

General Two-Stage Adaptive Designs in Clinical Trials

Tatsuki Koyama

Department of Biostatistics

Vanderbilt University School of Medicine

Allan R. Sampson and Leon J. Gleser

Department of Statistics

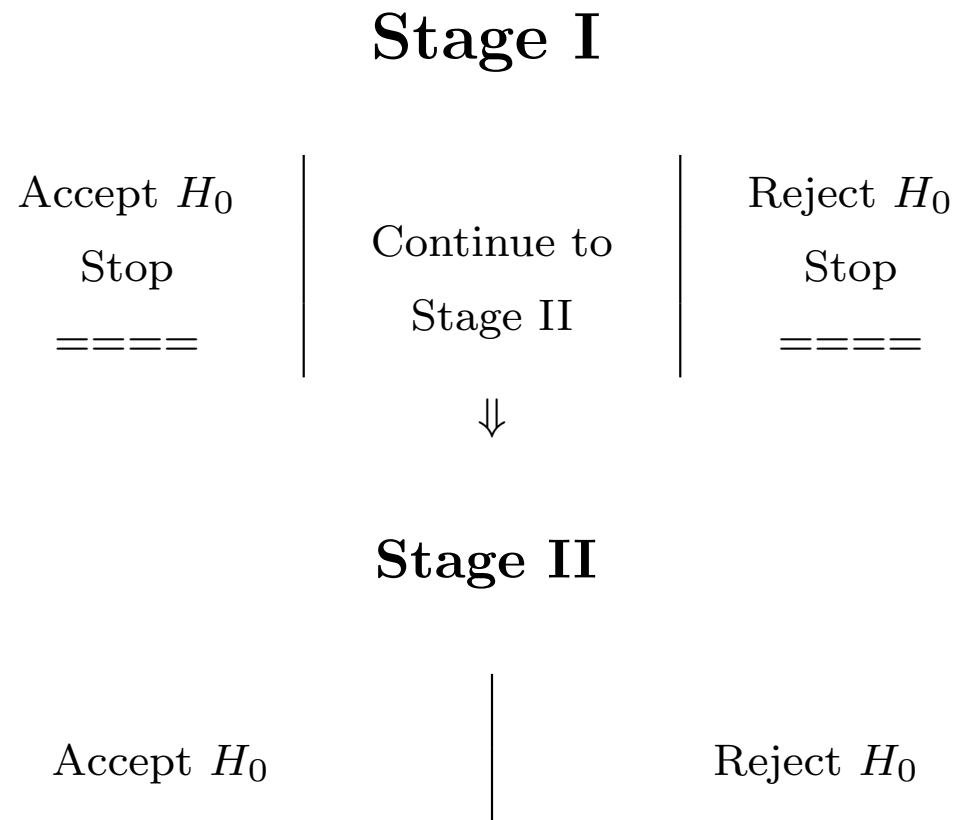
University of Pittsburgh

2/23/2005

General Two-Stage Adaptive Designs Outline

1. Nontechnical Introduction
2. Framework
3. Conditional and Unconditional Characteristics
4. p -value

Flowchart of a Two-Stage Adaptive Design



**Two-Stage Adaptive Designs, Two-Stage
Group Sequential Designs, Internal Pilot
Studies, Simon's Two-Stage Design and its
Extensions, Phase II/III Combined
Accelerated Trials, Meta Analysis,
Acceptance Sampling**

Tatsuki Koyama

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Introduction

Why two-stage (adaptive) design?

- reduce sample size
- expedite decision making
- update the design with new information

Two-Stage (Adaptive) Procedures -prespecified-

- The design of Stage II depends on **unblinded** Stage I data.
 - Stage II sample size and critical value are prespecified as functions of Stage I data.
 - Other modifications are possible.
- All the actions to be taken at the end of Stage I are determined prior to Stage I.

Two-Stage **Adaptive** Procedures -unspecified-

- The design of Stage II depends on **unblinded** Stage I data.
 - Stage II design (sample size, critical value, etc.) is determined after Stage I.

Prespecified or Unspecified?

- Type I error rate can be controlled with either approach.
- “Unspecified” gives more flexibility.
- “Prespecified” controls type II error rate (power).
- “Prespecified” allows computing expected sample size.
- “Prespecified” allows computing a p -value.

Framework - Stage I

Hypotheses to be tested

$$H_0 : \mu \leq 0$$

$$H_1 : \mu > 0$$

Data

$$X \sim \text{Normal}(\mu, 1)$$

Stage I

- Sample size : n_1
- Test Statistic : $Z_1 = \bar{X}_1 \sqrt{n_1} \sim \text{Normal}(\zeta, 1)$,
where $\zeta = \mu \sqrt{n_1}$.

Stop for futility if $Z_1 < k_1$.

Stop for efficacy if $Z_1 > k_2$.

Framework - Stage II

Stage II

- Sample size, $n_2(z_1)$
- Test Statistic : $Z_2 = \bar{X}_2 \sqrt{n_2(z_1)}$

Conditioned on $Z_1 = z_1$, $Z_2 \sim Normal\left(\mu \sqrt{n_2(z_1)}, 1\right)$

Combining Stage I and II data :

$$\bar{X}_c = (\bar{X}_1 n_1 + \bar{X}_2 n_2(z_1)) / (n_1 + n_2(z_1))$$

$$Z_c = \bar{X}_c \sqrt{n_1 + n_2(z_1)}$$

IF X_1 and X_2 are completely independent (i.e., not in a two-stage design), then $Z_c \sim Normal(\mu \sqrt{n_1 + n_2}, 1)$.

Stage II - continued-

Conditioned on $Z_1 = z_1$,

$$Z_c \sim \text{Normal} \left(\frac{n_1 \bar{x}_1}{\sqrt{n_1 + n_2(z_1)}} + \frac{n_2(z_1)\mu}{\sqrt{n_1 + n_2(z_1)}}, \frac{n_2(z_1)}{n_1 + n_2(z_1)} \right).$$

We let $r(z_1) = n_1/(n_1 + n_2(z_1))$ and write

$$Z_c \sim \text{Normal} \left(z_1 \sqrt{r(z_1)} + \zeta \frac{1 - r(z_1)}{\sqrt{r(z_1)}}, 1 - r(z_1) \right).$$

Conditional Power Functions

Decision rule :

Reject H_0 at the end of Stage II if $Z_c > c(z_1)$

Like $n_2(z_1)$, the critical value, $c(z_1)$, is also a function of z_1 .

$P[\text{Reject in Stage II} \mid Z_1 = z_1] = P[Z_c > c(z_1) \mid Z_1 = z_1]$.

Because we know the conditional distribution of Z_c given $Z_1 = z_1$.

We can compute the [conditional power](#).

$$A(z_1, \zeta) = 1 - \Phi \left[\frac{1}{\sqrt{1 - r(z_1)}} c(z_1) - \frac{\sqrt{r(z_1)}}{\sqrt{1 - r(z_1)}} z_1 - \frac{\sqrt{1 - r(z_1)}}{\sqrt{r(z_1)}} \zeta \right].$$

Terminating in Stage I

Suppose we want to terminate the trial in Stage I for futility if $Z_1 < k_1$, for efficacy if $Z_1 > k_2$.

For all ζ , let

$$A(z_1, \zeta) = 0 \text{ for all } z_1 < k_1.$$

$$A(z_1, \zeta) = 1 \text{ for all } z_1 > k_2.$$

In these ranges of z_1 , the sample size and critical value for Stage II are not required.

Conditional Power Functions -continued-

Some special conditional powers -

Conditional type I error rate :

$$A(z_1, 0) = 1 - \Phi \left[\frac{1}{\sqrt{1 - r(z_1)}} c(z_1) - \frac{\sqrt{r(z_1)}}{\sqrt{1 - r(z_1)}} z_1 \right]$$

Conditional power under the trend of stage I :

$$A(z_1, z_1) = 1 - \Phi \left[\frac{1}{\sqrt{1 - r(z_1)}} c(z_1) - \frac{1}{\sqrt{r(z_1)(1 - r(z_1))}} z_1 \right]$$

Controlling Error Rates

To control **unconditional** type I error rate and **unconditional** power, we require

$$\alpha = \int_{-\infty}^{\infty} A(z_1, 0) f(z_1, 0) dz_1$$
$$1 - \beta = \int_{-\infty}^{\infty} A(z_1, \zeta_1) f(z_1, \zeta_1) dz_1$$

where $f(z_1, \zeta)$ is a pdf of $Normal(\zeta, 1)$.

Four-Fold Methodology

Given $n_2(z_1)$ and $c(z_1)$, we can compute $A(z_1, \zeta)$ for any ζ .

Moreover ...

Given $A(z_1, 0)$ and $n_2(z_1)$, we can compute $c(z_1)$ and $A(z_1, \zeta)$ for any ζ .

Or ...

Given two $A(z_1, \zeta)$ at distinct ζ 's, we can compute $n_2(z_1)$, $c(z_1)$ and $A(z_1, \zeta)$ for any ζ .

