

Why randomized phase II?

■ Classic phase II studies:

- Single arm study where results are compared to 'historical control' rate.
- Problem: this is not always 'satisfying'
 - Requires patient populations to be comparable
 - Might not have information to derive control rate (e.g. disease progression is of interest and not response)

■ Comparative randomized studies (phase III):

- Allow us to compare two arms
- Problem:
 - Large sample size (more than twice a single arm study)
 - Costly
 - Large undertaking based on scant preliminary data

Why randomized phase II?

- Want to explore efficacy
- Not willing to invest in phase III (yet)
- Want some “control” or “prioritization”
- Primarily two different kinds of randomized phase II studies
 - Phase II selection design (prioritization)
 - Phase II designs with reference control arm (control)
- Also phase II/III studies

Common design of randomized phase II study

- Two parallel one arm studies (classic case)
- **Do not directly compare arms to each other.**
- Compare each to “null rate”
- Example: null response = 0.25, alternative response=0.50, alpha=0.10, power=0.90.
 - Two parallel one-arm studies:
 - Test each treatment to see if it is better than null rate
 - For two arm study, need N=70 patients (35 per arm)
 - Comparative study:
 - Test to see if one treatment is better than the other treatment
 - For two arm study, need N=170 patients (85 per arm)

Classic Randomized Phase II designs

- Phase II selection designs (Simon, 1985)
 - “pick the winner”
 - 90% chance of choosing better arm so long as difference in response rates is $>15\%$.
 - Appropriate to use when:
 - Selecting among NEW agents
 - Selecting among different schedules or doses
 - NOT appropriate when
 - Trying to directly compare treatment efficacies (not powered)
 - Uses 2+ Simon two-stage designs
 - Each arm is compared to a null rate
 - Must satisfy efficacy criteria of Simon design
 - Move the “winner” to phase III
 - Only have to pick winner if more than one arm shows efficacy
 - Can be used when the goal is prioritizing which (if any) experimental regimen should move to phase III when no a priori information to favor one.

Classic Randomized Phase II designs

- Randomized Phase II designs with reference arm
 - Includes reference arm to ensure that historical rate is “on target”
 - Reference arm is not directly compared to experimental arm(s) (due to small N)
 - Can see if failure (or success) is due to incomparability of patient populations
 - Problem: if it turns out that historical control rate used is very different from what is observed in reference arm, then trial should be repeated*

*Herson and Carter, Statistics in Medicine (1986)

Phase II/III studies

- Several versions {Schaid (1988), Storer (1990), Ellenberg and Eisenberger (1985), Schaid and Heller (2002)}
- General idea
 - Begin with randomized phase II study
 - Randomize to control arm & experimental arm(s)
 - If some threshold of efficacy is met, continue to phase III sample size for direct comparison
- Benefits:
 - Allow use of phase II data in phase III inference
 - Minimize delay in starting up phase III study
 - Uses concurrent control
- Cons:
 - The sample size for the phase II part is approximately twice as large as would be needed for standard phase II
 - Need phase III infrastructure developed even if it stops early.
- **Would be useful if MOST phase II studies showed efficacy**
- Really, these could be considered phase III designs with very aggressive early stopping rules.

Other randomized Phase II designs?

Lots of randomized studies are calling themselves randomized phase II studies these days:

- If outcome of interest is surrogate
 - Correlative (biomarker)
 - Clinical (response)
- If sample size is relatively small but direct comparison is made (current study?)
- If study is comparative, but is not definitive for whatever reason.