Conditional Power Based Group Sequential Design: Key Elements

Lei Li

June 19, 2025

Agenda

- Three Clinical Questions.
- Conditional Power.
- The B values.
- Interim Monitoring Efficacy.
- Interim Monitoring Futility.
- Case Study

Three Basic Questions for Calculating Conditional Power

For Continuous Monitoring, there are commonly three questions being asked for futility:

1. No effect trend: After an interim look, if there is no effect for the rest of the trial, will we reject?
2. Hypothetical trend: suppose we originally choose $X\%$ power, if that trend continues, will we reject?
3. Current trend: What if our observed value at n out of N subjects, will we reject?

Conditional Power

- Suppose $X_1, \ldots, X_N$ follows the i.i.d. $N(\mu, \sigma^2)$. Also, let $\bar{X}_n$ and S_n be the mean and sum of $X_1, \ldots, X_n$, respectively, where $n = 1, \ldots, N$.
- Now ***standardize*** $\bar{X}_n$ as $Z_n = \frac{\sqrt{n}\bar{X}_n}{\sigma} = \frac{S_n}{\sqrt{n}\sigma}$. Also, let the total "information parameter" be $\theta \equiv \boldsymbol{E}[Z_N] = \frac{\sqrt{N}\mu}{\sigma}$. Note that θ is essentially the expectation of standardized statistic Z_N. For instance, if $\hat{\mu}$ is an estimate of μ, then the standardized statistic of $\hat{\mu}$ is $\hat{Z} = \frac{\hat{\mu}}{\sqrt{Var(\hat{\mu})}}$.
- The interest is to test the hypothesis:

$$H_0 : \mu = 0 \qquad H_a : \mu > 0.$$

- The conditional power $CP(\theta)$ is defined as the probability of rejecting H_0 when H_a is true given an interim result.

$$\begin{aligned} CP(\theta) &= 1 - \Phi\left(\frac{z_{1-\alpha} - \sqrt{\frac{n}{N}}Z_n}{\sqrt{\frac{N-n}{N}}} - \frac{\sqrt{N-n}\mu}{\sigma}\right) \\ &= 1 - \Phi\left(\frac{z_{1-\alpha} - \sqrt{\frac{n}{N}}Z_n}{\sqrt{\frac{N-n}{N}}} - \sqrt{\frac{N-n}{N}}\theta\right), \end{aligned} \tag{1}$$

where $\Phi(\cdot)$ denotes the cumulative probability of standard normal distribution $N(0, 1)$.

Conditional Power Question 1: No Effect Trend

1. No Effect Trend: If there is no effect for the rest of the trial (i.e., $\mu = 0$), will we reject?

$$CP\left(\theta = \frac{\sqrt{N}\mu}{\sigma} = 0\right) = 1 - \Phi\left(\frac{z_{1-\alpha} - \sqrt{\frac{n}{N}}Z_n}{\sqrt{\frac{N-n}{N}}}\right).$$

- So, if the conditional power $CP(\cdot)$ is below a pre-specified threshold (e.g., 80%), then we may stop the trial.

Conditional Power Question 2: Hypothetical Trend

2. Hypothetical Trend: suppose we originally choose e.g., 90% power, if that trend continues, will we reject?

- Note that under hypothetical trend, the power is pre-defined as $1-\beta$, where β is type II error.

$$1-\beta = 1-\Phi\left(\frac{z_{1-\alpha}-\sqrt{\frac{n}{N}}Z_n}{\sqrt{\frac{N-n}{N}}}-\sqrt{\frac{N-n}{N}}\theta\right). \tag{2}$$

- The above equation implies that

$$z_{1-\beta}+\frac{z_{1-\alpha}}{\sqrt{\frac{N-n}{N}}}=\frac{\sqrt{\frac{n}{N}}Z_n}{\sqrt{\frac{N-n}{N}}}+\sqrt{\frac{N-n}{N}}\theta. \tag{3}$$

