

A conditional power approach to the evaluation of predictive power

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Outline

- Clinical trial interim analysis and Brownian motion
- Conditional power and predictive power for a fixed design
- CP and PP for a group sequential design
- The Bayesian prior distribution
- Unconditional power for a new study
- PP for small samples

What is information?

For the comparison of two means:

Information \approx number of patients.

(One patient provides one piece of information)

Incomplete measurements:

For the comparison of two survival distributions (logrank):

Information \approx number of events.

To simplify the discussion, we assume that complete measurements are available for all patients.

In the 1960's and 1970's, many NIH- sponsored clinical trials were designed as “fixed”, and during interim analyses, clinicians often asked the question:

If the current trend continues, what is the chance that we will have a positive study (Final $Z \geq 1.96$)?

How can we put this idea into a statistical framework and answer the question?

Distribution theory for a one-sample problem

Compare new treatment T with control treatment C.

Assume that there exists a large data base for C so the mean ν and variance σ^2 are known.

A new treatment patient's response Y can then be “standardized” by $X = (Y - \nu)/\sigma$.

$EX = \mu$ (>0 if new drug is beneficial), $\text{Var}(X)=1$.
To simplify our discussion, we further assume the distribution of X is normal.

Interim analyses of clinical trials (Brownian motion)

$X_1, X_2, \dots, X_n, X_{n+1}, \dots, X_N$ iid $N(\mu, 1)$.

($\mu > 0$ favors new treatment.)

$S_0 = 0; S_n = X_1 + X_2 + \dots + X_n, 1 \leq n \leq N$.

$\{S_n: 0 \leq n \leq N\}$ is a discrete Brownian motion.

- (i) $ES_n = \mu n; \text{var}[ES_n] = n$;
- (ii) $(S_{n1}, S_{n2}, \dots, S_{nk})$ is multivariate normal;
- (iii) Independent increments.

{Clinical trials: $Z(n) = S_n / \sqrt{n}; Z(N) = \text{final } Z.$ }

Design of a clinical trial

Test $H_0: \mu \leq 0$ versus $H_a: \mu > 0$ with one-sided $\alpha = 0.025$.

For a given $\mu > 0$ and desired power $= 1 - \beta$, solve for N from

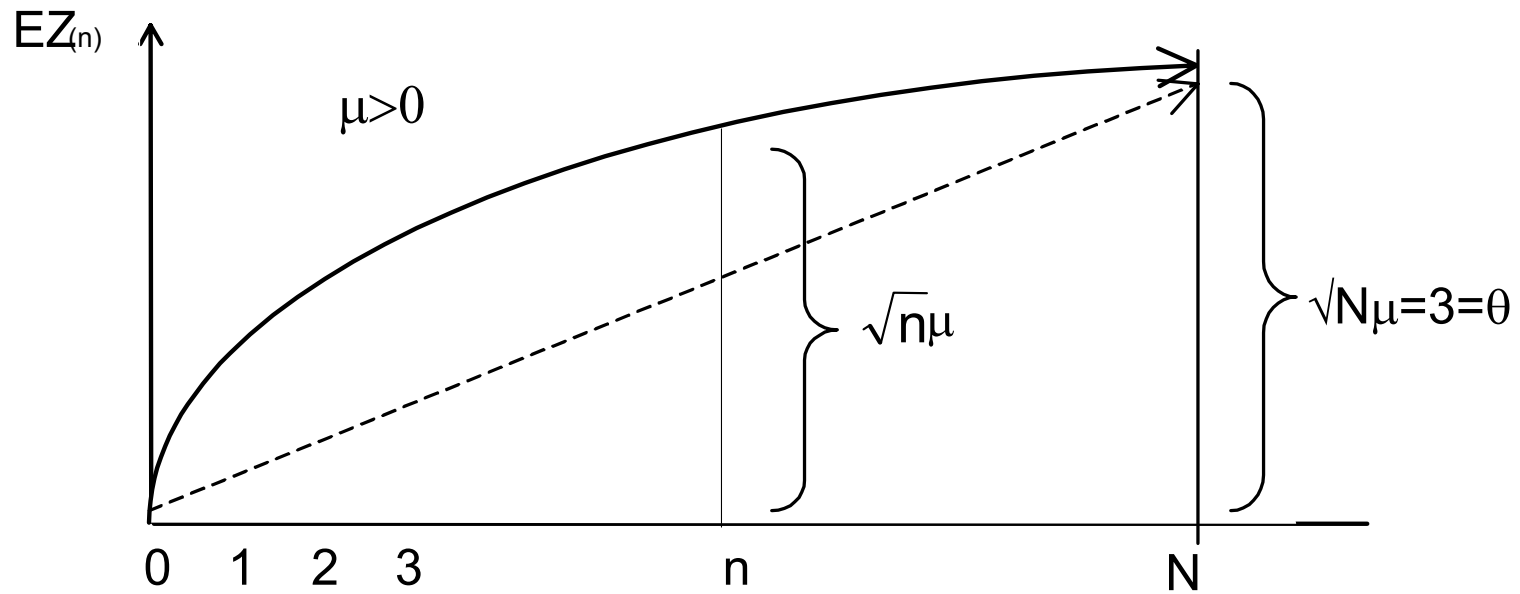
$$\theta = EZ(N) = \mu\sqrt{N} = z_\alpha + z_\beta = 1.96 + z_\beta.$$

