A Calculus For Design Of Two-Stage Adaptive Procedures

Tatsuki Koyama, Ph.D.

Tatsuki.Koyama@Vanderbilt.Edu

Department of Biostatistics
Vanderbilt University Medical Center

Leon J. Gleser, Ph.D.
Allan R. Sampson, Ph.D.

Department of Statistics
University of Pittsburgh

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Two-Stage Adaptive Procedures

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Two-Stage Adaptive Procedures

- The design of Stage II depends on unblinded Stage I data.
  - Stage II sample size and critical value are 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.

Prespecification of the Stage II

Without prespecification of the actions

- The sample size behavior is unknown.

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Prespecification of the Stage II

Without prespecification of the actions

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- The unconditional power cannot be specified.
- The Type I error cannot be rigorously defined.

  \- Liu, Proschan and Pledger (2002)

Motivating Example

Lan and Trost's procedure

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Lan and Trost's procedure

Lan and Trost (1996) give a procedure in which the results from Stage I are used to determine the sample size for Stage II.

Example - Background

Consider testing

$$H_0 : \mu_t - \mu_c \leq 0$$
$$H_1 : \mu_t - \mu_c > 0$$

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Assume that $\sigma = 4$

$\alpha = .025$ and $\rho \equiv 1 - \beta = .85$ at $\mu_t - \mu_c = 1$

Then conventional single-stage procedure's sample size is $N = 288$ from each group.

Example - CP

In Stage I, a sample of size $n_1 = 0.4 \times N = 115$ from each group is taken.

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Calculate CP, the conditional probability of rejecting H_0 in Stage II under the trend of Stage I (i.e. $\bar{X}_{1t} - \bar{X}_{1c}$) after $N - n_1 = 173$ more observations in Stage II.

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In Stage I, a sample of size $n_1 = 0.4 \times N = 115$ from each group is taken.

Calculate CP, the conditional probability of rejecting H_0 in Stage II under the trend of Stage I (i.e. $\bar{X}_{1t} - \bar{X}_{1c}$) after $N - n_1 = 173$ more observations in Stage II.

Their procedure's design is based on $\underline{CP}$

Example - Stage I Decision Rule

- If CP is less than $\mathbf{.05}$, stop the trial at the end of Stage I for futility.

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- If CP is between $.05$ and $.65$, extend the study so that the conditional probability of rejecting H_0 at the end of Stage II under the Stage I results is $.65$.

Example - Stage I Decision Rule

- If CP is less than $.05$, stop the trial at the end of Stage I for futility.
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$\underline{CP}$

Example - Characteristics

Characteristics of the resulting design

$$\text{P[Type I Error]} = \text{P[Reject } H_0 \text{ under } H_0] = .024$$

$$\text{Power} = \text{P[Reject } H_0 \text{ under } H_1] = .877$$

Sample size

In the Literature

There has been much interest in the field of two-stage adaptive procedures.

- Bauer and Köhne (1994)
- Proschan and Hunsberger (1995)
- Lan and Trost (1997)
- Lehmacher and Wassmer (1999)
- Liu and Chi (2001)

The Main Objectives

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Calculus

Hypotheses of interest:

$$H_0 : \mu_t - \mu_c \leq \Delta_0$$
$$H_1 : \mu_t - \mu_c > \Delta_0$$

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α = P[Type I error]

β = P[Type II error] at Δ_1.

$\rho = 1 - \beta$.

Calculus

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α = P[Type I error]

β = P[Type II error] at Δ_1.

$\rho = 1 - \beta$.

Suppose that

$$X_t \sim \text{Normal}(\mu_t,\, \sigma^2)$$
$$X_c \sim \text{Normal}(\mu_c,\, \sigma^2)$$

Stage I

- Take a sample of size n_1 from the treatment and control groups.

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We use the notation, $\xi = \dfrac{\mu_t - \mu_c}{\sqrt{2}\,\sigma}$.

Flowchart

Stage II

- Take a sample of size $n_2(y_1)$ from the treatment and control groups.

