Group Sequential Clinical Trial Designs for Normally Distributed Outcome Variables

Michael Grayling James Wason Adrian Mander

Hub for Trials Methodology Research
MRC Biostatistics Unit
Cambridge, UK

Stata UK Users Group Meeting, September 2017

Outline

Outline

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?

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?

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?

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?

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?

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?

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?
- This is where adaptive trial design comes in.
- Here discuss group sequential trials.

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?
- This is where adaptive trial design comes in.
- Here discuss group sequential trials.

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?
- This is where adaptive trial design comes in.
- Here discuss group sequential trials.

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?
- This is where adaptive trial design comes in.
- Here discuss group sequential trials.

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?
- This is where adaptive trial design comes in.
- Here discuss group sequential trials.

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?
- This is where adaptive trial design comes in.
- Here discuss group sequential trials.

Group Sequential Trials

- Can bring substantial administrative, ethical, monetary advantages.
- Origins in industrial sampling and Wald's SPRT.
- First proposals were fully sequential, but this proved to be impractical.
- 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.

Group Sequential Trials

- Can bring substantial administrative, ethical, monetary advantages.
- Origins in industrial sampling and Wald's SPRT.
- First proposals were fully sequential, but this proved to be impractical.
- 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.

Group Sequential Trials

- Can bring substantial administrative, ethical, monetary advantages.
- Origins in industrial sampling and Wald's SPRT.
- First proposals were fully sequential, but this proved to be impractical.
- 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.

Group Sequential Trials

- Can bring substantial administrative, ethical, monetary advantages.
- Origins in industrial sampling and Wald's SPRT.
- First proposals were fully sequential, but this proved to be impractical.
- 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.

Group Sequential Trials

- Can bring substantial administrative, ethical, monetary advantages.
- Origins in industrial sampling and Wald's SPRT.
- First proposals were fully sequential, but this proved to be impractical.
- 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.

Group Sequential Trials

- Can bring substantial administrative, ethical, monetary advantages.
- Origins in industrial sampling and Wald's SPRT.
- First proposals were fully sequential, but this proved to be impractical.
- 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.

Outline

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 $l = 1, \ldots, L$ 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 $\tau = \delta > 0$.

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 $l = 1, \ldots, L$ 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 $\tau = \delta > 0$.

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 $l = 1, \ldots, L$ 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 $\tau = \delta > 0$.

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 $l = 1, \ldots, L$ 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 $\tau = \delta > 0$.

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 $l = 1, \ldots, L$ 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 $\tau = \delta > 0$.

Analysis

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

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

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

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

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

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

- Means operating characteristics can be calculated analytically...

Analysis

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

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

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

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

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

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

- Means operating characteristics can be calculated analytically...

Analysis

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

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

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

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

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

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

- Means operating characteristics can be calculated analytically...

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.
  - If $Z_l < f_l$ stop and accept H_0.
  - otherwise continue to stage $l + 1$.
- Then

$$\begin{aligned}\mathbb{P}(\text{Reject } H_0 \mid \tau) &= \sum_{l=1}^{L} \mathbb{P}(\text{Reject } H_0 \text{ at stage } l \mid \tau), \\ &= \mathbb{P}(Z_1 \geq e_1 \mid \tau) \\ &\quad + \sum_{l=2}^{L} \mathbb{P}(f_1 \leq Z_1 < e_1, \ldots, f_{l-1} \leq Z_{l-1} < e_{l-1}, Z_l \geq e_l \mid \tau).\end{aligned}$$

- Similar formulae for $\mathbb{E}(N \mid \tau)$.
- Evaluate these formulae using `mvnormal_mata()`.

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.
  - If $Z_l < f_l$ stop and accept H_0.
  - otherwise continue to stage $l + 1$.
- Then

$$\begin{aligned}\mathbb{P}(\text{Reject } H_0 \mid \tau) &= \sum_{l=1}^{L} \mathbb{P}(\text{Reject } H_0 \text{ at stage } l \mid \tau), \\ &= \mathbb{P}(Z_1 \geq e_1 \mid \tau) \\ &\quad + \sum_{l=2}^{L} \mathbb{P}(f_1 \leq Z_1 < e_1, \ldots, f_{l-1} \leq Z_{l-1} < e_{l-1}, Z_l \geq e_l \mid \tau).\end{aligned}$$

- Similar formulae for $\mathbb{E}(N \mid \tau)$.
- Evaluate these formulae using `mvnormal_mata()`.