$\theta = \mu\sqrt{N}$ is called the drift parameter.

Example: $\alpha = 0.025$; $\beta = 0.15$ (power $= 1 - \beta = 85\%$),

$$z_\alpha + z_\beta = 1.96 + 1.04 = 3.0 = \theta.$$

The trend of the data



$$(n, Z_{(n)}) \rightarrow (\tau, Z_\tau) \rightarrow (\tau, B_\tau) \quad \text{where } \tau = n/N \text{ \& } B_\tau = Z_\tau \sqrt{\tau}.$$

If we define $\tau = n/N$, $B_\tau = S_n / \sqrt{N}$ and use linear interpolation between n/N and $(n+1)/N$, then we have an approximate Brownian motion process:

- (i) $EB_\tau = \theta\tau$; $\text{var}[B_\tau] = \tau$;
- (ii) $(B_{\tau_1}, B_{\tau_2}, \dots, B_{\tau_k})$ is multivariate normal;
- (iii) Independent increments.

In a Brownian motion approach, rewrite $Z(n)$ as Z_τ ,

$$B_\tau = Z_\tau \sqrt{\tau}.$$

We use B-values in BM and Z-values in clinical trials.

$\theta = \mu\sqrt{N}$ in practice. (see next slide)

Decomposition of $Z_1=B_1$:

$$\begin{aligned} Z_1 = B_1 &= \frac{X_1 + \dots + X_n + X_{n+1} + \dots + X_N}{\sqrt{N}} \\ &= \frac{X_1 + \dots + X_n}{\sqrt{n}} \sqrt{\frac{n}{N}} + \frac{X_{n+1} + \dots + X_N}{\sqrt{N-n}} \sqrt{\frac{N-n}{N}} \\ &= B_\tau + (B_1 - B_\tau) \end{aligned}$$

During interim look at time τ , B_τ is observed (fixed),
 $B_1 - B_\tau$ is random.