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- Take a sample of size $n_2(y_1)$ from the treatment and control groups.
- Test Statistic is

$$Y_2 = \frac{\bar{X}_{2t} - \bar{X}_{2c}}{\sqrt{2}\,\sigma}$$

Flowchart

Summary

- Stage I
  - Sample size $\cdots$ n_1
  - Critical values $\cdots$ k_1 and k_2

- Stage II
  - Sample size function $\cdots$ $n_2(y_1)$
  - Critical value function $\cdots$ $w(y_1)$

Stage I Error Probabilities

- $\alpha_1 =$ P[Reject H_0 in Stage I under H_0]
- $\beta_1 =$ P[Accept H_0 in Stage I under H_1]

Stage I Error Probabilities

- $\alpha_1 =$ P[Reject H_0 in Stage I under H_0]
- $\beta_1 =$ P[Accept H_0 in Stage I under H_1]

- We can write α_1 as a function of n_1 and k_2.
- We can write β_1 as a function of n_1 and k_1.

Stage I Components

Stage I is characterized by the following 5 “specification components” :

$$\boldsymbol{\alpha_1,\ \beta_1,\ n_1,\ k_1,\ k_2.}$$

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These specification components need to satisfy :

- $\alpha_1 = P_{\xi_0}[Y_1 > k_2] = 1 - \Phi[\sqrt{n_1}(k_2 - \xi_0)]$
- $\beta_1 = P_{\xi_1}[Y_1 < k_1] = \Phi[\sqrt{n_1}(k_1 - \xi_1)]$

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If 3 components are specified, we can obtain the other 2 using the above relationships.

Stage I Components

- $\alpha_1 = 1 - \Phi[\sqrt{n_1}(k_2 - \xi_0)]$
- $\beta_1 = \Phi[\sqrt{n_1}(k_1 - \xi_1)]$

If 3 components are specified, we can obtain the other 2 using the above relationships.

At least 1 component needs to come from α_1 group and β_1 group.

"Conditional Power Functions"

For Stage II, define the "conditional power functions" as :

$$A(y_1, \xi) = P_\xi[\text{Reject } H_0 \text{ in Stage II} \,|\, Y_1 = y_1\,]$$

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For Stage II, define the “conditional power functions” as :

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- $A(y_1, \xi_1) =$ Conditional power at the original alternative

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ξ can depend on y_1. e.g., $\xi(y_1) = y_1$

- $A(y_1, y_1)$ = Conditional power at y_1, an estimate of ξ

Stage II Components

Stage II is characterized by the following 4 “specification components” :

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- $A(y_1, \xi_0) = 1 - \Phi\left[\sqrt{n_2(y_1)}(w(y_1) - \xi_0)\right]$
- $A(y_1, \xi_1) = 1 - \Phi\left[\sqrt{n_2(y_1)}(w(y_1) - \xi_1)\right]$

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- $A(y_1, \xi_1) = 1 - \Phi\left[\sqrt{n_2(y_1)}(w(y_1) - \xi_1)\right]$
- 2 components from these 4 are sufficient to determine the other 2.

Type I and Type II Error Rates

To control Type I error rate and to specify power, we need

$$\alpha_2 \equiv \alpha - \alpha_1 = \int_{k_1}^{k_2} A(y_1, \xi_0) g_{\xi_0}(y_1)\, dy_1$$

$$\rho_2 \equiv \rho - \rho_1 = \int_{k_1}^{k_2} A(y_1, \xi_1) g_{\xi_1}(y_1)\, dy_1$$

where $g_\xi(y_1)$ is the pdf of Normal(ξ, $1/n_1$).

Components

A two-stage adaptive procedure is characterized by the following 9 components:

- Stage I
  α_1, β_1, n_1, k_1, k_2
- Stage II
  $A(y_1, \xi_0)$, $A(y_1, \xi_1)$, $n_2(y_1)$, $w(y_1)$

Instead of $A(y_1, \xi_0)$ and $A(y_1, \xi_1)$, we can choose any $A(y_1, \xi)$ at two distinct ξ's.