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.
  - If $Z_l < f_l$ stop and accept H_0.
  - otherwise continue to stage $l + 1$.
- Then

$$\begin{aligned}\mathbb{P}(\text{Reject } H_0 \mid \tau) &= \sum_{l=1}^{L} \mathbb{P}(\text{Reject } H_0 \text{ at stage } l \mid \tau), \\ &= \mathbb{P}(Z_1 \geq e_1 \mid \tau) \\ &\quad + \sum_{l=2}^{L} \mathbb{P}(f_1 \leq Z_1 < e_1, \ldots, f_{l-1} \leq Z_{l-1} < e_{l-1}, Z_l \geq e_l \mid \tau).\end{aligned}$$

- Similar formulae for $\mathbb{E}(N \mid \tau)$.
- Evaluate these formulae using `mvnormal_mata()`.

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.
  - If $Z_l < f_l$ stop and accept H_0.
  - otherwise continue to stage $l + 1$.
- Then

$$\begin{aligned}\mathbb{P}(\text{Reject } H_0 \mid \tau) &= \sum_{l=1}^{L} \mathbb{P}(\text{Reject } H_0 \text{ at stage } l \mid \tau), \\ &= \mathbb{P}(Z_1 \geq e_1 \mid \tau) \\ &\quad + \sum_{l=2}^{L} \mathbb{P}(f_1 \leq Z_1 < e_1, \ldots, f_{l-1} \leq Z_{l-1} < e_{l-1}, Z_l \geq e_l \mid \tau).\end{aligned}$$

- Similar formulae for $\mathbb{E}(N \mid \tau)$.
- Evaluate these formulae using `mvnormal_mata()`.

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.
  - If $Z_l < f_l$ stop and accept H_0.
  - otherwise continue to stage $l + 1$.
- Then

$$\begin{aligned}\mathbb{P}(\text{Reject } H_0 \mid \tau) &= \sum_{l=1}^{L} \mathbb{P}(\text{Reject } H_0 \text{ at stage } l \mid \tau), \\ &= \mathbb{P}(Z_1 \geq e_1 \mid \tau) \\ &\quad + \sum_{l=2}^{L} \mathbb{P}(f_1 \leq Z_1 < e_1, \ldots, f_{l-1} \leq Z_{l-1} < e_{l-1}, Z_l \geq e_l \mid \tau).\end{aligned}$$

- Similar formulae for $\mathbb{E}(N \mid \tau)$.
- Evaluate these formulae using `mvnormal_mata()`.

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.
  - If $Z_l < f_l$ stop and accept H_0.
  - otherwise continue to stage $l + 1$.
- Then

$$\begin{aligned}\mathbb{P}(\text{Reject } H_0 \mid \tau) &= \sum_{l=1}^{L} \mathbb{P}(\text{Reject } H_0 \text{ at stage } l \mid \tau), \\ &= \mathbb{P}(Z_1 \geq e_1 \mid \tau) \\ &\quad + \sum_{l=2}^{L} \mathbb{P}(f_1 \leq Z_1 < e_1, \ldots, f_{l-1} \leq Z_{l-1} < e_{l-1}, Z_l \geq e_l \mid \tau).\end{aligned}$$

- Similar formulae for $\mathbb{E}(N \mid \tau)$.
- Evaluate these formulae using `mvnormal_mata()`.

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.
  - If $Z_l < f_l$ stop and accept H_0.
  - otherwise continue to stage $l + 1$.
- Then

$$\begin{aligned}\mathbb{P}(\text{Reject } H_0 \mid \tau) &= \sum_{l=1}^{L} \mathbb{P}(\text{Reject } H_0 \text{ at stage } l \mid \tau), \\ &= \mathbb{P}(Z_1 \geq e_1 \mid \tau) \\ &\quad + \sum_{l=2}^{L} \mathbb{P}(f_1 \leq Z_1 < e_1, \ldots, f_{l-1} \leq Z_{l-1} < e_{l-1}, Z_l \geq e_l \mid \tau).\end{aligned}$$

- Similar formulae for $\mathbb{E}(N \mid \tau)$.
- Evaluate these formulae using `mvnormal_mata()`.