Hypothetical trend means at design stage $n=0$. So, the above equation becomes

$$z_{1-\beta}+z_{1-\alpha}=\theta. \tag{4}$$

Plug (4) into (2), we get the conditional power under hypothetical trend:

$$CP(\theta=z_{1-\alpha}+z_{1-\beta})=1-\Phi\left(\frac{z_{1-\alpha}-\sqrt{\frac{n}{N}}Z_n}{\sqrt{\frac{N-n}{N}}}-\sqrt{\frac{N-n}{N}}\left(z_{1-\alpha}+z_{1-\beta}\right)\right). \tag{5}$$

Conditional Power Question 3: Current Trend

3. Current Trend: What if our observed value Z_n at n, will we reject?

- Given $Z_n = \frac{\sqrt{n}\bar{X}_n}{\sigma}$, the current estimate of μ is $\hat{\mu} = \frac{Z_n \sigma}{\sqrt{n}}$, so the estimated θ is $\hat{\theta} = \frac{\sqrt{N}\hat{\mu}}{\sigma} = \sqrt{\frac{N}{n}} Z_n$. Thus, the conditional power in this case becomes

$$CP\left(\hat{\theta} = \sqrt{\frac{N}{n}} Z_n\right) = 1 - \Phi\left(\frac{z_{1-\alpha} - \sqrt{\frac{n}{N}} Z_n}{\sqrt{\frac{N-n}{N}}} - \sqrt{\frac{N-n}{n}} Z_n\right). \tag{6}$$

Conditional Power Based on B Values

- Note that $Z_N = \frac{S_N}{\sqrt{N}\sigma} = \frac{1}{\sigma}\left(\sqrt{\frac{n}{N}}\frac{S_n}{\sqrt{n}} + \sqrt{\frac{N-n}{N}}\frac{S_N - S_n}{\sqrt{N-n}}\right) = \left(\sqrt{\frac{n}{N}}Z_n\right) + \left(Z_N - \sqrt{\frac{n}{N}}Z_n\right)$. $\sqrt{\frac{n}{N}}Z_n$ and $Z_N - \sqrt{\frac{n}{N}}Z_n$ are independent.
- For simplicity, now let $t = n/N$, $t \in [0,1]$. Also, define the B value at time t as $B_t = \sqrt{t}Z_t$, where $t \in [0,1]$.
- Note that $B_t \sim N(t\theta, t)$. Also, the mean and variance of B_t are given as follows.

$$
\begin{aligned}
\boldsymbol{E}[B_t] &= \boldsymbol{E}\left[\sqrt{\frac{n}{N}}\frac{S_n}{\sqrt{n}\sigma}\right] = \sqrt{\frac{n}{N}}\frac{n\mu}{\sqrt{n}\sigma} = \sqrt{\frac{n}{N}}\frac{n}{\sqrt{n}\sigma}\frac{\theta\sigma}{\sqrt{N}} = t\theta. && (7)\\
\boldsymbol{Var}(B_t) &= \boldsymbol{Var}\left(\sqrt{\frac{n}{N}}\frac{S_n}{\sqrt{n}\sigma}\right) = \frac{1}{N\sigma^2}\boldsymbol{Var}(S_n) = \frac{n\sigma^2}{N\sigma^2} = t. && (8)
\end{aligned}
$$

- Conditional Distribution: $B_1 | B_t \sim N(B_t + (1-t)\theta, 1-t)$.

$$
\begin{aligned}
\boldsymbol{E}[B_1|B_t] &= \boldsymbol{E}[B_t + B_1 - B_t|B_t] = B_t + (1-t)\theta, && (9)\\
\boldsymbol{Var}(B_1|B_t) &= \boldsymbol{Var}(B_t + B_1 - B_t|B_t) = \boldsymbol{Var}[B_1 - B_t] = 1-t. && (10)
\end{aligned}
$$

B Values Properties

Properties of B_t:

- The conditional power $CP(\theta)$ based on B_t is (could be derived from equation (1)).