$$Z_1 = B_1 = B_\tau + (B_1 - B_\tau)$$

Unconditionally,

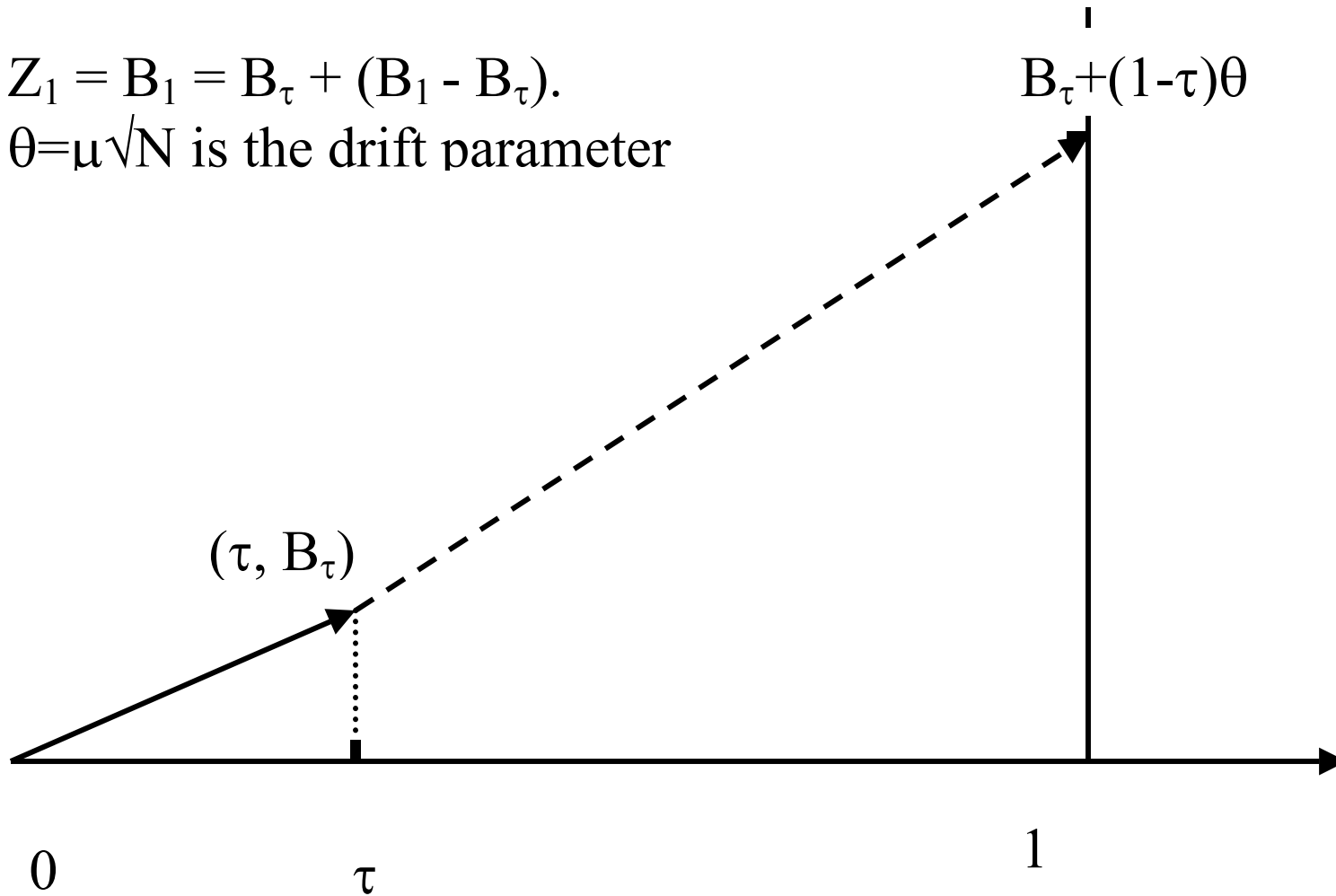
$$EZ_1 = \theta = \tau\theta + (1-\tau)\theta;$$

$$\text{Var}(Z_1) = 1 = \tau + (1-\tau).$$

Conditionally (after B_τ has been observed), the conditional mean and variance of $Z_1 = B_1$ are:

$$E_C Z_1 = B_\tau + (1-\tau)\theta; \text{Var}_C[Z_1] = 1-\tau.$$

$Z_1 = B_1 = B_\tau + (B_1 - B_\tau).$
 $\theta = \mu\sqrt{N}$ is the drift parameter