Four-Fold Methodology in Action

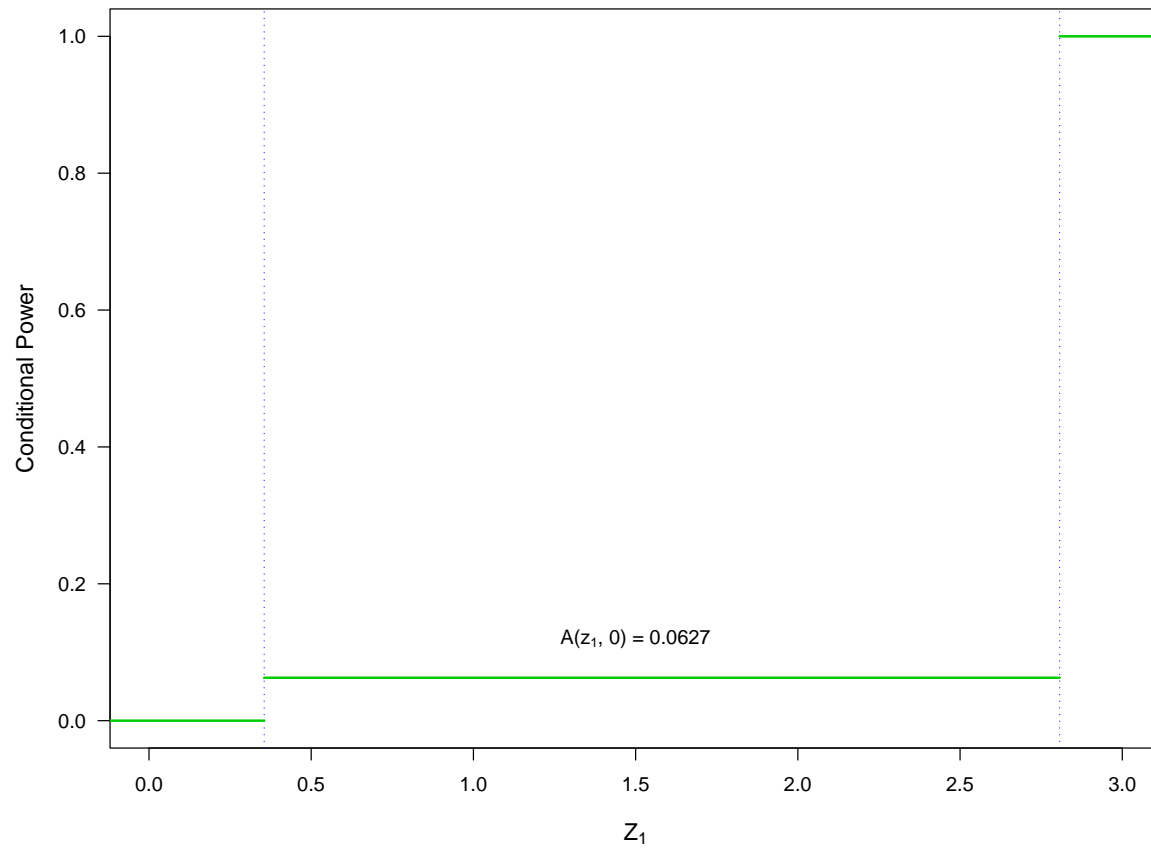
$$\mu_0 = 0, \mu_1 = 0.20, \sigma = 1$$

$$\alpha = 0.025, \beta = 0.20$$

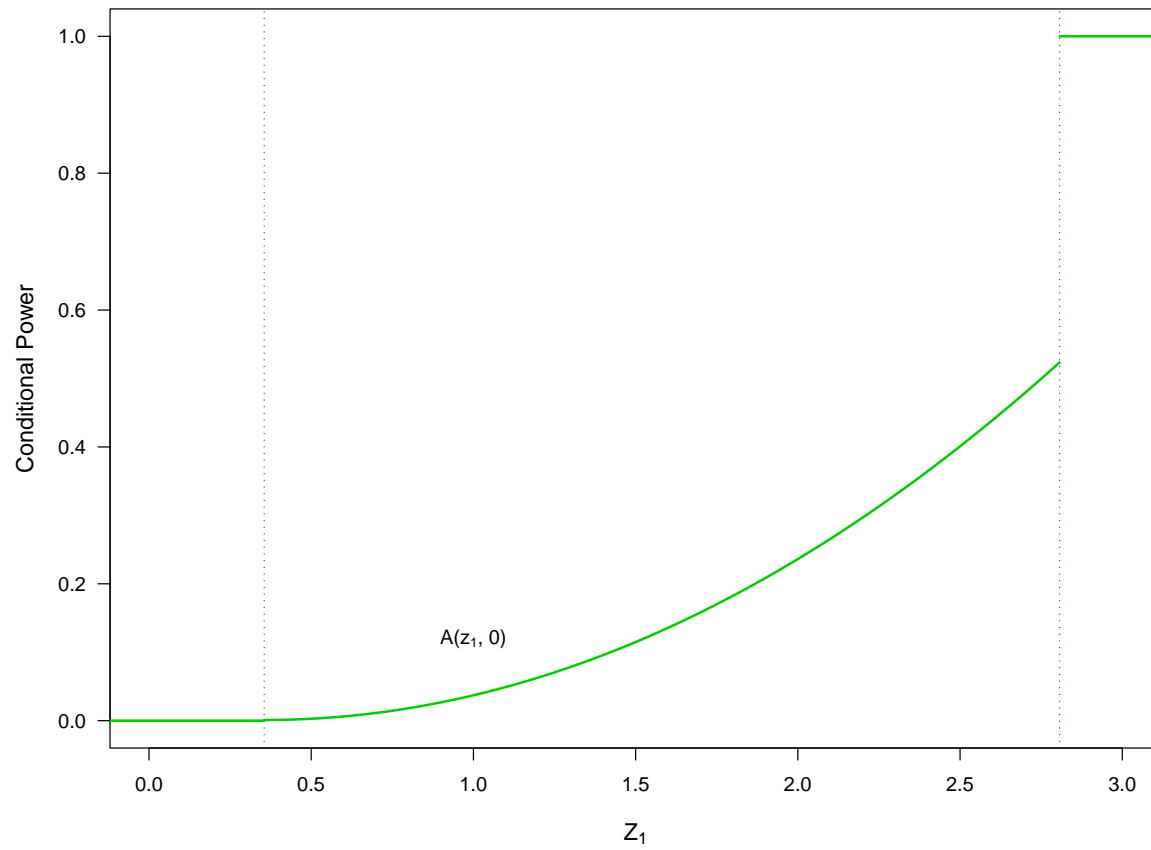
$$n_1 = 100 \quad k_1 = 0.355, k_2 = 0.2807.$$