$$CP(\theta) = P\left(Z \geq \frac{z_{1-\alpha} - B_t}{\sqrt{1-t}} - \sqrt{1-t}\theta\right), \tag{11}$$

  where $\sqrt{1-t}\theta$ is called drift parameter.
- B_t and $B_1 - B_t$ are independent. Also, let $t_1 < t_2$, then B_{t_1} and $B_{t_2} - B_{t_1}$ are independent.
- $E[B_t] = \theta t$, $Var(B_t) = t$.
- Information fractions $t_1, t_2, \ldots, t_k$, the distribution of $(B_{t_1}, B_{t_2}, \ldots, B_{t_k})$ follow multivariate normal distribution with variance-covariance matrix Σ_T, where

$$\Sigma_T = \begin{pmatrix} t_1 & t_1 & t_1 & \cdots & t_1 \\ t_1 & t_2 & t_2 & \cdots & t_2 \\ t_1 & t_2 & t_3 & \cdots & t_3 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ t_1 & t_2 & t_3 & \cdots & t_k \end{pmatrix}.$$

- Proof of Σ_T: WLOG, assume $t_1 < t_2$, it's enough to show the covariance of B_{t_1} and B_{t_2}:

$$Cov(B_{t_1}, B_{t_2}) = Cov(B_{t_1}, B_{t_2} - B_{t_1}) + Cov(B_{t_1}, B_{t_1}) = 0 + Var(B_{t1}) = t_1.$$

Revisit the three clinical questions using B Values

Using the formula (11),

1. No effect trend: Under the null, $CP(\theta = 0) = P\left(Z \geq \frac{z_{1-\alpha} - B_t}{\sqrt{1-t}}\right)$.
2. Hypothetical trend:
   $CP(\theta = z_{1-\alpha} + z_{1-beta}) = P\left(Z \geq \frac{z_{1-\alpha} - B_t}{\sqrt{1-t}} - \sqrt{1-t}(z_{1-\alpha} + z_{1-\beta})\right)$.
3. current trend: given $Z_n = \frac{\sqrt{n}\bar{X}_n}{\sigma}$, one can estimate μ as $\hat{\mu} = \bar{X}_n = \frac{Z_n \sigma}{\sqrt{n}}$ then estimate θ as $\hat{\theta} = \frac{\sqrt{N}\hat{\mu}}{\sigma} = \frac{Z_n}{\sqrt{t}} = \frac{B_t}{t}$. Then, the conditional power is $CP(\theta = \hat{\theta} = \frac{B_t}{t}) = P\left(Z \geq \frac{z_{1-\alpha} - B_t}{\sqrt{1-t}} - \sqrt{1-t}\frac{B_t}{t}\right)$.

Information Fraction t

The information fraction is essentially Fisher Information fraction. Suppose there is a two sample problem: $X_1, \ldots, X_{M_1} \overset{i.i.d.}{\sim} N(\mu_X, \sigma_X^2)$ and $Y_1, \ldots, Y_{M_2} \overset{i.i.d.}{\sim} N(\mu_Y, \sigma_Y^2)$.

- Hypothesis: $H_0 : \mu_X = \mu_Y \quad vs \quad H_a : \mu_X > \mu_Y$.
- Construct standardized statistic $Z_N = \frac{\bar{X}_{M_1} - \bar{Y}_{M_2}}{\sqrt{Var(\bar{X}_{M_1} - \bar{Y}_{M_2})}}$, where $Var(\bar{X}_{M_1} - \bar{Y}_{M_2}) = \frac{\sigma_X^2}{M_1} + \frac{\sigma_Y^2}{M_2}$.
- So the information fraction at $n = m_1 + m_2$ and θ are

$$t = \frac{\frac{\sigma_X^2}{m_1} + \frac{\sigma_Y^2}{m_2}}{\frac{\sigma_X^2}{M_1} + \frac{\sigma_Y^2}{M_2}} \quad \text{and} \quad \theta = \boldsymbol{E}[B_1] = \boldsymbol{E}[Z_N] = \frac{\mu_Y - \mu_Y}{\sqrt{\frac{\sigma_X^2}{M_1} + \frac{\sigma_Y^2}{M_2}}}. \tag{12}$$