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Example

In this example, we show that

- a fairly complicated procedure can be placed under our formulation.

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In this example, we show that

- a fairly complicated procedure can be placed under our formulation.
- our framework allows manipulation of design parameters to control many aspects of the design, such as the Type I error rate, Type II error rate (power), maximum sample size and so on.

Lan & Trost's Procedure

$$H_0 : \mu_t - \mu_c \leq 0$$
$$H_1 : \mu_t - \mu_c > 0$$

- $\sigma = 4$
- $\alpha = .025$
- Power $= .85$ at $\mu_t - \mu_c = 1$. ($\xi_1 = .1768$)

Conventional single-stage design's sample size is $N = 288$ from each group.

$\underline{A(y_1, y_1)}$

Stage I Components

- $n_1 = 115$
- k_1 satisfies $CP(k_1) = .05. \;\Rightarrow\; k_1 = .0405$
- $k_2 = \infty$
- (κ satisfies $CP(\kappa) = .65. \;\Rightarrow\; \kappa = .1332$)

Stage I Components

- $n_1 = 115$
- k_1 satisfies $CP(k_1) = .05. \;\Rightarrow\; k_1 = .0405$
- $k_2 = \infty$
- (κ satisfies $CP(\kappa) = .65. \;\Rightarrow\; \kappa = .1332$)

We can calculate the remaining 2 components, α_1 and β_1 for Stage I.

$\{\, \alpha_1 = 0,\, \beta_1 = .072,\, n_1 = 115,\, k_1 = .0405,\, k_2 = \infty \,\}$

Stage II Components

- Stage II is divided into "extension" and "continuation" regions based on y_1.
- Using $A(y_1, y_1) = CP(y_1)$ and the facts that the critical value is constant in terms of z-value and that $n_2(y_1)$ is constant in the "continuation" region, we can obtain $A(y_1, \xi)$, $n_2(y_1)$ and $w(y_1)$ for the entire range of y_1 in (k_1, ∞).

$A(y_1, \xi)$ and sample size

Problems of Lan & Trost's Design

- Sample size
  $\boldsymbol{max(n_2(y_1)) = 3223.}$

Problems of Lan & Trost's Design

- Sample size
  $max(n_2(y_1)) = 3223.$
- $\underline{A(y_1, \xi_1)}$ is not monotone.

  Under H_1,
  conditional power is virtually 1 if $y_1 = .0403$.
  conditional power is about .8 if $y_1 = .1332$.

Type I Error and Power

Our framework permits numerical integration to find :

$$\text{Type I Error Rate} = \int_{-\infty}^{\infty} \boldsymbol{A(y_1, \xi_0) g_{\xi_0}(y_1)\, dy_1 = .024}$$

$$\text{Power at } \boldsymbol{\xi_1} = \int_{-\infty}^{\infty} \boldsymbol{A(y_1, \xi_1) g_{\xi_1}(y_1)\, dy_1 = .877}$$

Type I Error and Power

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$$\text{Power at } \xi_1 = \int_{-\infty}^{\infty} A(y_1, \xi_1) g_{\xi_1}(y_1)\, dy_1 = .877$$

Lan and Trost were unable to obtain the above probabilities through integration. Their results are based on simulation.

Modification

Lan and Trost's Design is modified using our calculus.

Our framework allows to design a procedure with the following characteristics:

- $\boldsymbol{\alpha = .024}$
- power = .877 at $\boldsymbol{\xi = \xi_1 = .1768}$

$\longrightarrow \boldsymbol{N = 337}$.

Sample Size Restriction

Our framework also permits specification of the minimum and maximum sample size.

- $n_1 + max(n_2(y_1)) = 442$
- $n_1 + min(n_2(y_1)) = 317$

The total sample size for Stages I and II when continuing to Stage II is between $N = 317$ and $N \times 1.4 = 442$.

