

# Adaptive Clinical Trials: The Promise and the Caution

Author: Donald A. Berry  
Anderson Cancer Center, Houston

Presented by: Hamsa Bastani

# Korn and Freidlin (2011)

- Two-armed trial

Assignment probability to experimental treatment arm

$$= \frac{[P(E > C)]^a}{[P(E > C)]^a + [1 - P(E > C)]^a} \quad (1)$$

- $a = 0$ : exploration
- $a = \infty$ : exploitation
- $a = 1$ : Thompson sampling

# Giles Phase II trial

- Acute myeloid leukemia
- Complete remission (CR) by day 50
- n=24, arm1 dropped (0/5 CRs)
- n = 34, arm2 dropped (3/11 = 27% CRs)
- Standard therapy (11/18 = 61% CRs)

# Giles Phase II trial

- As opposed to equal randomization of 75 patients
  - 7 standard therapy, 20 arm1, 14 arm2 instead of 41 standard therapy
  - Estimate extra 17.6/41 patients achieved CRs (23% incremental CR rate overall)

# Strengths of Adaptive Trials

- Multiple drugs & regimens + biomarker signatures (e.g. BATTLE)
- Phase II/III trials with different doses / schedules of drugs, combination therapy, different responding subpopulations

# I-SPY 2 Trial

- Phase II drug screening in neoadjuvant breast cancer
  - 6 treatment arms
  - Adaptive randomization within biomarker subsets
  - Arms replaced / dropped in Phase III
  - Better-performing drugs move faster (shortening drug development) and poorly-performing drugs waste fewer resources

# Disadvantages of Adaptive Trials

- Information security
  - If probability of assigning patients to the experimental arm becomes known, relative performance of the drug can be inferred
  - Investigators who enroll a large population of patients can observe these trends and may create selection bias (particularly in Phase III trials)
  - Not a problem in randomized trials

# Disadvantages of Adaptive Trials

- Complex logistics
  - Need all the data in a central location, software
- How to choose design?
  - What is a?
  - Convincing regulators
  - Population drift
- Getting pharmaceutical company funding
  - If experimental arm performs poorly, only a minority of patients may be assigned to their drug