- Case 1: If $\sigma_X^2 = \sigma_Y^2 = \sigma^2$ and $M_1 = M_2$, then $t = \frac{n}{N}$.
- Case 2: If $\sigma_X^2 = \sigma_Y^2 = \sigma^2$, then $t = \frac{\frac{1}{m_1} + \frac{1}{m_2}}{\frac{1}{M_1} + \frac{1}{M_2}}$.

Continuous Monitoring

1. Question: What happens if we monitor every patient?
   Theorem 1: Under H_0,
   $$P(B(t) \geq z_{1-\alpha} | H_0) = 2\alpha. \tag{13}$$
   Theorem 1 says if one does continuous monitoring (e.g., monitor after enrolling each patient), then the type I error will be inflated to 2α.
2. Theorem 2: Under H_a,
   $$P(B(t) \geq c|\theta) = \Phi(\theta - c) + \exp{(2\theta c)}\Phi(-\theta - c), \quad \text{where} \tag{14}$$
   $\Phi(\cdot)$ is the cumulative probability of standard normal. Note that continuous monitoring is approximated by B_t continuous time Brownian motion.

Continuous Monitoring Example

- Assume that $N = 4$, then by Theorem 1,

$$P(B_{\frac{1}{4}} \geq 1.96 \text{ or } B_{\frac{2}{4}} \geq 1.96 \text{ or } B_{\frac{3}{4}} \geq 1.96 \text{ or } B_{\frac{4}{4}} \geq 1.96) = 2 * 0.025.$$

  Also, noted that $Z_t = B_t/\sqrt{t}$, the above corresponds to

$$P\left(Z_{\frac{1}{4}} \geq 1.96/\sqrt{\frac{1}{4}} \text{ or } Z_{\frac{2}{4}} \geq 1.96/\sqrt{\frac{2}{4}} \text{ or } Z_{\frac{3}{4}} \geq 1.96/\sqrt{\frac{3}{4}} \text{ or } Z_{\frac{4}{4}} \geq 1.96/\sqrt{\frac{4}{4}}\right) = 2 * 0.025.$$

- This implies that the B critical value boundaries are always the same, comparing to the decreasing Z critical value boundaries.

α-spending function

- A spending function is a function $\alpha * (t), t \in [0,1]$ which is non-decreasing satisfying $\alpha^*(0) = 0$ and $\alpha^*(1) = \alpha$.
- O'Brien-Fleming boundary (very conservative boundary):

$$\alpha^*(t) = 2\left(1 - \Phi\left(\frac{z_{1-\alpha/2}}{\sqrt{t}}\right)\right).$$

- Pocock boundary (anti-conservative boundary):

$$\alpha^*(t) = \alpha \log\left(1 + (e-1)t\right).$$

Of note, the Pocock α-spending function is an **approximate** of the real Pocock boundary, when sample size is small, the boundaries have little difference. The idea of Pocock boundary assumes equal Z value at each interim look.