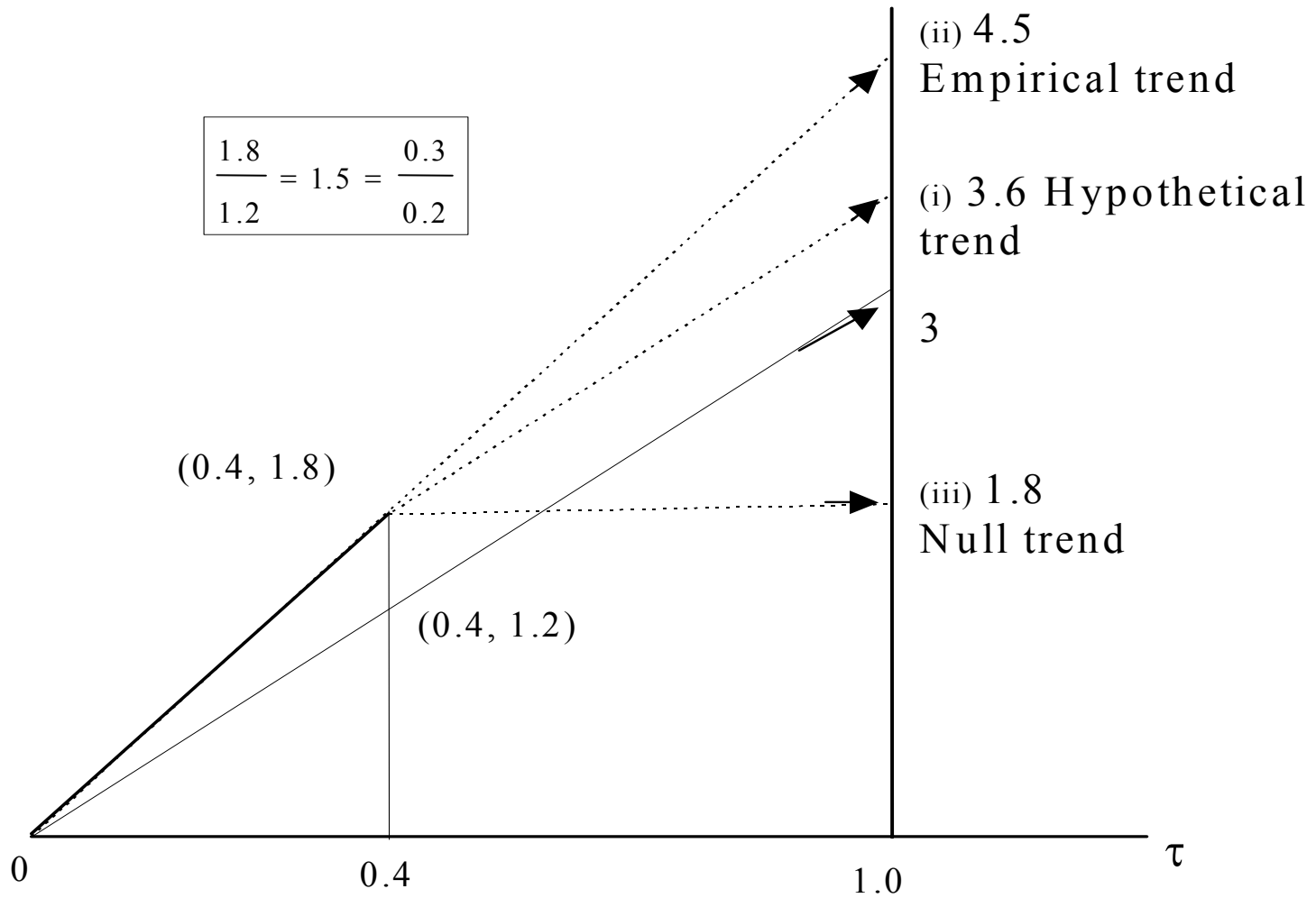
Example

$$\mu = 0.2, \theta = \sqrt{N}\mu = 3 \Rightarrow N = 225.$$

When $n = 90$, $\tau = 90/225 = 0.4$; $Z_{.4} = 2.846$.

$$CP(\theta) = P(Z_1 \geq 1.96 | Z_{.4} = 2.846, \theta) = ?$$

$$B_{0.4} = 2.846 \sqrt{0.4} = 1.8.$$



$$\begin{aligned}
\text{(i)} \quad & P[Z_1 = B_1 \geq 1.96 | B_{.4} = 1.8, \theta = 3] \\
& = P\left[\frac{Z_1 - 3.6}{\sqrt{.6}} \geq \frac{1.96 - 3.6}{\sqrt{.6}} \mid B_{.4} = 1.8, \theta = 3\right] \\
& = P[N(0,1) \geq -2.12] \\
& = 0.9830 \\
\text{(ii)} \quad & P[Z_1 \geq 1.96 | B_{.4} = 1.8, \theta = 4.5] \\
& = P\left[\frac{B_1 - 4.5}{\sqrt{.6}} \geq \frac{1.96 - 4.5}{\sqrt{.6}} \mid B_{.4} = 1.8, \theta = 4.5\right] \\
& = P[N(0,1) \geq -3.28] \\
& = .9995 \\
\text{(iii)} \quad & P[B_1 \geq 1.96 | B_{.4} = 1.8, \theta = 0] \\
& = P\left[N(0,1) \geq \frac{1.96 - 1.8}{\sqrt{.6}}\right] \\
& = P[N(0,1) \geq 0.21] \\
& = 0.4168
\end{aligned}$$

Quick review: Conditional power depends on τ , B_τ and the drift parameter θ .

$$CP(\tau, B_\tau, \theta) = \Phi\left[\frac{B_\tau + (1-\tau)\theta - 1.96}{\sqrt{1-\tau}}\right] \quad (\text{Eq 1})$$

- (i) It is easy to evaluate.
- (ii) It communicates easily to clinicians.

It seems to be natural to take $\theta = \theta_E = B_\tau/\tau$. Under this empirical drift,

$$CP(\tau, B_\tau, \theta_E) = \Phi\left[\frac{B_\tau/\tau - 1.96}{\sqrt{1-\tau}}\right] \quad (\text{Eq 2})$$

However, $\theta_E = B_\tau/\tau$ is only a point estimate of θ .

Conditional power

$\tau=0.4, Z_\tau=1.6.$

-2.0 SD	0.0433
-1.5 SD	0.1353
-1.0 SD	0.3124
-0.5 SD	0.5491
Empirical	0.7690
+0.5 SD	0.9112
+1.0 SD	0.9750
+1.5 SD	0.9950
+2.0 SD	0.9993

How can we choose another fixed drift, say θ_M , to replace θ_E to evaluate the chance of a positive study through CP?