Stage I Components

We choose :

$n_1 = 115$ (same as the original design)
$k_1 = .0405$ (same as the original design)
$\alpha_1 = .005$

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Then using our framework we can obtain the two remaining components, β_1 and k_2.

$\{\alpha_1 = .005, \beta_1 = .072, n_1 = 115, k_1 = .0405, k_2 = .2406\}$

Stage II Components

We choose :

$$A(y_1, \xi_0) = .02 + 6.93(y_1 - k_1)^2$$

This satisfies $\alpha_2 = .020 = \int_{k_1}^{k_2} A(y_1, \xi_0) g_{\xi_0}(y_1)\, dy_1$.

$$A(y_1, \xi_1) = .925$$

This satisfies $\rho_2 = .602 = \int_{k_1}^{k_2} A(y_1, \xi_1) g_{\xi_1}(y_1)\, dy_1$.

<u>$A(y_1, \xi)$ and sample size</u>

Stage II Components

We choose :

$$A(y_1, \xi_0) = .02 + 6.93(y_1 - k_1)^2$$

The same as before

$$A(y_1, \xi_1) = .89 + 2.4(y_1 - k_1)^2$$

$A(y_1, \xi)$ and sample size

Stage II Components

Our framework allows modification of the sample size function directly so that it does not exceed the maximum and it does not increase.

Sample size

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Sample size

We keep $A(y_1, \xi_0) = .02 + 6.93(y_1 - k_1)^2$ unchanged.

Then with this new $n_2(y_1)$ function, $A(y_1, \xi_1)$ and $w(y_1)$ are modified.

$A(y_1, \xi)$

Comparison of the Two Designs

the Original Lan and Trost's Design

μ	Stage I Accept	Stage I Continue	Stage I Reject	Stage II Reject	Power	$n_1 + E[n_2(Y_1)]$
0.00	.668	.332	0	.024	.024	397.4
0.25	.484	.516	0	.178	.178	476.6
0.50	.304	.696	0	.457	.457	501.1
0.75	.162	.838	0	.706	.706	468.7
1.00	.072	.928	0	.877	.877	407.7
1.25	.026	.974	0	.961	.961	350.8

the Modified Design

μ	Stage I Accept	Stage I Continue	Stage I Reject	Stage II Reject	Power	$n_1 + E[n_2(Y_1)]$
0.00	.668	.327	.005	.019	.024	208.1
0.25	.484	.498	.018	.103	.121	251.6
0.50	.304	.645	.051	.308	.359	284.4
0.75	.162	.715	.123	.542	.665	294.3
1.00	.072	.681	.247	.630	.877	278.0
1.25	.026	.557	.417	.548	.965	242.7

Significant Design Parameters

We conducted a computational experiment to see which design components have significant influence on the characteristics of the resulting design.

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What enabled us to conduct this study is our ability to place many two-stage adaptive procedures under one formulation indexed by the following design parameters:

Design Parameters

- $\boldsymbol{\alpha_1}$
- $\boldsymbol{\beta_1}$
- $\boldsymbol{f}$, the ratio of $\boldsymbol{n_1}$ to $\boldsymbol{N}$
- $\boldsymbol{A(y_1, \xi_0)}$
- $\boldsymbol{A(y_1, \xi_1)}$

Also various $\boldsymbol{\sigma}$'s are included in the study.

Performance Characteristics

Different combinations of the design parameters yield designs with different performance characteristics (power and expected sample sizes).

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A design parameter that demonstrates relatively substantial variability in the “response surface” is considered influential and thus important.

Summary of the Results

- α_1, β_1, f, $f \times \alpha_1$ and $f \times \beta_1$ explain most of variation in power and expected sample sizes.

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- $\boldsymbol{\alpha_1}$, $\boldsymbol{\beta_1}$, $\boldsymbol{f}$, $\boldsymbol{f} \times \boldsymbol{\alpha_1}$ and $\boldsymbol{f} \times \boldsymbol{\beta_1}$ explain most of variation in power and expected sample sizes.
- A small $\boldsymbol{\alpha_1}$ and a large $\boldsymbol{\beta_1}$ seem to perform well.