α-spending function O'Brien-Fleming boundary example

- Suppose there are 1000 patients and we monitor after enrolling each 250 patients. So there are 4 looks in total. Also, pre-define $\alpha = 0.025$. Also, suppose we use O'Brien-Fleming boundary: $\alpha^*(t) = 2\left(1 - \Phi\left(\frac{z_{1-\alpha/2}}{\sqrt{t}}\right)\right)$.
- After 1st look, the total spent type I error is $\alpha(t = \frac{250}{1000}) = 2\left(1 - \Phi\left(\frac{2.24}{\sqrt{1/4}}\right)\right) = 7.464 * 10^{-6}$.
- The critical B value b_1 is determined as $P(B_{1/4} \geq b_1) = 7.464 * 10^{-6}$, where $B_{1/4} \sim N(0, 1/4)$, so $b_1 = 2.165$. (Use the fact $B_t \sim N(\theta t, t)$). Under the H_0, $\theta = 0$, so $B_{1/4} \sim N(0, \frac{1}{4})$. R code: qnorm(7.464* 10^{-6}, mean = 0, sd = 1/2, lower.tail = FALSE)). For the critical Z value determination in the 1st look, note that $P(B_{1/4} \geq b_1) = P(\sqrt{\frac{250}{1000}} Z_{250} \geq b_1) = P(Z_{250} \geq 2b_1)$. So $z_1 = 2b_1 = 2 * 2.165 = 4.33$.
- After 2nd look, the total spent type I error is $\alpha(t = \frac{500}{1000}) = 2\left(1 - \Phi\left(\frac{2.24}{\sqrt{2/4}}\right)\right) = 1.536 * 10^{-3}$. So the type I error spent between 1st and 2nd interim look is $1.536 * 10^{-3} - 7.464 * 10^{-6} = 1.528 * 10^{-3}$.
- The critical B value b_2 for the 2nd look is determined such that $P(B_{1/4} < b_1$ and $B_{1/2} > b_2) = 1.528 * 10^{-3}$. Note that from previous step, $b_1 = 2.165$. so the critical Z value is $z_2 = \sqrt{2} b_2 = 2.09 = 2.96$.
- Continue this procedure, for the 3rd look, $\alpha^*(t = 3/4) = 2 * (1 - \Phi(2.24/\sqrt{3/4})) = 0.009695$, $P(B_{3/4} \geq b_3) = 0.009695$, where $B_{3/4} \sim N(0, 3/4)$, so $b_3 = 2.02$. The critical Z value is $z_3 = \sqrt{\frac{4}{3}} b_3 = 2.33$.
- For the final look, $\alpha(1) = 2(1 - \Phi(2.24/\sqrt{4/4})) = 0.025$. $P(B_{4/4} \geq b_4) = 0.025$, where $B_{4/4} \sim N(0, 4/4)$, so $b_4 = 1.96$. $z_4 = z_4 \sqrt{1000/1000} = 1.96$.

Futility

We use B values to do the analysis.

- Note that $B_t = \sqrt{t}Z_t \sim N(\theta t, t)$. Let $\hat{\theta} = \frac{B_t}{t}$ (current trend), it follows that $\hat{\theta} \sim (\theta, \frac{1}{t})$. Let $U_t = B_1 - B_t$, then $U_t \sim N(\theta(1-t), 1-t)$.
- Notation: t is the information fraction at the interim inspection, θ_I denotes the drift parameter for the distribution of data up to time t, θ_F denotes the drift parameter for the distribution of data after time t (unobserved).
- $\boldsymbol{E}[B_1|B_t, \theta_F] = \boldsymbol{E}[B_t + B_1 - B_t|B_t, \theta_F] = B_t + \theta_F(1-t) = t\hat{\theta} + \theta_F(1-t)$; $\boldsymbol{Var}(B_1|B_t, \theta_F) = \boldsymbol{Var}(B_t + B_1 - B_t|B_t, \theta_F) = 0 + 1 - t = 1 - t$.
- So $B_1|B_t, \theta_F \sim N(t\hat{\theta} + \theta_F(1-t), 1-t)$.
- The conditional power at time t is

$$
\begin{aligned}
CP(t, \theta_F) &= P(B_1 \geq z_{1-\alpha}|\theta_F, B_t) \\
&= P\left(\frac{B_1 - t\hat{\theta} - \theta_F(1-t)}{\sqrt{1-t}} \geq \frac{z_{1-\alpha} - t\hat{\theta} - \theta_F(1-t)}{\sqrt{1-t}}\right) \\
&= P\left(Z \geq \frac{z_{1-\alpha} - t\hat{\theta} - \theta_F(1-t)}{\sqrt{1-t}}\right) \\
&= \Phi\left(\frac{t\hat{\theta} + \theta_F(1-t) - z_{1-\alpha}}{\sqrt{1-t}}\right).
\end{aligned}
$$

Futility (Contd.)