- (i) θ_M depends on θ_E ; and
- (ii) θ_M depends on the “accuracy” of θ_E as a point estimate of θ .

Do we expect $\theta_M \geq \theta_E$ or $\theta_M \leq \theta_E$?

Predictive power (considers θ as random)

Note that $\theta_E = B_\tau/\tau$ is a point estimate of θ . If we consider θ as random with distribution function G

$$\begin{aligned} \text{PP} &= \text{PP}[\tau, B_\tau, G(\theta)] = \int \text{CP}(\tau, B_\tau, \theta) dG(\theta) \\ &= \int \text{CP}(\tau, B_\tau, \theta) g(\theta) d\theta \end{aligned}$$

(Note that we did not introduce a prior distribution and went directly to the posterior distribution of θ .)

Choice of G (for a fixed n)

Since \bar{X}_n is $N(\mu, 1/n)$,

let us consider μ to be $N(\bar{X}_n, 1/n)$.

This is equivalent to $\theta \sim N(\theta_E, 1/\tau)$.

Conceptually, this is similar to calling

$[\bar{X}_n \mp 1.96\sqrt{1/n}]$ a 95% c.i. for μ .

Avoid introducing PP as an integral to the clinicians

If G is taken to be $N(\theta_E, 1/\tau)$, then

$$PP(\tau, B_\tau, G) = \Phi\left[\frac{(\theta_E - 1.96)\sqrt{\tau}}{\sqrt{1-\tau}}\right].$$

Compare this expression with

$$CP(\tau, B_\tau, \theta_E) = \Phi\left[\frac{\theta_E - 1.96}{\sqrt{1-\tau}}\right].$$

Reference: *Statistical Monitoring of Clinical Trials:*

A unified approach (2006 Springer) By Proschan, Lan & Wittes, pages 60-61. Also, see slide 32.

$$PP(\tau, B_\tau, G) = \Phi\left[\frac{(\theta_E - 1.96)\sqrt{\tau}}{\sqrt{1-\tau}}\right]$$

If we modify the empirical drift θ_E to

$$\theta_M = \frac{(1-\sqrt{\tau})(B_\tau + 1.96\sqrt{\tau})}{(1-\tau)\sqrt{\tau}}, \text{ then}$$

$$CP(\tau, B_\tau, \theta_M) = PP.$$

$$PP(\tau, B_\tau, G) = \Phi\left[\frac{(\theta_E - 1.96)\sqrt{\tau}}{\sqrt{1-\tau}}\right]$$

$$CP(\tau, B_\tau, \theta_E) = \Phi\left[\frac{\theta_E - 1.96}{\sqrt{1-\tau}}\right].$$

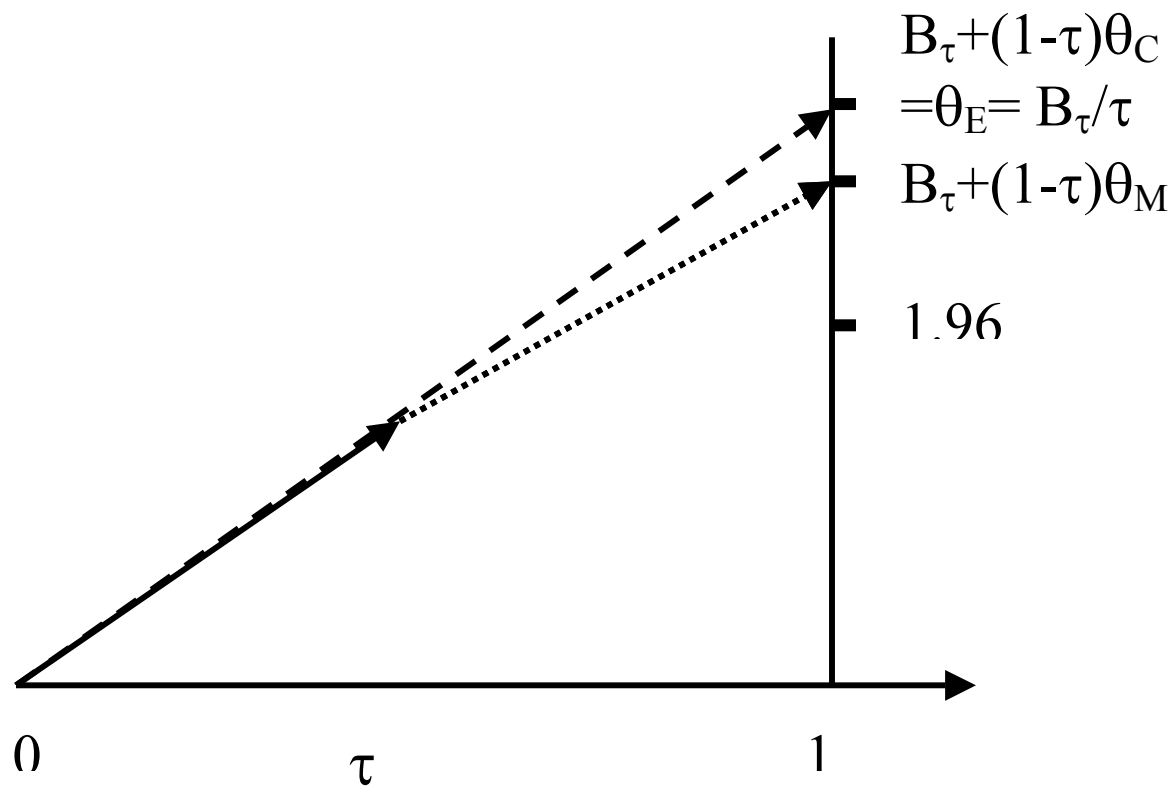
When $\theta_E = 1.96$, $CP = PP = 50\%$;