$$\alpha_1 = 0.0025, \beta_1 = 0.05$$

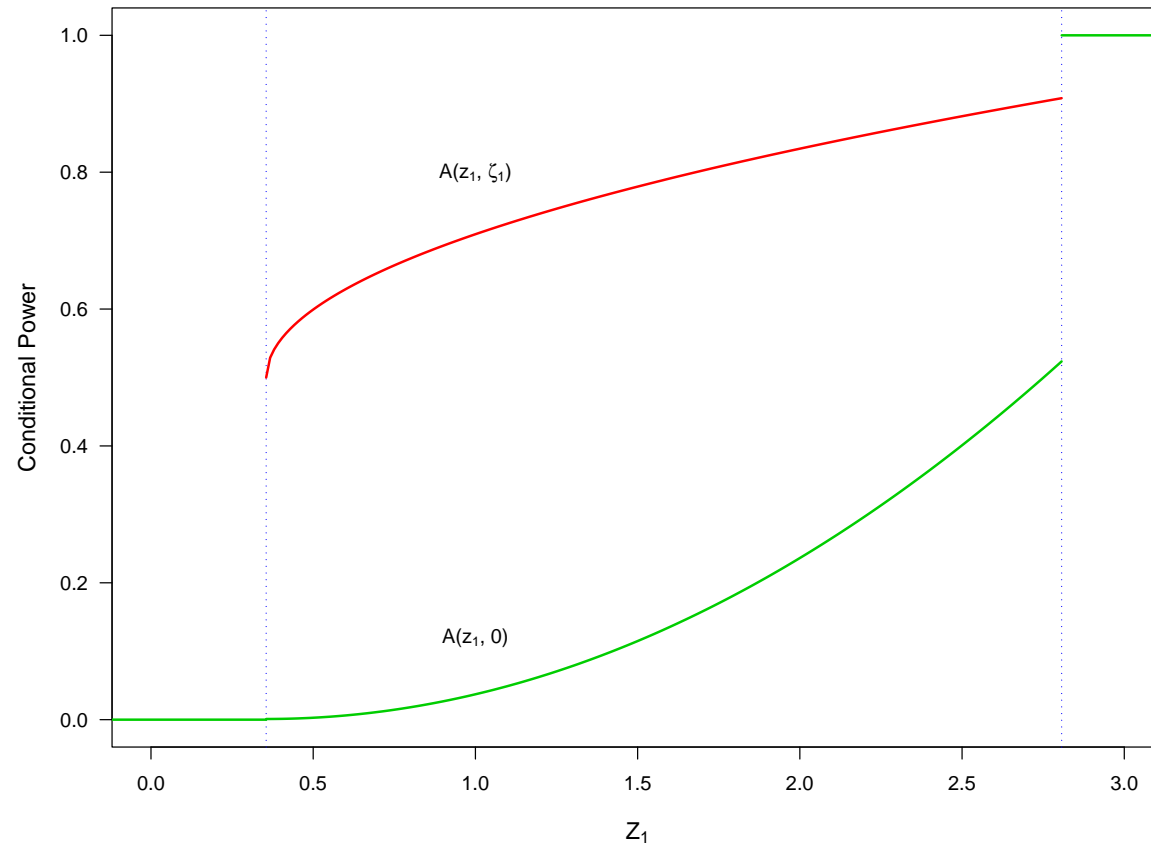
$$A(z_1, 0)$$



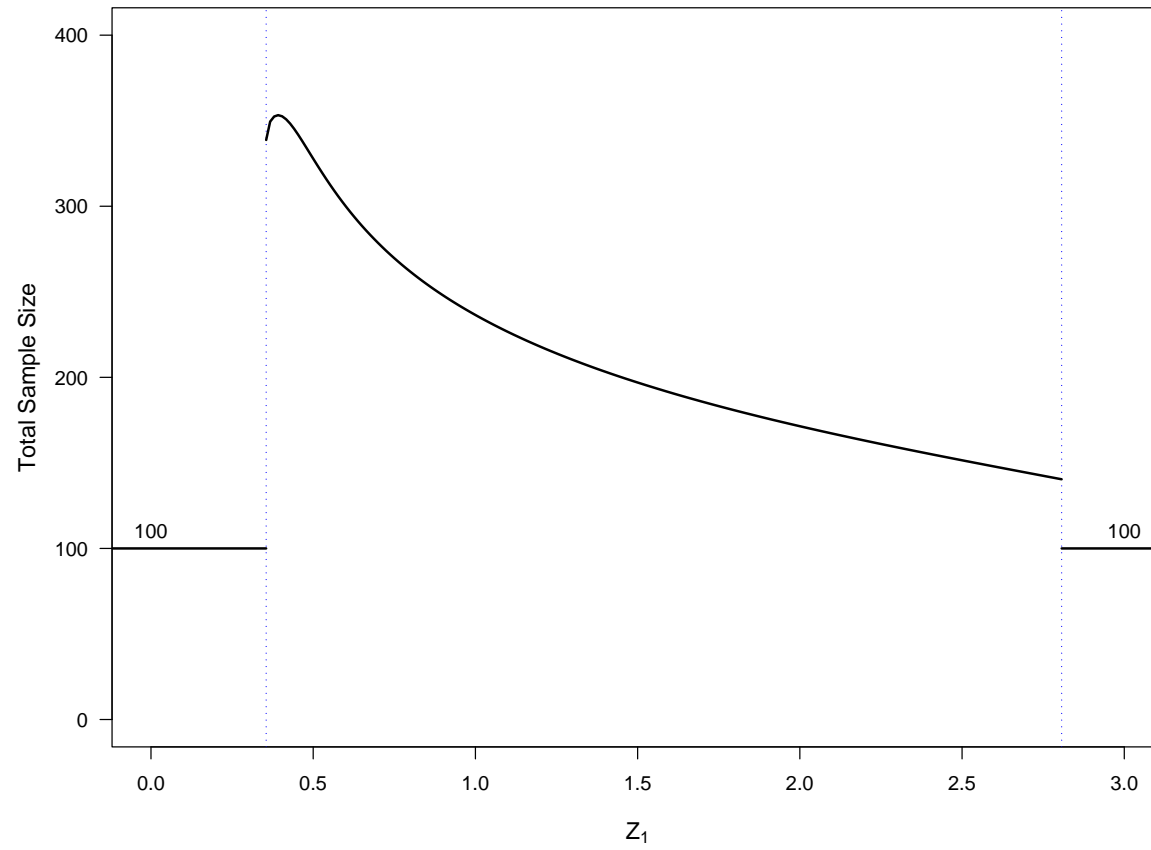
$$A(z_1, 0)$$



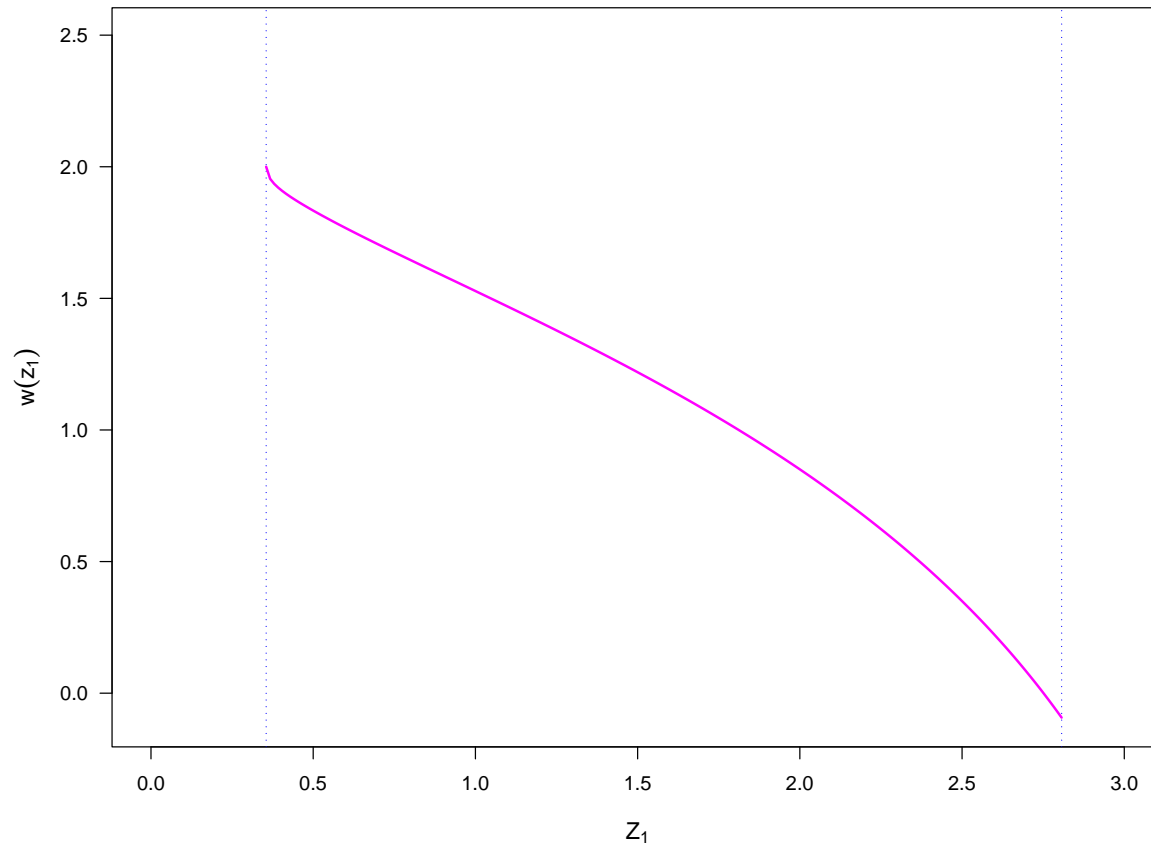
... and $A(z_1, \zeta_1)$



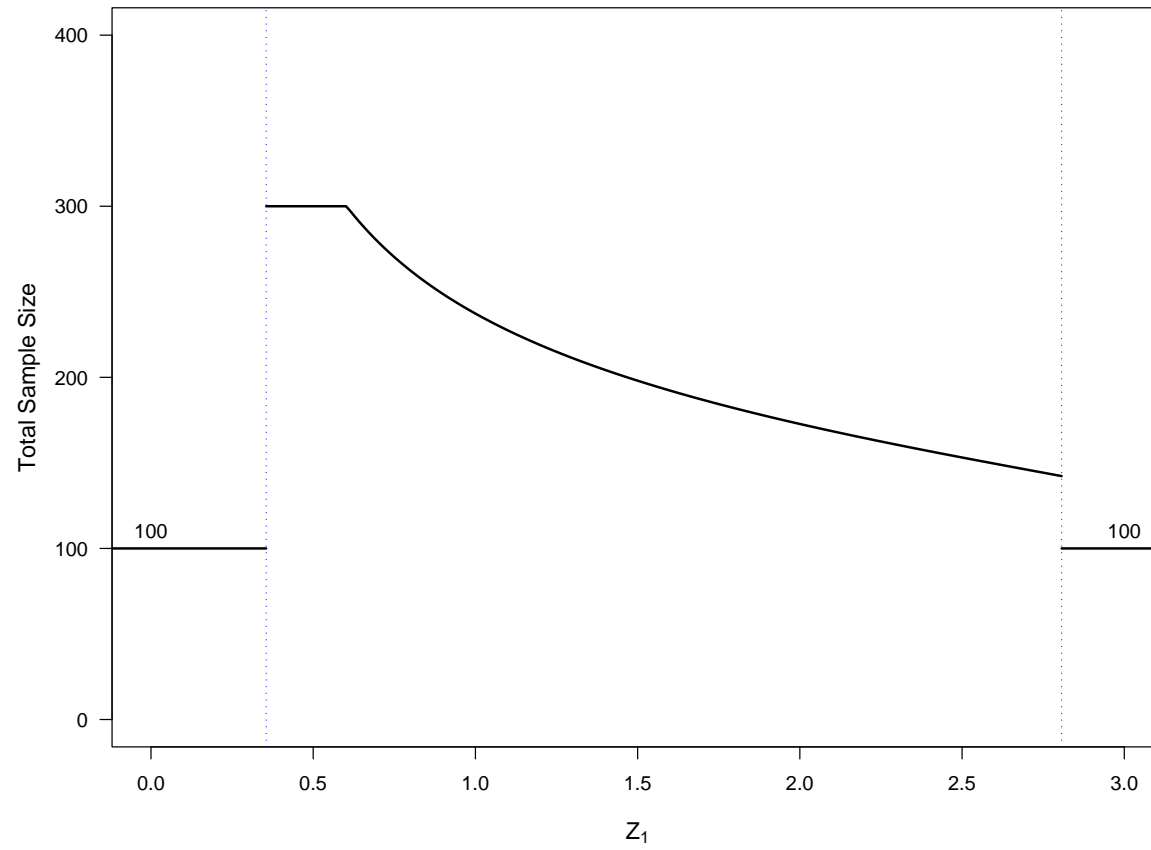
Sample Size



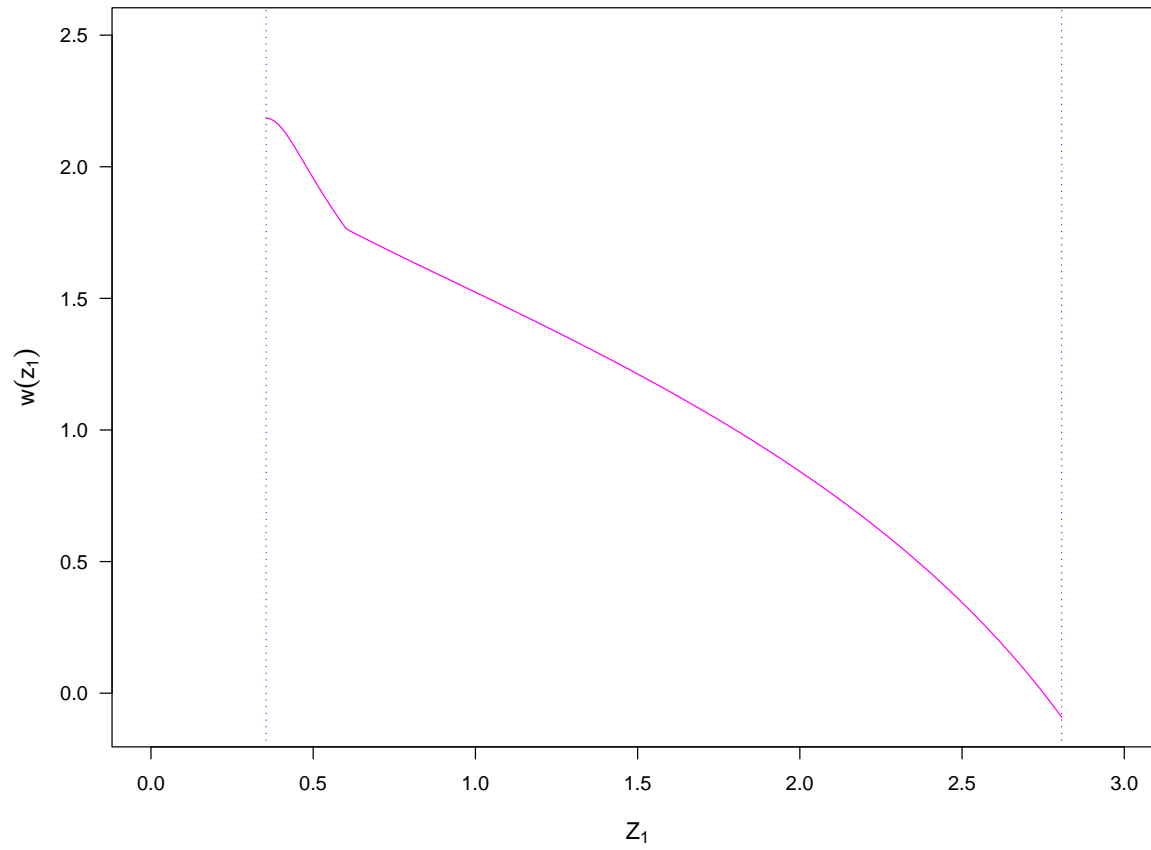
Critical Value



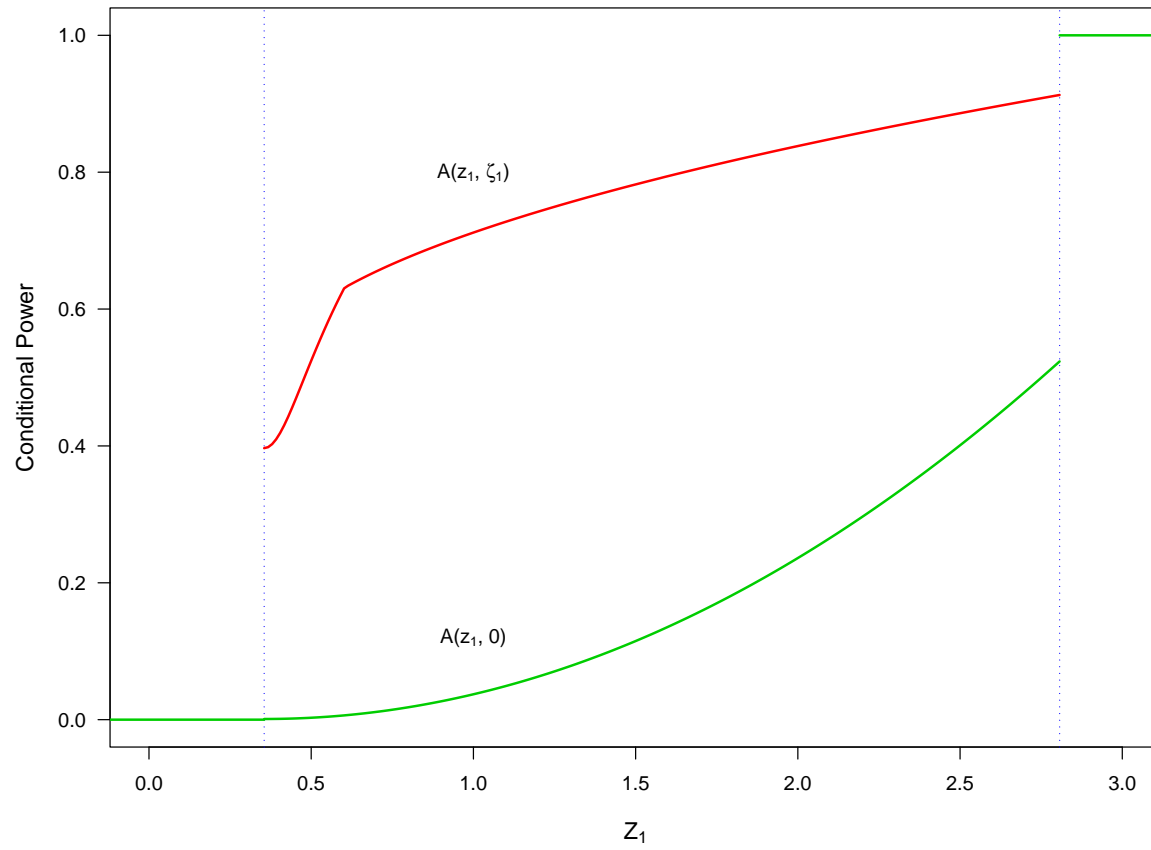
New Sample Size



New Critical Value



New $A(z_1, \zeta_1)$



Conditional and Unconditional Characteristics

There are two approaches to adaptive designs.