- Denote the conditional power random variable $Z_{CP}(t,\theta_F) = \frac{t\hat{\theta}+\theta_F(1-t)-z_{1-\alpha}}{\sqrt{1-t}}$. Note that the randomness of $Z_{CP}(t,\theta_F)$ is a random variable comes from $\hat{\theta}$.
- The expectation of $Z_{CP}(t,\theta_F)$ is $\boldsymbol{E}[Z_{CP}(t,\theta_F)] = \boldsymbol{E}\left[\frac{t\hat{\theta}+\theta_F(1-t)-z_{1-\alpha}}{\sqrt{1-t}}\right] = \frac{t\theta_I+\theta_F(1-t)-z_{1-\alpha}}{\sqrt{1-t}}$.
- The variance is $\boldsymbol{Var}[Z_{CP}(t,\theta_F)] = \boldsymbol{Var}\left(\frac{t\hat{\theta}+\theta_F(1-t)-z_{1-\alpha}}{\sqrt{1-t}}\right) = \boldsymbol{Var}\left(\frac{B_t}{\sqrt{1-t}}\right) = \frac{t}{1-t}$.
- Thus, the distribution of conditional power random variable $Z_{CP}(t,\theta_F)$ is

$$Z_{CP}(t,\theta_F) \sim N\left(\frac{t\theta_I+\theta_F(1-t)-z_{1-\alpha}}{\sqrt{1-t}}, \frac{t}{1-t}\right). \tag{15}$$

Probability of Stopping (due to Futility)

- Suppose at time t, we stop for futility (due to low conditional power): $CP(t, \theta_F) \leq c_L$. So the probability of stopping is

$$
\begin{aligned}
P_L &= P(CP(t,\theta_F) \leq c_L) \\
&= P\left(Z_{CP}(t,\theta_F) \leq \Phi^{-1}(c_L)\right) \\
&= P\left(Z_{CP}(t,\theta_F) \leq z_L\right) \\
&= P\left(\frac{Z_{CP}(t,\theta_F) - \boldsymbol{E}[Z_{CP}(t,\theta_F)]}{\sqrt{\boldsymbol{Var}(Z_{CP}(t,\theta_F))}} \leq \frac{z_L - \boldsymbol{E}[Z_{CP}(t,\theta_F)]}{\sqrt{\boldsymbol{Var}(Z_{CP}(t,\theta_F))}}\right) \\
&= P\left(Z \leq \frac{z_L - \frac{t\theta_I + \theta_F(1-t) - z_{1-\alpha}}{\sqrt{1-t}}}{\sqrt{\frac{t}{1-t}}}\right) \qquad \text{by (15)} \\
&= \Phi\left(\frac{b_L - \theta_I t}{\sqrt{t}}\right), \quad \text{where} \quad b_L = z_L\sqrt{1-t} - \theta_F(1-t) + z_{1-\alpha}.
\end{aligned}
$$

- b_L, a function of c_L through $z_L = \Phi^{-1}(c_L)$, is the early stopping boundary based on B value,
- Case 1. If there's no effect, $\theta_F = 0$, then $b_L = z_L\sqrt{1-t} + z_{1-\alpha}$.
- Case 2. For hypothetical trend, $\theta_F = z_{1-\alpha} + z_{1-\beta}$, then $b_L = z_L\sqrt{1-t} - (z_{1-\alpha} + z_{1-\beta})(1-t) + z_{1-\alpha}$.
- Case 3. For current trend, $\theta_F = \hat{\theta} = B_t/t$, then $b_L = z_L\sqrt{1-t} - B_t\frac{1-t}{t} + z_{1-\alpha}$.

