Group Sequential Clinical Trial Designs for Normally Distributed Outcome Variables

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Outline

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Randomised Controlled Trial Design

- Choose a sample size that provides some level of statistical power for a target treatment effect.
- Recruit the number of patients required.
- Perform an analysis after all patients have been assessed.
- Design, analysis, and reporting of such trials well characterised.
- Incredibly effective way to assess the efficacy of a treatment.
- But is this the best we can do?

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Adaptive Trial Design

- Trials gather a lot of data during their progress!
- What if we are unsure about the sample size to use?
- What if the new treatment is harmful?
- What if the new treatment works only in a subset of patients?
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Group Sequential Trials

- Can bring substantial administrative, ethical, monetary advantages.
- Origins in industrial sampling and Wald's SPRT.
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- Idea therefore is to conduct analyses after particular landmark numbers of patients recruited.
- Trial may be stopped early to accept or reject null hypotheses.
- Expected sample size typically reduced.

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Overview

- Focus on the design of a two-arm group sequential trial testing for superiority, with normally distributed outcomes.
- Assume a maximum of L analysis planned, and that analysis $l = 1, \dots, L$ takes place after $n_{0l} = ln$ and $n_{1l} = rln$ patients evaluated in arms 0 and 1 respectively.
- Suppose that $Y_{dli} \sim N(\mu_d, \sigma_d^2)$ for $d = 0, 1$.
- Defining $\tau = \mu_1 - \mu_0$, interest is in testing

$$H_0 : \tau \leq 0, \qquad H_1 : \tau > 0.$$

- Want overall type-I error-rate when $\tau = 0$ of α, and power of $1 - \beta$ when $\tau = \delta > 0$.

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Analysis

- To test H_0, the following test statistic is used after analysis $l = 1,\dots,L$

$$Z_l = \left(\frac{1}{n_{1l}} \sum_{j=1}^{l} \sum_{i=1}^{rn} Y_{1jl} - \frac{1}{n_{0l}} \sum_{j=1}^{l} \sum_{i=1}^{n} Y_{0jl} \right) I_l^{1/2},$$

$$I_l = \left(\frac{\sigma_0^2}{n_{0l}} + \frac{\sigma_1^2}{n_{1l}} \right)^{-1}.$$

- Importantly $(Z_1,\dots,Z_L)$ is multivariate normal with

$$\mathbb{E}(Z_l) = \tau I_l^{1/2}, \qquad l = 1,\dots,L,$$

$$\mathrm{Cov}(Z_l, Z_k) = (I_l/I_k)^{1/2}, \qquad 1 \le l \le k \le L.$$

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Stopping Rules

- ...given choices for $f_1, \ldots, f_L$ and $e_1, \ldots, e_L$. Use these in the following stopping rules at analysis $l = 1, \ldots, L$
  - If $Z_l \geq e_l$ stop and reject H_0.
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Boundaries

- Functional form assumed, then search to find group size and exact values for correct operating characteristics.
- For example

$$e_l = C_e(l/L)^{\Omega-1/2},$$
$$f_l = \delta I_l^{1/2} - C_f(l/L)^{\Omega-1/2}.$$

- Then take $I_L^{1/2} = (C_e + C_f)/\delta$, to ensure $e_L = f_L$.
- Search over C_e and C_f using `optimize()`.

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2. Group Sequential Design Theory
3. Commands
4. Discussion

Commands

- Six commands in total. Four for two-sided tests, and two for one-sided tests as discussed here.
- One-sided tests as follows

```
powerFamily, [l(integer 3) delta(real 0.2)
              alpha(real 0.05) beta(real 0.2)
              sigma(numlist) ratio(real 1) Omega(real 0.5)
              performance *]

triangular, [l(integer 3) delta(real 0.2) alpha(real 0.05)
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```

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Example Output

```
. powerFamily, l(3) alpha(0.05) beta(0.2) delta(0.2) sigma(1, 2) omega(-0.5) r(2)

3-stage Group Sequential Trial Design
_____________________________________

The hypotheses to be tested are as follows:

  H0: tau <= 0  H1: tau > 0,

with the following error constraints:

  P(Reject H0 | tau = 0)  = .05,
  P(Reject H0 | tau = .2) = 1 - .2.