Summary of the Results

- α_1, β_1, f, $f \times \alpha_1$ and $f \times \beta_1$ explain most of variation in power and expected sample sizes.
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- When f is large, there are very small differences in the performance characteristics for different choices of α_1 and β_1.

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- A small α_1 and a large β_1 seem to perform well.
- When f is large, there are very small differences in the performance characteristics for different choices of α_1 and β_1.
- $A(y_1, \xi_0)$ and $A(y_1, \xi_1)$ are both insignificant.

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  - Computer program to manipulate specification components
- puts into perspective previously proposed procedures.
  - Two-Stage Group Sequential Procedure
  - Comparison of designs to assess the importance of each specification component on the resulting design

Extensions

- Unequal Sample Sizes

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- Unequal Sample Sizes
  - Planned unequal sample sizes

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- Unequal Sample Sizes
  - Planned unequal sample sizes
  - Missing observations

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- Unequal Sample Sizes
  - Planned unequal sample sizes
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Extensions

- Unequal Sample Sizes
  - Planned unequal sample sizes
  - Missing observations
- Unknown Variance
- Switching study objectives between superiority and noninferiority

Future Research

- Inference (e.g., unbiased estimator and confidence interval)

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- Multi-stage procedure

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Group Sequential Procedures

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- The Stage II sample size, n_2, does not vary with y_1.

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Group Sequential Procedures

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Jennison and Turnbull (1999) give the Stage I and II critical values in terms of Z.

Specification Components

- Stage I

$$\{\, \boldsymbol{n_1}, \boldsymbol{k_1}, \boldsymbol{k_2} \,\}$$

- Stage II

$$\{\, \boldsymbol{n_2}(\boldsymbol{y_1}), \boldsymbol{w}(\boldsymbol{y_1}) \,\}$$

Example

Suppose that $\boldsymbol{\mu_0 = 0}$, $\boldsymbol{\mu_1 = 1}$, $\boldsymbol{\sigma = 4}$, $\boldsymbol{\alpha = .05}$, $\boldsymbol{\beta = .10}$.

- For Stage I, $\boldsymbol{n_1 = 143}$, $\boldsymbol{z_a = .2298}$ and $\boldsymbol{z_b = 2.343}$.
- For Stage II, $\boldsymbol{n_2 = 143}$ and $\boldsymbol{z_c = 1.657}$.

Example

Suppose that $\mu_0 = 0$, $\mu_1 = 1$, $\sigma = 4$, $\alpha = .05$, $\beta = .10$.

- For Stage I, $n_1 = 143$, $z_a = .2298$ and $z_b = 2.343$.
- For Stage II, $n_2 = 143$ and $z_c = 1.657$.

- For Stage I, $n_1 = 143$, $k_1 = .0192$, $k_2 = .1959$.
- For Stage II, $n_2 = 143$, $w(y_1) = .1960 - y_1$.

Example

Suppose that $\mu_0 = 0$, $\mu_1 = 1$, $\sigma = 4$, $\alpha = .05$, $\beta = .10$.

