitivity to other assumptions
- Compare study designs (crossover?)
- Compare analysis methods (linear reg. vs. ordinal reg.)

# Thanks!

Code available here:

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