- Prespecified adaptive designs

The design of stage II is specified as functions of z_1 a priori.

- Unspecified adaptive designs

The design of stage II is determined after stage I.

Either way, the conditional type I error rate, $A(z_1, 0)$, **must** be prespecified.

Otherwise, type I error rate cannot be controlled.

Example : Simon's Design

$$H_0 : \pi = 0.4$$

$$H_1 : \pi = 0.6$$

$$\alpha = 0.10, \beta = 0.10$$

$n_1 = 18$.

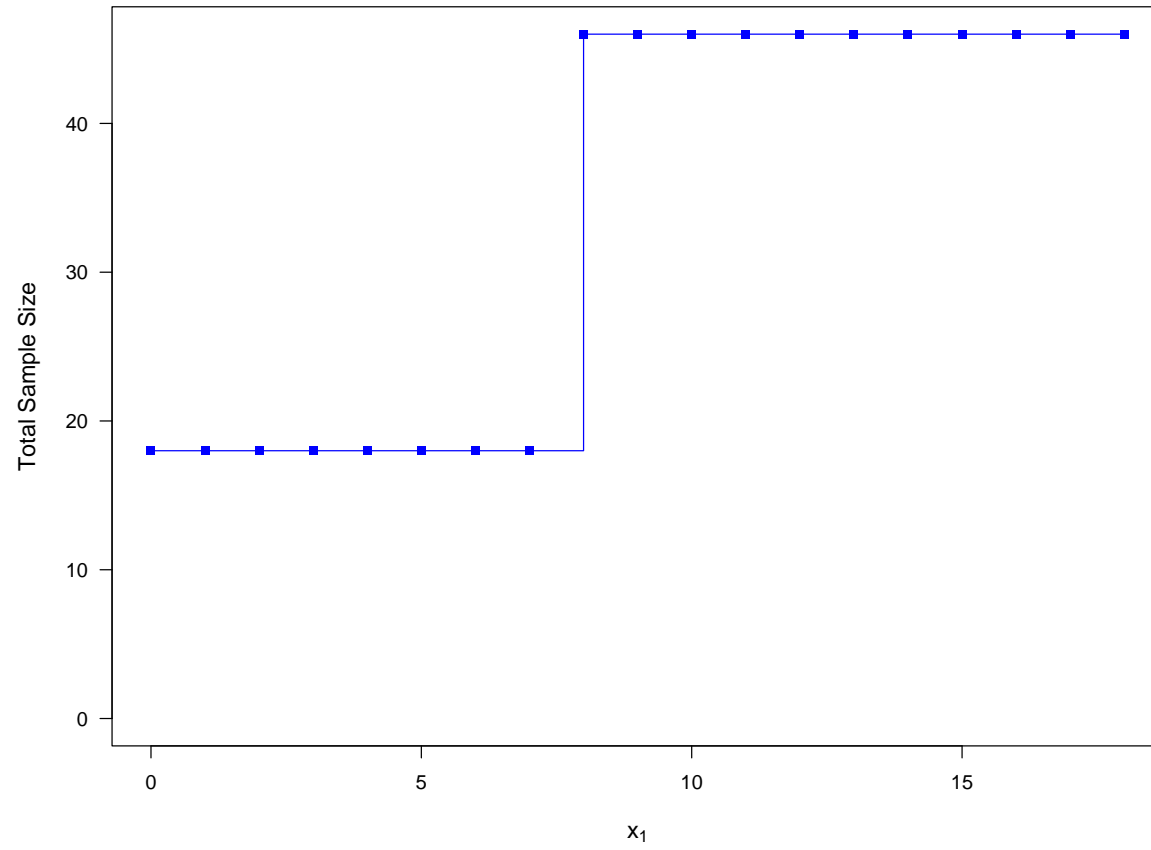
Accept H_0 (futility) in stage I if $x_1 \leq 7$.