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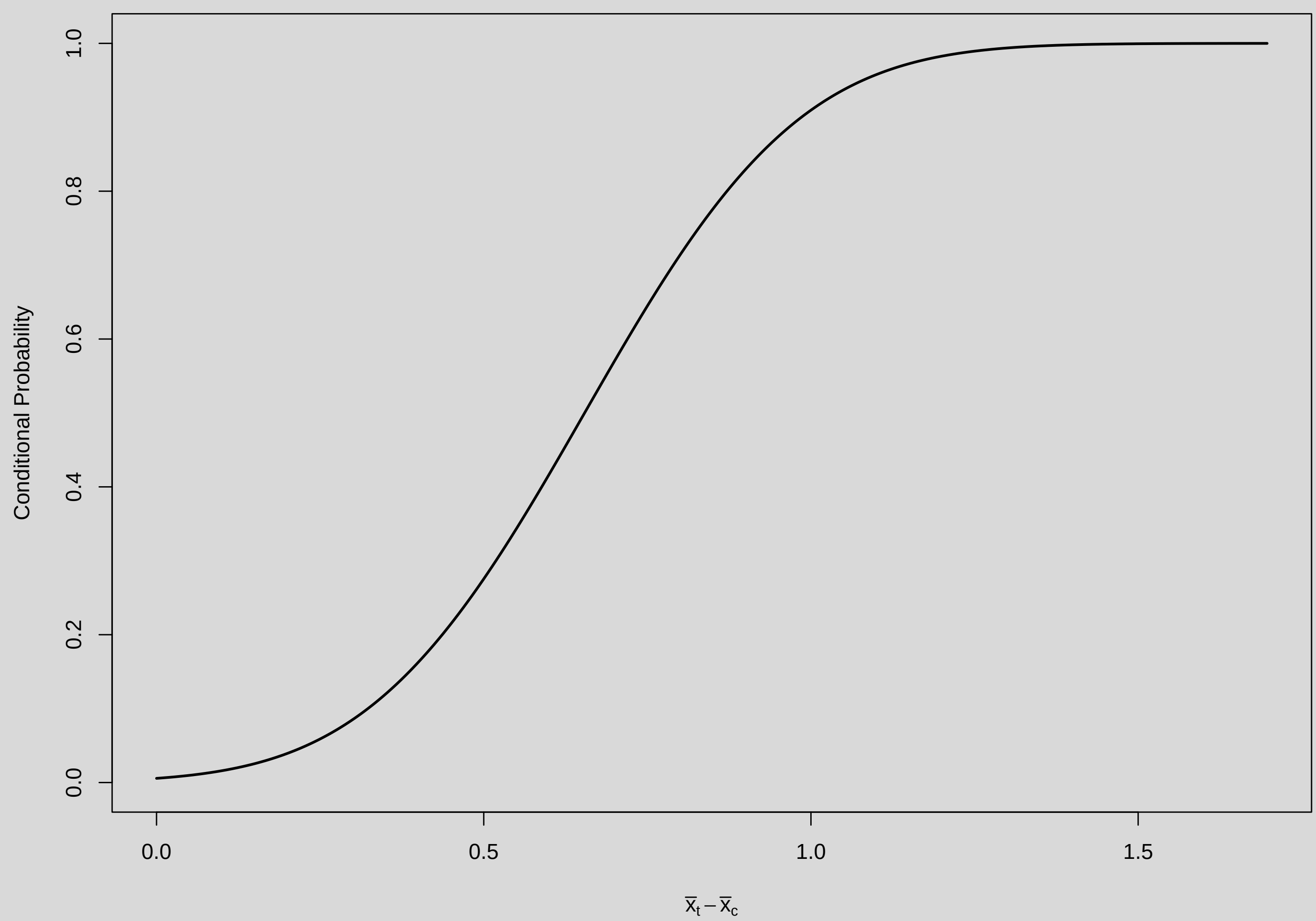
- For Stage I, $n_1 = 143$, $k_1 = .0192$, $k_2 = .1959$.
- For Stage II, $n_2 = 143$, $w(y_1) = .1960 - y_1$.

