Biostat Methods STAT 5820/6910
Handout #8a: Intro. to Group Sequential Designs

As a clinical trial progresses, data accumulates (with new participants)

- Could conduct a significance test after each additional observation becomes available, or at other steps
- Why?
  - Ethical: If tmt works, should not withhold it (if worse than ctl, shouldn't expose patients to risk)
  - Statistical: Larger sample size → greater power (want to find effect if it exists)
- A special case of multiple hypothesis testing → need to control FWER at α
- The most recent solutions tend to look at how to:
  "spend" α across the interim analyses (simple Bonf. approach spends equally α/k at each test)

Interim analysis (group sequential methods)

- Careful planning at design stage will protect: overall Type I error rate α
- Final analysis conducted at some level $\leq$ α, so sample size requirements are generally larger than in fixed sample size studies
- Stopping Rules: (many others exist)
  - Pocock - final analysis at level much smaller than α
  - O'Brien-Fleming - assumes equally-spaced intervals
  - Lan-DeMets - relaxes equal spacing; more flexible for lengthy trials where patient enrollment is not uniform over time (example: every 6 months)

"Wang-Tsiatis" designs

- Software implementation:
  - SAS: PROC SEQDESIGN, PROC SEQTEST
  - R: package gsDesign (authors at Merck) → HUGE pharma

Most α-spending functions focus on two-tailed symmetric tests (but variations exist)

Lan-DeMets α-spending function

- k total analyses planned – including final analysis
- Analyses assumed *roughly* equally spaced (in sample size, not time)
- Let t be information fraction at a given interim analysis
  ↳ usually sample size ratio, relative to fixed final sample size
- Plan to "spend" α_i at interim analysis i to preserve overall α
  α_i corresponds to some information fraction t_i
- Test at information fraction t is conducted at level

$$f(t,\alpha) = 2\left(1-\Phi\left(\frac{\Phi^{-1}(\alpha/2)}{\sqrt{t}}\right)\right) \leq \sum_{t_i \leq t} \alpha_i$$

where

cdf $\Phi(1.96) = 1 - \frac{.05}{2}$

and

$$\Phi^{-1}(0.05/2) = -1.96$$

Adaptive allocation

- As evidence accumulates, may change proportion of new subjects assigned to a particular group
- Bayesian methods exist to allocate new participants to treatment groups based on outcomes (interim analyses) of previous patients
- Rules often called "Bayesian adaptive designs"

Additional reading: Jennison C and Turnbull BW (2000), *Group Sequential Methods with Applications to Clinical Trials*. Boca Raton: Chapman and Hall.