Otherwise, take $n_2 = 28$ and accept H_0 in stage II if $x_1 + x_2 \leq 22$.

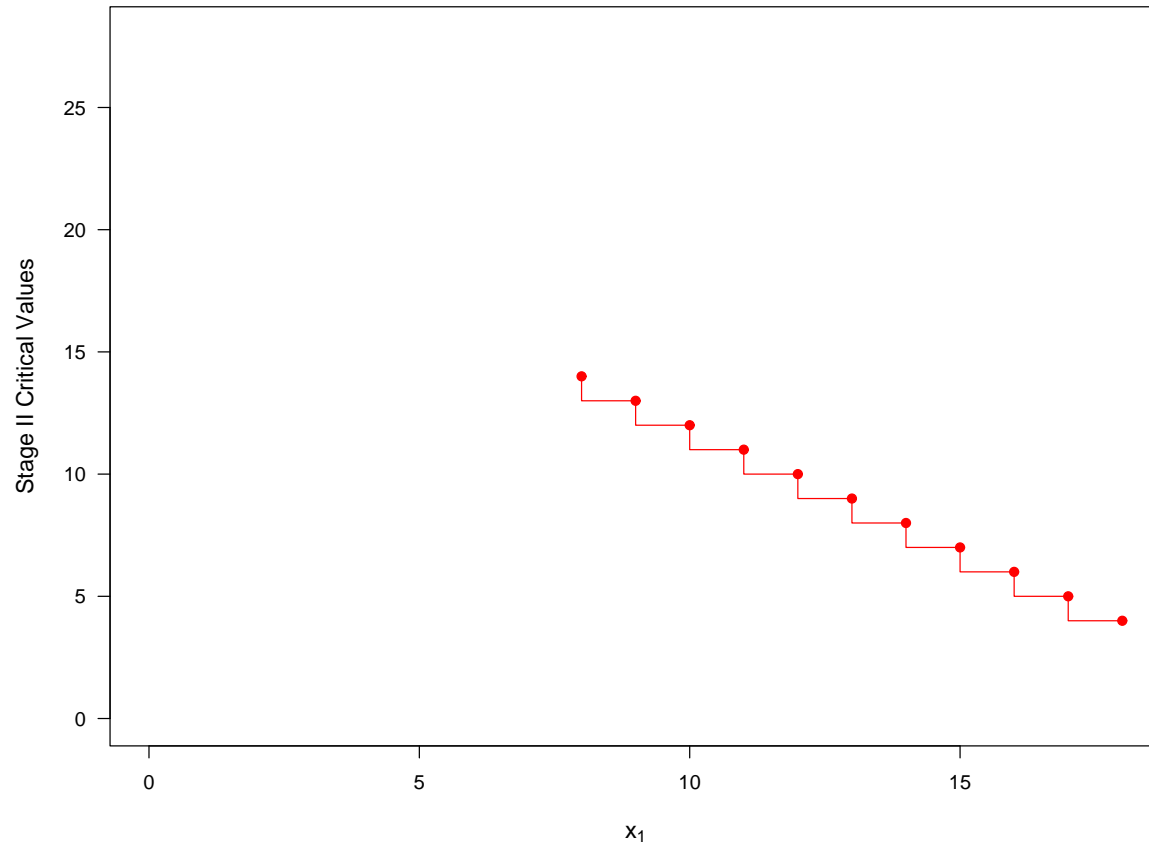
Actual type I error rate = 0.0952.

Actual type II error rate = 0.0996.