Error Probabilities: Type II Error One-Sided

A type II error is committed if under the alternative hypothesis H_a, we stop for futility. Type II Error One-Sided Version:

$$
\begin{aligned}
\beta &= P(\text{Type II error}) = P(B_1 < z_{1-\alpha} | H_a) \\
&= P(\text{Stop for futility at t and fail to reject } H_0 \text{ at final} | H_a) \\
&\quad + P(\text{Do not stop for futility at t and fail to reject } H_0 \text{ at final} | H_a) \\
&= P(B_t < b_L \cap B_1 < z_{1-\alpha} | H_a) + P\left(B_t > b_L \cap B_1 < z_{1-\alpha} | H_a\right) \\
&= P(B_t < b_l \cap B_1 < z_{1-\alpha} | H_a) + P\left((B_t > b_L | \theta_I) \cap (B_1 - B_t < z_{1-\alpha} - B_t | \theta_F)\right) \\
&= P(B_t < b_L | H_a) + P\left((B_t > b_L | \theta_I) \cap (U_t < z_{1-\alpha} - B_t | \theta_F)\right) \\
&= \Phi\left(\frac{b_L - \theta_I t}{\sqrt{t}}\right) + P\left((B_t > b_L | \theta_I)\right) P\left((U_t < z_{1-\alpha} - B_t | \theta_F)\right) \quad \text{As } B_t \text{ and } U_t \text{ are indep} \\
&= \Phi\left(\frac{b_L - \theta_I t}{\sqrt{t}}\right) + \int_{b_L}^{\infty} f(b, \theta_I) \int_{-\infty}^{z_{1-\alpha}-b} g(u, \theta_F) db du, \quad \text{where}
\end{aligned}
$$

$f(b, \theta_I) \stackrel{d}{=} N(\theta_T t, t)$ and $g(u, \theta_F) \stackrel{d}{=} N(\theta_F(1-t), 1-t)$.

Error Probabilities: Type II Error: Two-Sided

- Two-sided version:

$$\beta = \Phi\left(\frac{b_L - \theta_I t}{\sqrt{t}}\right) + \int_{b_L}^{\infty} f(b,\theta_I) \int_{-z_{1-\alpha/2}-b}^{z_{1-\alpha/2}-b} g(u,\theta_F) dbdu, \quad \text{where}$$

$f(b,\theta_I) \overset{d}{=} N(\theta_T t, t)$ and $g(u,\theta_F) \overset{d}{=} N(\theta_F(1-t), 1-t)$.

- Now do variable changes, let $x = \frac{u-\theta_F(1-t)}{\sqrt{1-t}}$ and $y = \frac{b-\theta_I t}{\sqrt{t}}$. So,

$$\begin{aligned}
\beta &= \Phi\left(\frac{b_L - \theta_I t}{\sqrt{t}}\right) + \int_{\frac{b_L-\theta_I t}{\sqrt{t}}}^{\infty} \phi(y) \int_{\frac{-z_{1-\alpha/2}-b-\theta_F(1-t)}{\sqrt{1-t}}}^{\frac{z_{1-\alpha/2}-b-\theta_F(1-t)}{\sqrt{1-t}}} \phi(x) dxdy \\
&= \Phi\left(\frac{b_L - \theta_I t}{\sqrt{t}}\right) + \\
&\quad \int_{\frac{b_L-\theta_I t}{\sqrt{t}}}^{\infty} \phi(y) \left[\Phi\left(\frac{z_{1-\alpha/2} - b - \theta_F(1-t)}{\sqrt{1-t}}\right) - \Phi\left(\frac{-z_{1-\alpha/2} - b - \theta_F(1-t)}{\sqrt{1-t}}\right)\right] dy,
\end{aligned}$$

where $\phi(\cdot)$ is the standard normal pdf.