   Power family boundaries selected with Omega = -.5...
...now determining design............................
...output from optimize() to follow..................
Iteration 0:   f(p) =  .01419449
Iteration 1:   f(p) =  .00121018
Iteration 2:   f(p) =  .00105648
```

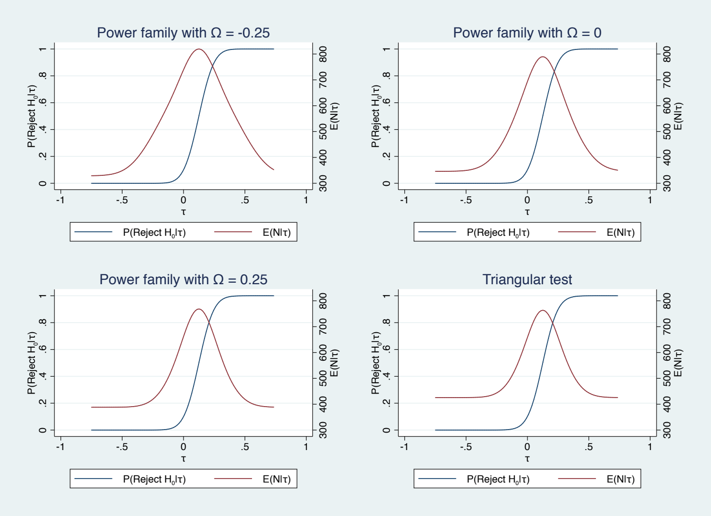
Example Output

```
Iteration 15:  f(p) =  1.956e-08
...design determined. Returning the results...........
...Exact required group size n determined to be:

  159.

...Efficacy boundaries e determined to be:

  (4.87,2.44,1.62).

...Futility boundaries f determined to be:

  (-1.24,.71,1.62).

...Operating characteristics of the design are:

  P(Reject H0 | tau = 0)  = .0499,
  P(Reject H0 | tau = .2) = .7999,
  E(N | tau = 0)          = 1013,
  E(N | tau = .2)         = 1218.2,
  max_tau E(N | tau)      = 1241.3,
  max N                   = 1431.4.
```

Example: Comparison

```
. qui powerFamily, l(3) alpha(0.1) beta(0.1) delta(0.25) sigma(1, 2) omega(-0.25)
>  r(2) perf saving(gsdesign1) nodraw title(Power family with {&Omega} = -0.25)
> scale(0.75)

. qui powerFamily, l(3) alpha(0.1) beta(0.1) delta(0.25) sigma(1, 2) omega(0) r(2
> ) perf saving(gsdesign2) nodraw title(Power family with {&Omega} = 0) scale(0.7
> 5)

. qui powerFamily, l(3) alpha(0.1) beta(0.1) delta(0.25) sigma(1, 2) omega(0.25)
> r(2) perf saving(gsdesign3) nodraw title(Power family with {&Omega} = 0.25) sca
> le(0.75)

. qui triangular, l(3) alpha(0.1) beta(0.1) delta(0.25) sigma(1, 2) r(2) perf sav
> ing(gsdesign4) nodraw title(Triangular test) scale(0.75)

. graph combine gsdesign1.gph gsdesign2.gph gsdesign3.gph gsdesign4.gph, ycommon
```

Example: Comparison



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Discussion

- Group sequential designs provide gains in efficiency, easy to find (at least in this case).
- Key commands working.
- Only considered design so far.
- Only considered two-arm; multi-arm multi-stage designs of increasing interest.
- An option to use simulation instead of integration would also be a good step.

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1. Jennison C, Turnbull BW (2000) *Group Sequential Methods with Applications to Clinical Trials*. Boca Raton, FL: Chapman & Hall/CRC.
2. Pampallona S, Tsiatis AA (1994) Group sequential designs for one-sided and two-sided hypothesis testing with provision for early stopping in favor of the null hypothesis. *Journal of Statistical Planning and Inference* 42(1-2):19-35.
3. Whitehead J (1997) *The Design and Analysis of Sequential Clinical Trials*. Revised 2nd ed. Chichester: John Wiley & Sons.