When $\theta_E > 1.96$, $CP > PP > 50\%$;

When $\theta_E < 1.96$, $CP < PP < 50\%$.

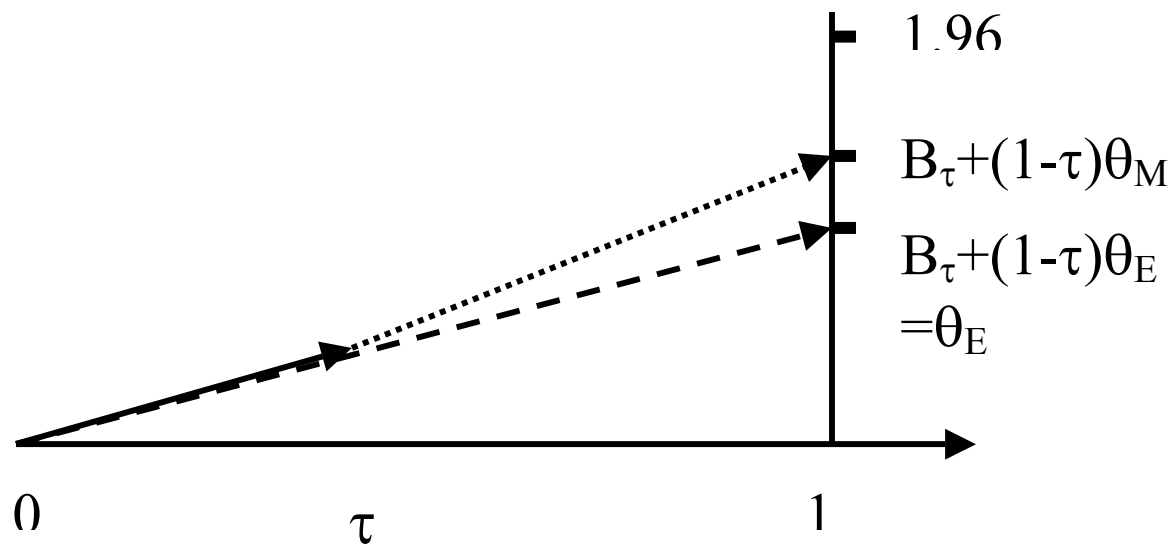
When $\theta_E > 1.96$, $CP > PP > 50\%$.

There is a drift $\theta_M < \theta_E$ so that $CP(\tau, B_\tau, \theta_M) = PP$.



When $\theta_E < 1.96$, $CP < PP < 50\%$.

There is a drift $\theta_M > \theta_E$ so that $CP(\tau, B_\tau, \theta_M) = PP$.



Quick summary:

Under the empirical trend $\theta_E = B_\tau / \tau$:

If $CP > 50\%$, $CP > PP > 50\%$.

If $CP < 50\%$, $CP < PP < 50\%$.

$B_\tau + (1 - \tau)\theta_M$ is somewhere between 1.96 and θ_E .

The critical value 1.96 may be replaced by any other critical value.

Group sequential design

Example: Spending function = 0.25τ , $0 \leq \tau \leq 1$.