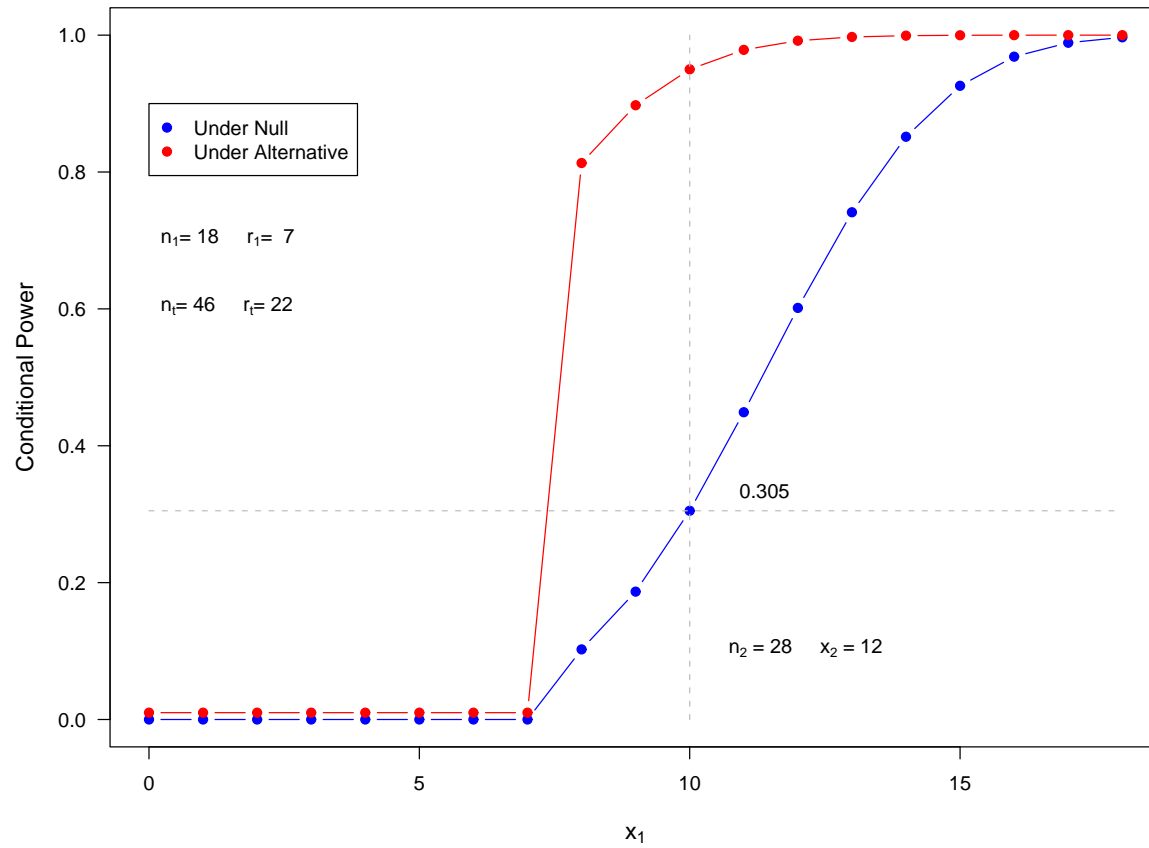
Sample Size



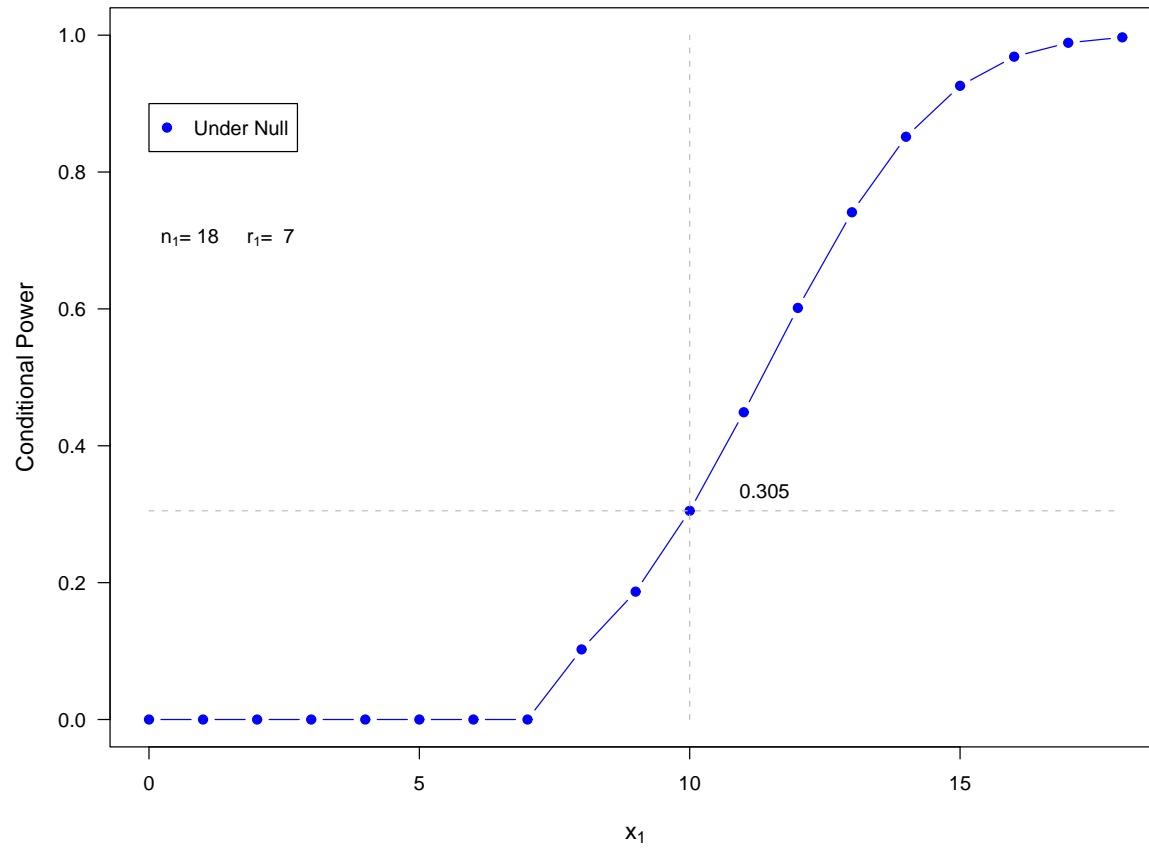
Stage II Critical Value



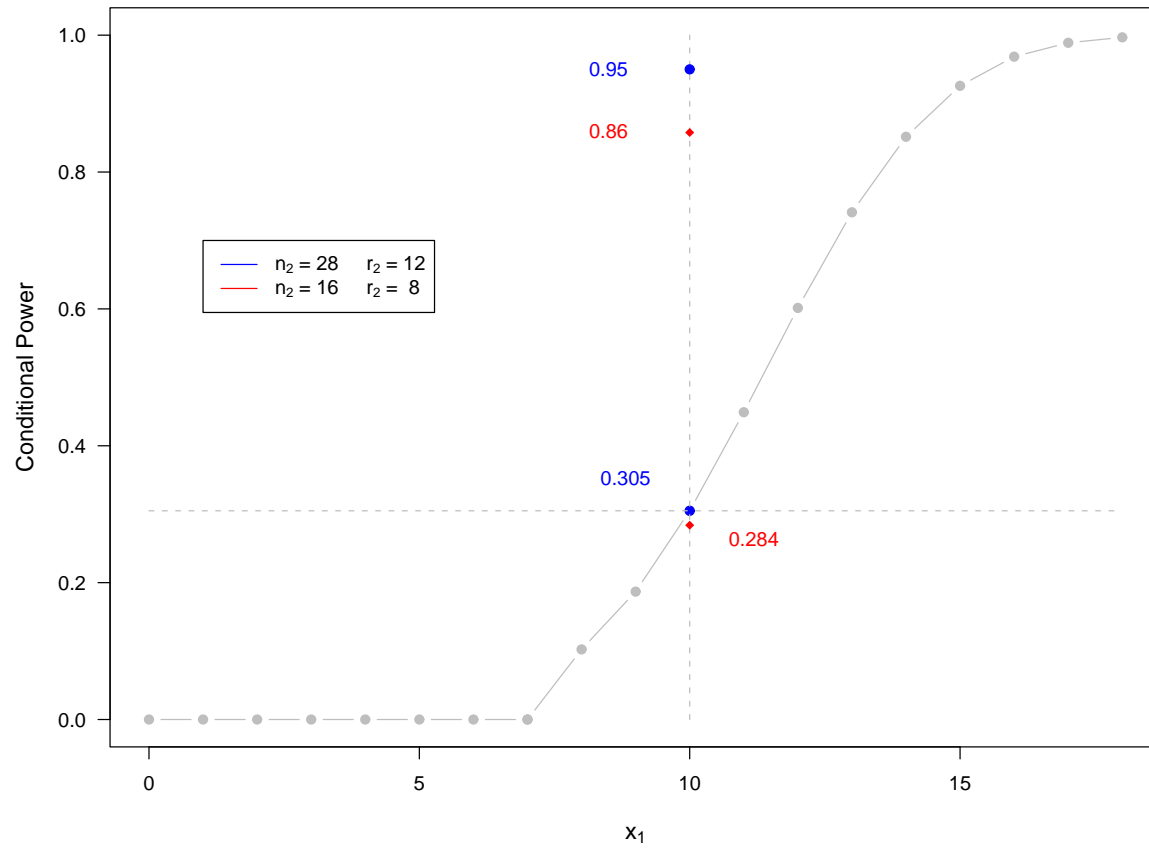
Conditional Powers



Conditional Type I Error Rate



Unspecified Procedure

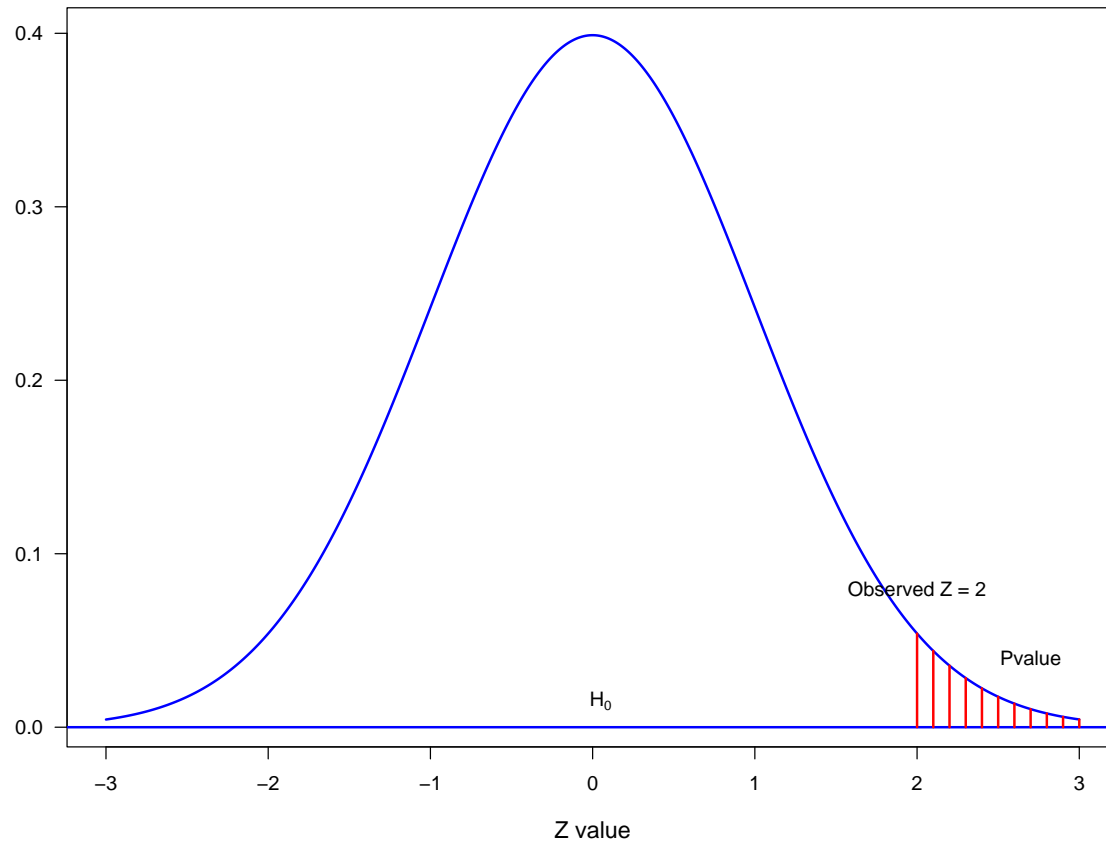


Inference Procedure (p -value)

p -value = The probability of getting a test statistic as extreme as or more extreme than the observed one, computed on the basis that the null hypothesis is true.

We need to be able to order the possible outcomes. (In a single stage procedure, $z^* \prec z^+$ if $z^* < z^+$.)

Very Simple in a Single Stage Design



Why So Complicated in a Two-Stage Design?

Let's try to order the following three sample paths. ($n_1 = 100$)

1. $Z_1 = 2.7$ and H_0 is rejected in stage I.
2. $Z_1 = 2.5$ and $n_2(z_1) = 200$, $Z_c = 2.8$ and H_0 is rejected.
3. $Z_1 = 2.4$ and $n_2(z_1) = 250$, $Z_c = 2.9$ and H_0 is not rejected.

Conditional p -value

Given that $k_1 < z_1 < k_2$

define the stage II conditional p -value as

$$p_2(z_1, z_c) = P[Z_c > z_c | Z_1 = z_1].$$

It can be shown that “reject H_0 if $Z_c > c(z_1)$ ” is equivalent to “reject H_0 if $p_2(z_1, z_2) < A(z_1, 0)$ evaluated at the observed z_1 .”

The size of $p_2(z_1, z_2)$ is judged with respect to $A(z_1, 0)$ evaluated at the observed z_1 .

Toward Unconditional p -value

Recall that

$$p_2(z_1, z_c) = P[Z_c > z_c | Z_1 = z_1].$$

$$A(z_1, \zeta) = P[Z_c > c(z_1) | Z_1 = z_1].$$

For a given $p_2(z_1, z_c)$ we can find ζ^* such that

$$p_2(z_1, z_c) = A(z_1, \zeta^*)$$

at the observed z_1 .

Interpretation :

$H_0 : \zeta \leq \zeta_0$ would have been rejected for ζ_0 that is smaller than ζ^* .

$$\zeta^* = r(z_1)(c(z_1) - z_c)$$

Ordering

Let $S = 1$ if stopped in stage I and $S = 2$ if continue to stage II.

Say $(S', z'_1, z'_c) \prec (S^*, z_1^*, z_c^*)$ if any of the following three conditions hold.

1. $S' = S^* = 1$ and $z'_1 < z_1^*$
2. $S' \neq S^*$ and $z'_1 < z_1^*$
3. $S' = S^* = 2$ and $\zeta' < \zeta^*$

where $\zeta' = r(z'_1)(c - z'_c)$ and $\zeta^* = r(z_1^*)(c - z_c^*)$.