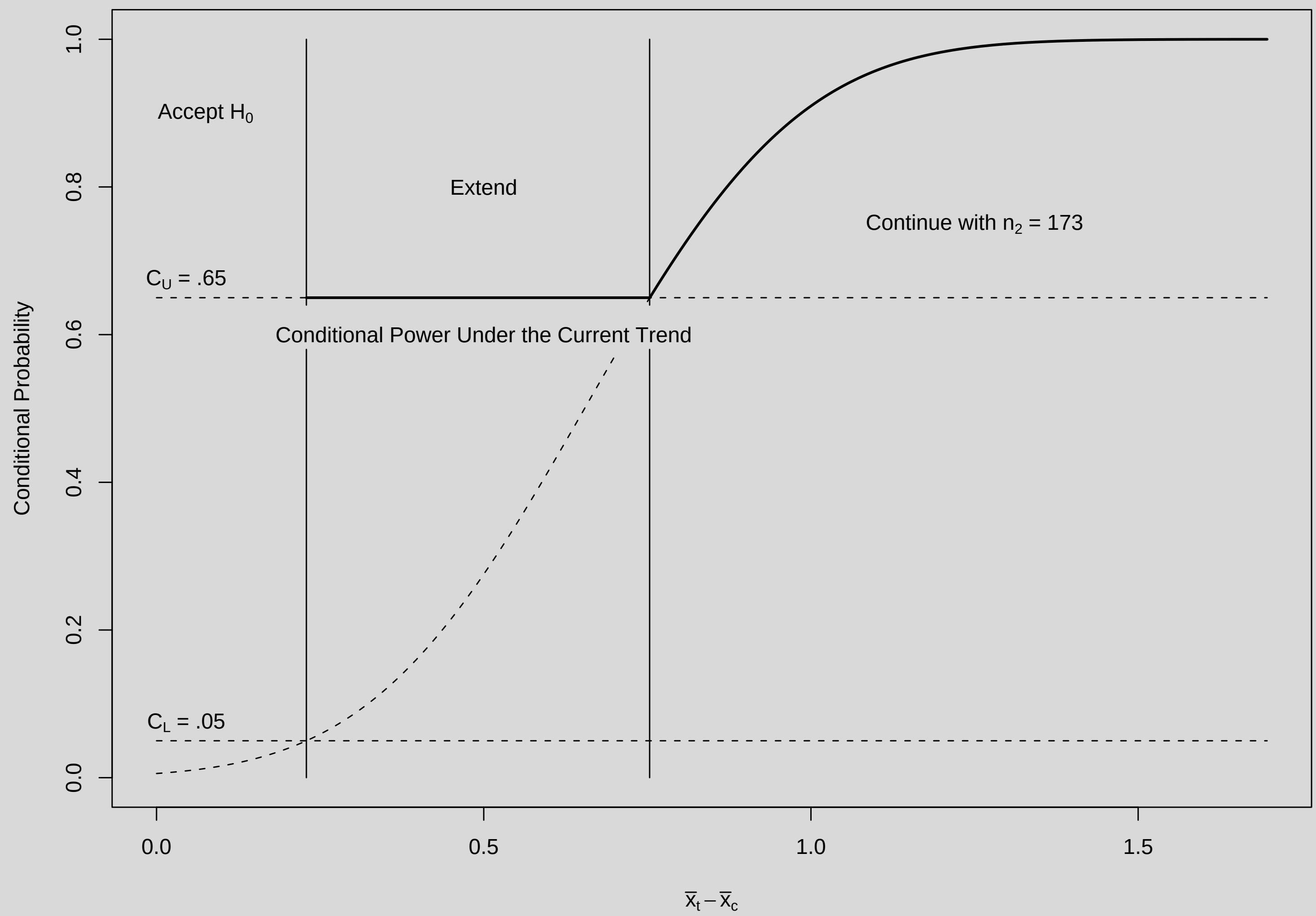
$A(y_1, \xi_0)$, $A(y_1, \xi_1)$ for Group Sequential Procedure