Error Probabilities: Type I Error Two-Sided

Type I error is calculated as follows.

$$
\begin{aligned}
P(\text{Type I error}) &= P(B_1 > z_{1-\alpha/2} \text{ or } B_1 < -z_{1-\alpha/2} | H_0) \\
&= P(\text{Stop for futility at t and reject } H_0 \text{ at final} | H_0) \\
&\quad + P(\text{Do not stop for futility at t and reject } H_0 \text{ at final} | H_0) \\
&= 2P(B_t < b_L \cap B_1 > z_{1-\alpha/2} | H_0) + 2P\left(B_t > b_L \cap B_1 > z_{1-\alpha/2} | H_0\right) \\
&= 0 + 2P\left(B_t > b_L | B_1 - B_t > z_{1-\alpha/2} - B_t\right) \\
&= 2P\left(B_t > b_L | \theta_I = 0\right) P\left(U_t > z_{1-\alpha/2} - B_t | \theta_F = 0\right) \\
&= 2\int_{b_L}^{\infty} f(b,0) \int_{z_{1-\alpha/2}-b}^{\infty} g(u,0) dbdu \\
&= 2\int_{b_L/\sqrt{t}}^{\infty} \int_{\frac{z_{1-\alpha/2}-x\sqrt{t}}{\sqrt{1-t}}}^{\infty} \phi(y)\phi(x) dydx \\
&= 2\int_{b_L/\sqrt{t}}^{\infty} \left(1 - \Phi\left(\frac{z_{1-\alpha/2} - x\sqrt{t}}{\sqrt{1-t}}\right)\right) \phi(x) dx.
\end{aligned}
$$

Study Design through Error Probabilities

Question: Suppose fixed error rate, I want a final critical value z_F, under what z_F I can achieve $\alpha = 0.05$?

- Recall from type I error calculation:

$$P(\text{Type I error}) = 2\int_{b_L}^{\infty} f(b,0)\int_{z_F-b}^{\infty} g(u,0)dudb. \tag{16}$$

  To answer the question, we can iterate over values of z_F until $\alpha = 0.05$.

- We can even simultaneously find a stopping value b_L and a critical value z_F such that $\alpha = \alpha_D$ (α_D is designed α) and $\beta = \beta_{increase}\beta_D$, then we loop through (z_F, b_L): outside loop increase b_L until $\theta \geq \beta_{increase}\beta_D$, inside loop decrease z_F until $\alpha = \alpha_D$.

Backup Slides: Conditional Power Derivation

- The conditional power $CP(\theta)$ is defined as the probability of rejecting H_0 when H_a is true given an interim result.

$$
\begin{aligned}
CP(\theta) &= P(Z_N \geq z_{1-\alpha} | H_a, Z_n) \\
&= P\left(\sqrt{\frac{n}{N}} \frac{S_n}{\sqrt{n}\sigma} + \frac{S_N - S_n}{\sqrt{N}\sigma} \geq z_{1-\alpha} | H_a, Z_n\right) \\
&= P\left(\sqrt{\frac{N-n}{N}} \frac{S_N - S_n}{\sqrt{N-n}\sigma} \geq z_{1-\alpha} - \sqrt{\frac{n}{N}} Z_n | H_a, Z_n\right) \\
&= P\left(\frac{S_N - S_n - (N-n)\mu}{\sqrt{N-n}\sigma} \geq \sqrt{\frac{N}{N-n}}(z_{1-\alpha} - \sqrt{\frac{n}{N}} Z_n) - \frac{\sqrt{N-n}\mu}{\sigma} | H_a, Z_n\right) \\
&= P\left(Z \geq \frac{z_{1-\alpha} - \sqrt{\frac{n}{N}} Z_n}{\sqrt{\frac{N-n}{N}}} - \frac{\sqrt{N-n}\mu}{\sigma} | H_a, Z_n\right) \\
&= 1 - \Phi\left(\frac{z_{1-\alpha} - \sqrt{\frac{n}{N}} Z_n}{\sqrt{\frac{N-n}{N}}} - \frac{\sqrt{N-n}\mu}{\sigma}\right).
\end{aligned}
$$

End

End