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()`.

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()`.

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()`.

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()`.

Outline

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)
             beta(real 0.2) sigma(numlist) ratio(real 1)
             performance *]
```

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)
             beta(real 0.2) sigma(numlist) ratio(real 1)
             performance *]
```

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
```

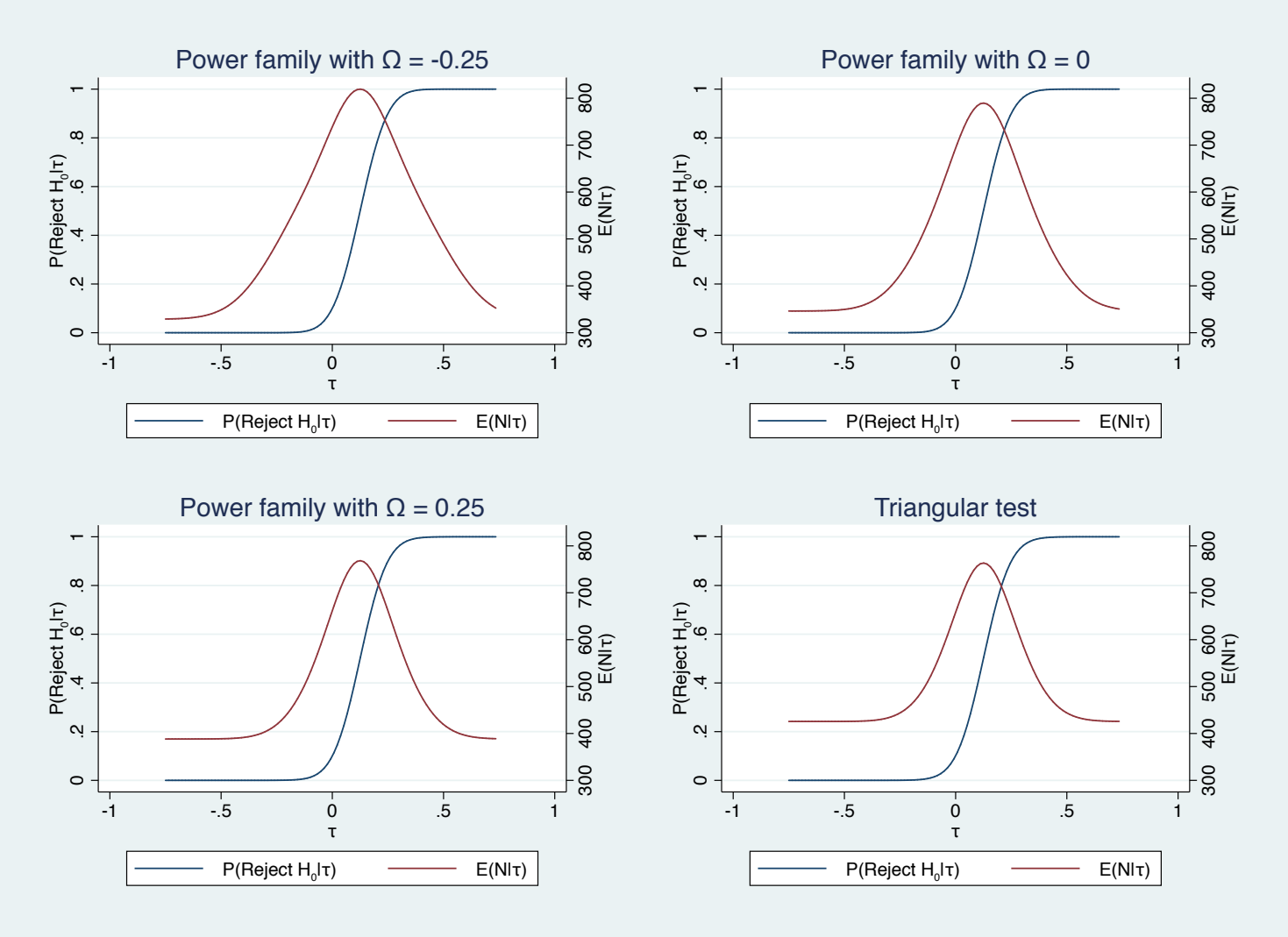
Example Output

```
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



Outline

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.

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.

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.

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.

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.

References

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.