τ	Z-boundary	B-boundary	Observed B
0.3	2.4324	1.3323	1.0
0.6	2.3358	1.8093	1.63
1.0	2.1768	2.1768	?

$$CP = \Phi\left[\frac{B_\tau / \tau - 2.1768}{\sqrt{1-\tau}}\right] = 80\%; PP = 74\%.$$

Another look at 0.8? (No simple answer. One-step PP is an approximately correct answer.)

Early termination of clinical trials:

For benefit: Use group sequential methods

For futility: Use CP or PP.

Note that: If $CP < 50\%$, $CP < PP < 50\%$.

The use of PP to predict final outcome is more “optimistic” than the use of CP.

Example: Design a study with one-sided $\alpha=0.025$, power=85% and $\mu = 0.2$. $N=225$.

After 45 measurements, sample mean=0.

CP = 1.4%, PP=16.4%.

$\tau =$	0.2	0.3	0.4	0.5	0.6	0.7	0.8
CP	.014	.010	.006	.003	.001	.000	.000
PP	.164	.100	.055	.025	.008	.000	.000

Example: Design a study with one-sided $\alpha=0.025$, power=85% and $\mu = 0.2$. $N=225$.

Sample mean = 30% of 0.2 = 0.06.

$\tau =$	0.2	0.3	0.4	0.5	0.6	0.7	0.8
CP	.118	.110	.086	.067	.047	.026	.009
PP	.298	.270	.193	.145	.097	.053	.017

(Mechanism of the new compound)

What is the prior distribution of μ so that after observing \bar{X}_n , the posterior is $\mu \sim \text{N}(\bar{X}_n, 1/n)$?

Consider a family of priors $F(\Omega) = N(0, \Omega)$ for μ .

Given μ, X_1, X_2, \dots are iid $N(\mu, 1)$.

That is, $X = \mu + N(0, 1)$.

It can be shown that the posterior distribution of μ given \bar{X}_n

is normal with mean $(\frac{\Omega}{\Omega+1/n})\bar{X}_n$ and variance $(\frac{\Omega}{\Omega+1/n})\frac{1}{n}$.

Under this posterior distribution,

$B_1 - B_\tau \sim N[(1-\tau)\theta_E + o(\Omega), (1-\tau)/\tau + o(\Omega)]$ and as $\Omega \rightarrow \infty$,

$$P[Z_1 = B_1 \geq 1.96] \rightarrow \Phi[(\theta_E - 1.96)\sqrt{\frac{\tau}{1-\tau}}].$$

What is the meaning of $\mu \sim F(\Omega) = N(0, \Omega)$ with very large Ω ?

For any fixed $K > 0$,

$$P[\mu > K] = P[\mu < -K] \rightarrow 0.5 \text{ as } \Omega \rightarrow \infty.$$

The prior belief of the new compound:

Either extremely beneficial or extremely harmful.

The prior is NOT reasonable, but the posterior is.

Evaluation of unconditional power

Pilot: sample size=10, sample mean =0.3, sample sd=1.