For a sample path (S^*, z_1^*, z_c^*) , the unconditional p -value is

$$P[(S^*, z_1^*, z_c^*) \prec (S, Z_1, Z_c)]$$

***p* -value**

When $S^* = 1$,

$$p\text{-value} = \int_{z_1=z_1^*}^{\infty} f(z_1, 0) dz_1$$

When $S^* = 2$,

$$p\text{-value} = \int_{z_1=k_1}^{\infty} A(z_1, \zeta^*) f(z_1, 0) dz_1$$

“Reject H_0 ” is equivalent to “ $p\text{-value} < \alpha$.”

Illustrative Example

$$\mu_0 = 0, \mu_1 = 0.25, \sigma = 1$$

$$\alpha = 0.025, \beta = 0.10$$

$N = 168$ (Sample size for a conventional single-stage design)

Maximum sample size allowed is 240.

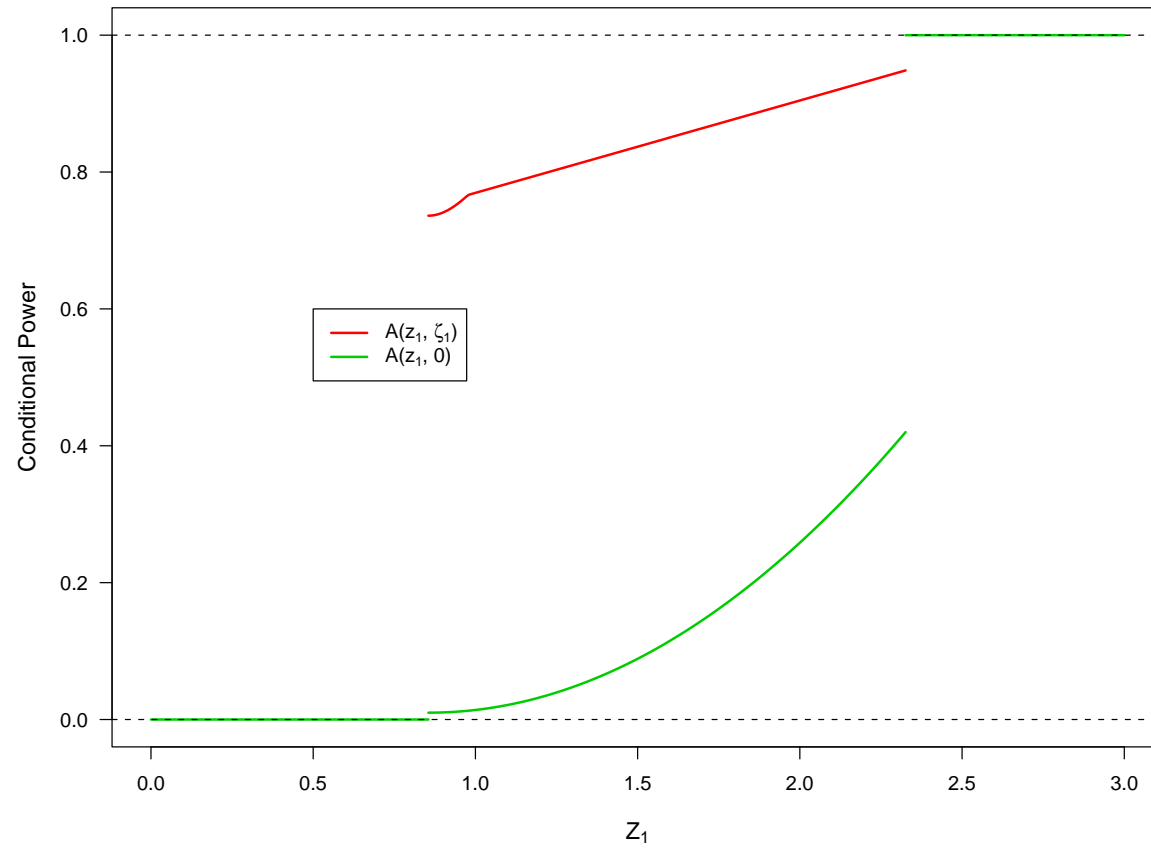
$$n_1 = 100$$

$$\alpha_1 = 0.010$$

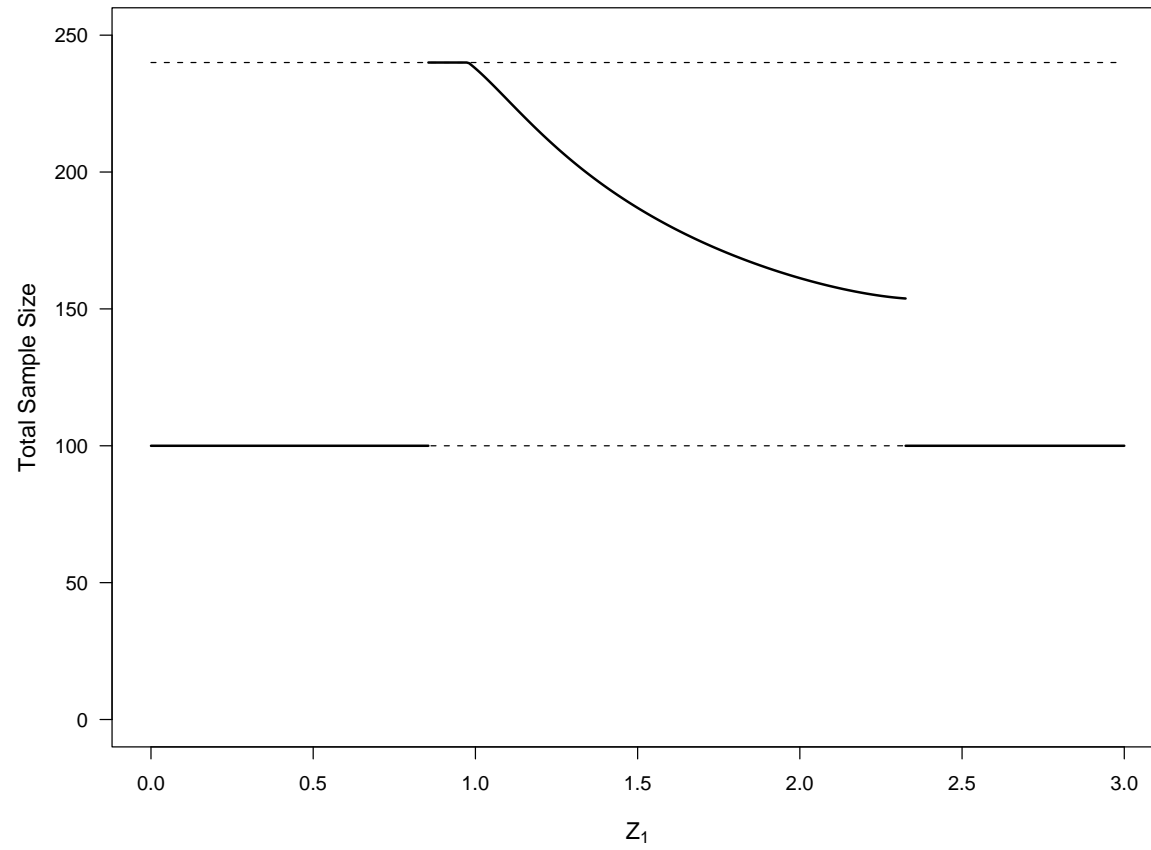
$$\beta_1 = 0.050$$

$$k_1 = 0.855, k_2 = 2.326 \text{ (Stage I critical values)}$$

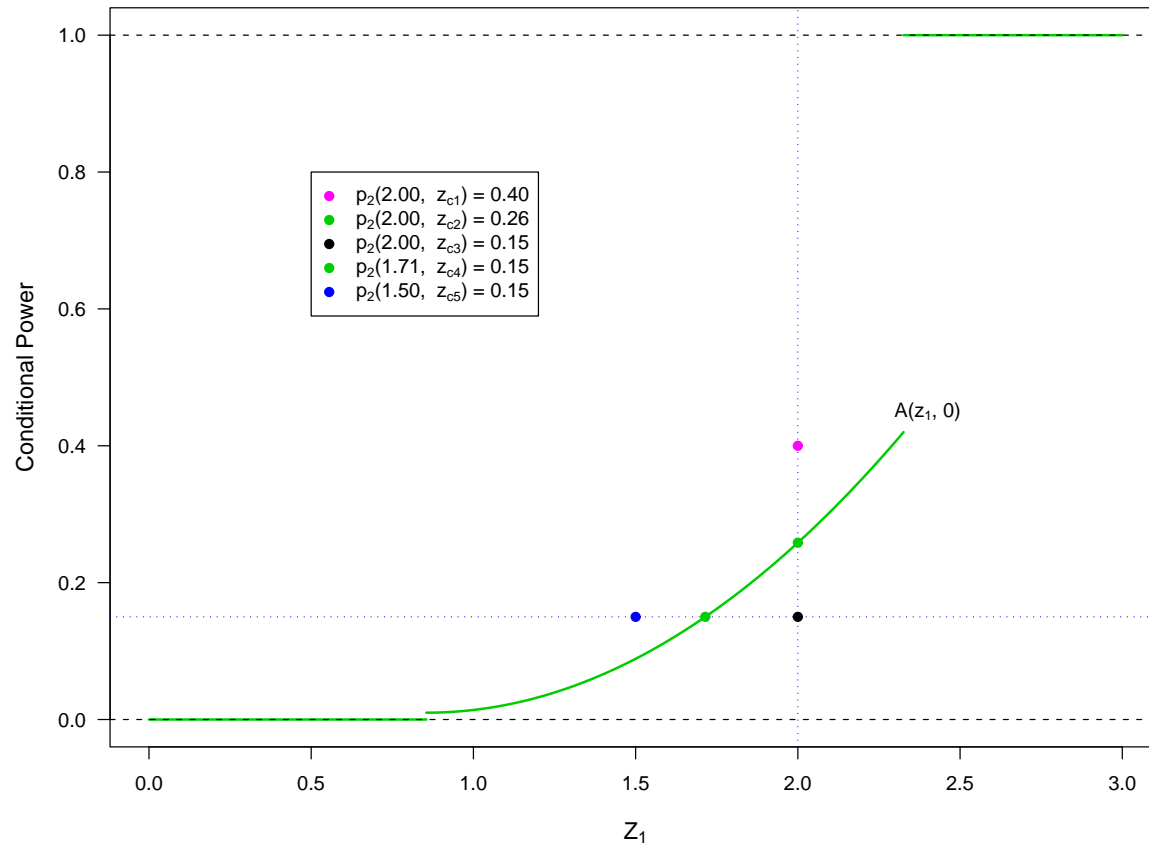
Conditional α and Conditional Power for Stage II