New study sample size=100. $[0.3\sqrt{100}=3]$

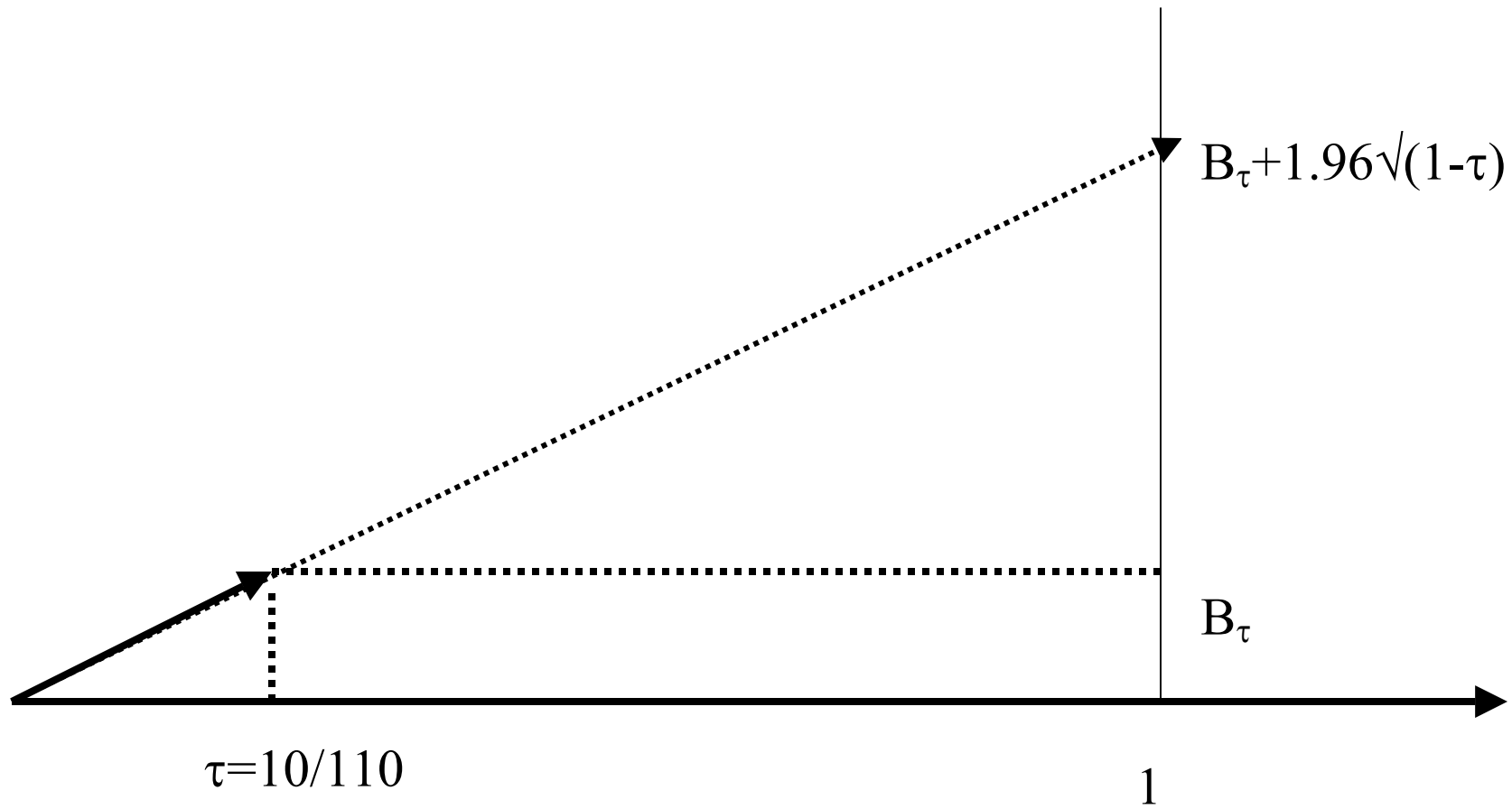
$$\tau = 10/110=0.0909$$

$$B_\tau = Z_\tau \sqrt{\tau} = 0.2860, \theta_E = 3.1643.$$

Critical value:

$$\frac{B_1 - B_\tau}{\sqrt{1-\tau}} \geq 1.96 \Leftrightarrow B_1 \geq 2.1548 = cv$$

$$CP = \Phi\left(\frac{3.1464 - 2.1548}{\sqrt{1-\tau}}\right) = 85\%, PP = \Phi\left(\frac{(3.1464 - 2.1548)\sqrt{\tau}}{\sqrt{1-\tau}}\right) \approx 62.3\%.$$



In general, for a traditional design with power $1-\beta$,

Unconditional power = CP = $1 - \beta = \Phi(z_\beta)$,

PP = $\Phi(z_\beta \sqrt{\tau})$.

Again, see page 61 of Proschan et al. (2006)

Other prior distributions

Assume $\mu \sim N(\mu_0, \Omega)$ for some fixed μ_0 .

It can be shown that the posterior distribution of μ given \bar{X}_n

is normal with mean $(\frac{1/n}{\Omega+1/n})\mu_0 + (\frac{\Omega}{\Omega+1/n})\bar{X}_n$ and variance $(\frac{\Omega}{\Omega+1/n})\frac{1}{n}$.

Note that $(\frac{1/n}{\Omega+1/n})\mu_0$ is $o(\Omega)$.

$B_1 - B_\tau \sim N[(1-\tau)\theta_E + o(\Omega), (1-\tau)/\tau + o(\Omega)]$ and as $\Omega \rightarrow \infty$,

$$P[Z_1 = B_1 \geq 1.96] \rightarrow \Phi[(\theta_E - 1.96)\sqrt{\frac{\tau}{1-\tau}}].$$

Small Samples

Sample size = N , take interim look after n observations.

Mike Proschan has derived a formula (as an integral) and an approximate formula (without integration) for PP. We found that the large sample formula for PP gives very good approximations when $N \geq 20$.

Prior and posterior distributions

DMC members

5 clinicians

1 biostatistician

1 medical ethicist

Prior: May not be the same for everyone

Accumulating information: May not be the same

Posterior: May not be the same.

May not use Bayes formula to derive the posterior (mechanism of the new treatment)