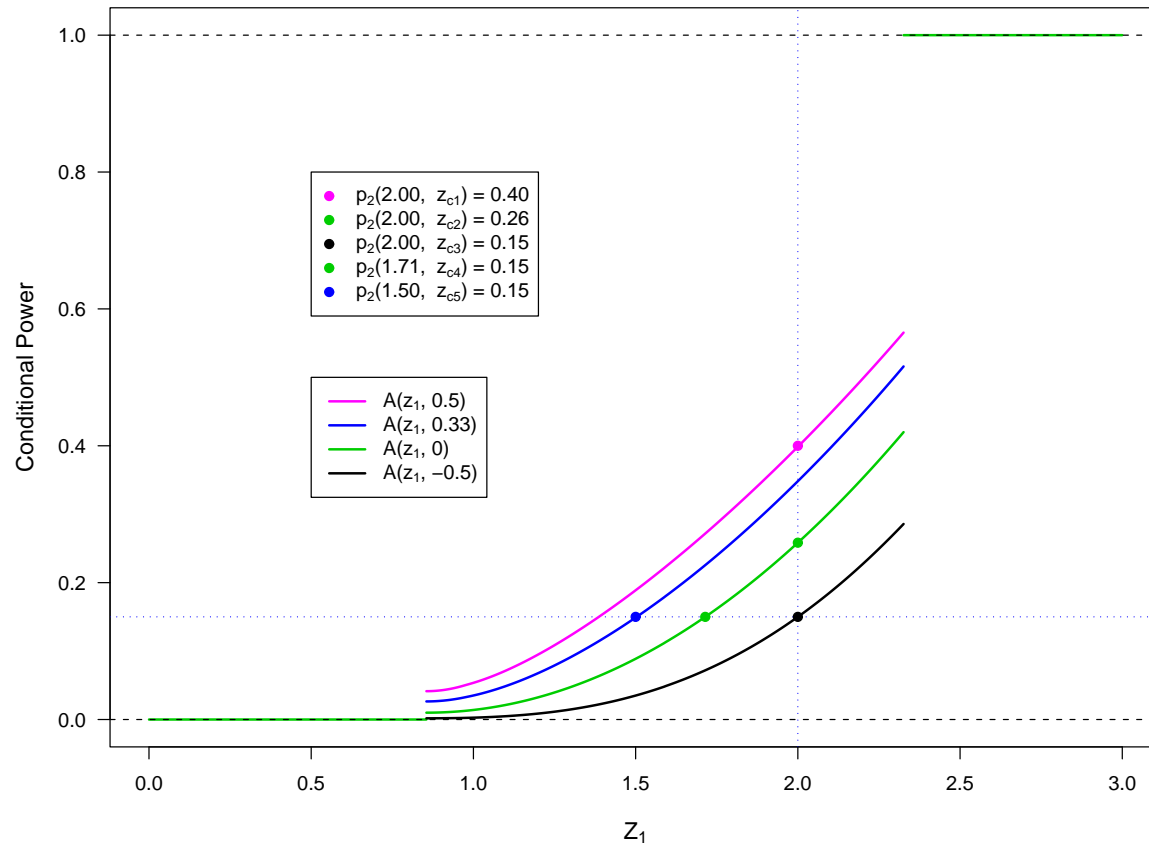
Sample Size



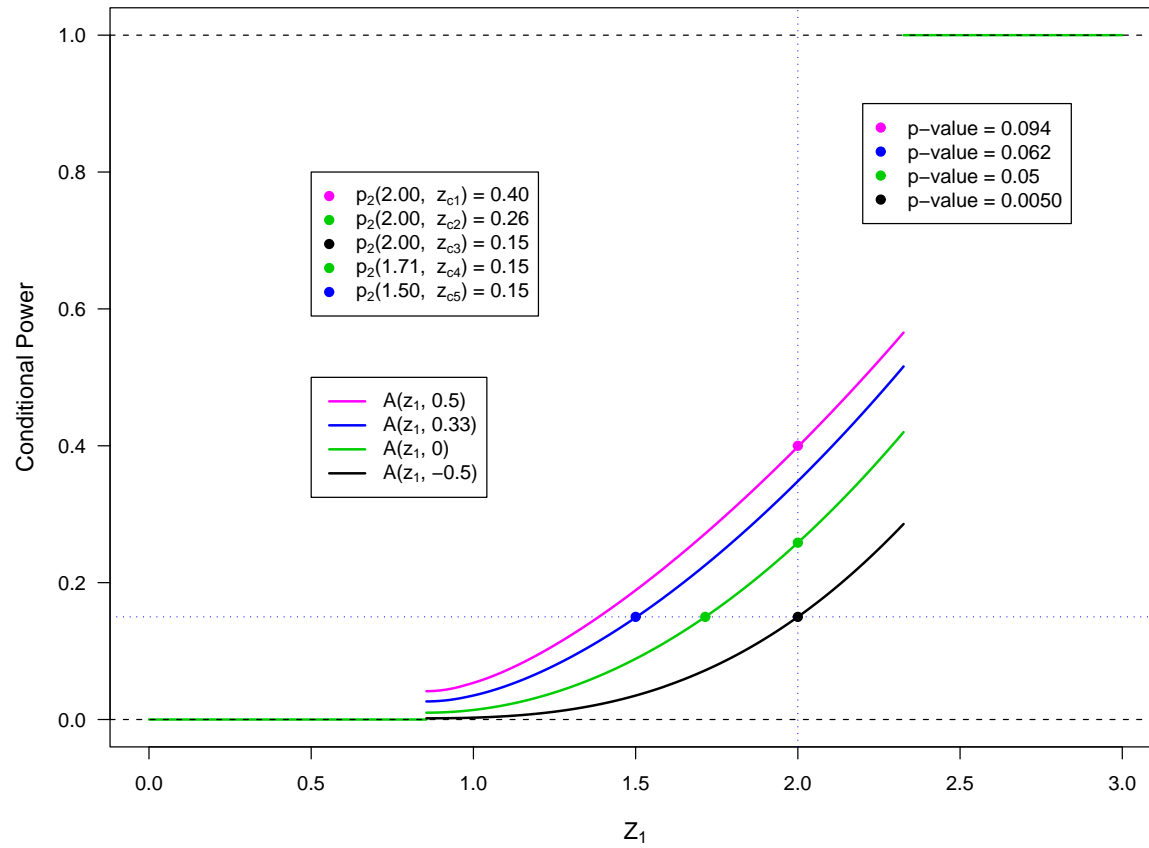
Comparing Conditional p -values



Comparing Conditional p -values



Unconditional p -values



Others in the Past

The proposed ordering is an extension of “Stage-wise ordering” proposed by Armitage (1957) and later discussed by Siegmund (1978), Fairbanks and Madsen (1982), Tsiatis, Rosner and Mehta (1984).

It reduces to “Stage-wise ordering” if

- $n_2(z_1) = n_2$ (constant for all z_1)
 - $c(z_1) = c$ (constant for all z_1)
-

An issue ... We need to know $n_2(z_1)$ for all z_1 to compute a p -value even though only one $n_2(z_1^*)$ is realized.

Additional Topics

Additional Topics

- Confidence Interval
- Variations in Unblinding

Confidence Interval

$S = 2$ (Continued to stage II)

From an observed sample path, (z_1, z_c) , we can compute ζ^* such that $H_0 : \zeta \leq \zeta^*$ would have been rejected.

A $(1 - \alpha) \times 100\%$ one sided confidence interval is $(\zeta : \zeta \geq \zeta^*)$.

So if we observe the **blue** data point, a 97.5% one sided confidence interval (for ζ) would be $(0.33, \infty)$.

Note that we don't need to know the entire **blue** line to obtain a confidence interval.

Variations in Unblinding

- Unblinded ($\bar{X}_{Control}$, $\bar{X}_{Treatment}$, $S_{Control}^2$, $S_{Treatment}^2$)
- Blinded ($\bar{X}_{Overall}$, $S_{Overall}^2$)
- Partially Unblinded ($\bar{X}_?$, $\bar{X}_!$, $S_?^2$, $S_!^2$)
- Partially Unblinded (S_{Pooled}^2)

Partial Unblinding is Total Unblinding

Without breaking the blind, we can compute $\bar{X}_{Overall}$ and $S_{Overall}^2$.
If we know the pooled variance, S_{Pooled}^2 , then we can compute

$$(\bar{X}_T - \bar{X}_C)^2 = \frac{N_T + N_C}{N_T N_C} [(N_T + N_C - 1)S_O^2 - (N_T + N_C - 2)S_P^2]$$

if $N = N_T = N_C$ then

$$= \left(4 - \frac{2}{N}\right) S_O^2 - \left(4 - \frac{4}{N}\right) S_P^2$$

“Between $SS = \text{Total } SS - \text{Within } SS$ ”