CP



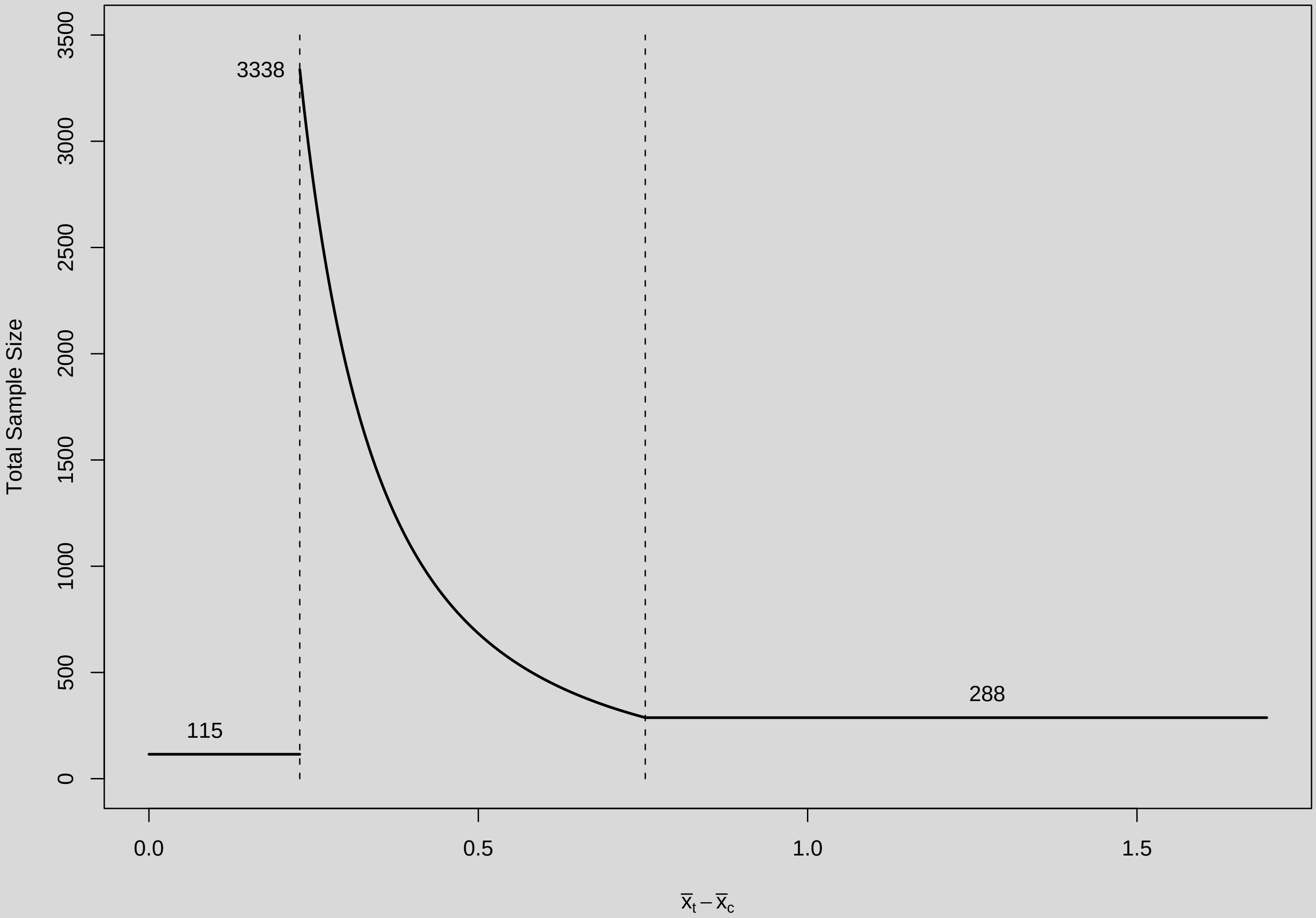
1.0
0.8
0.6
0.4
0.2
0.0
Conditional Probability
0.0
0.5
1.0
1.5
$\bar{x}_t - \bar{x}_c$

CP



Accept H0
Extend
Continue with n2 = 173
CU = .65
Conditional Power Under the Current Trend
CL = .05
Conditional Probability
0.0
0.2
0.4
0.6
0.8
1.0
0.0
0.5
1.0
1.5
x̄t – x̄c

Total Sample Size



Flowchart

Stage I

Sample size = n_1

Accept H_0 $\quad k_1$	Continue to Stage II	$k_2 \quad$ Reject H_0
Stop		Stop
====		====

$\Downarrow$

Flowchart

Stage I

Sample size = n_1

Accept H_0	k_1	Continue to Stage II	k_2	Reject H_0
Stop				Stop
====				====

$\Downarrow$

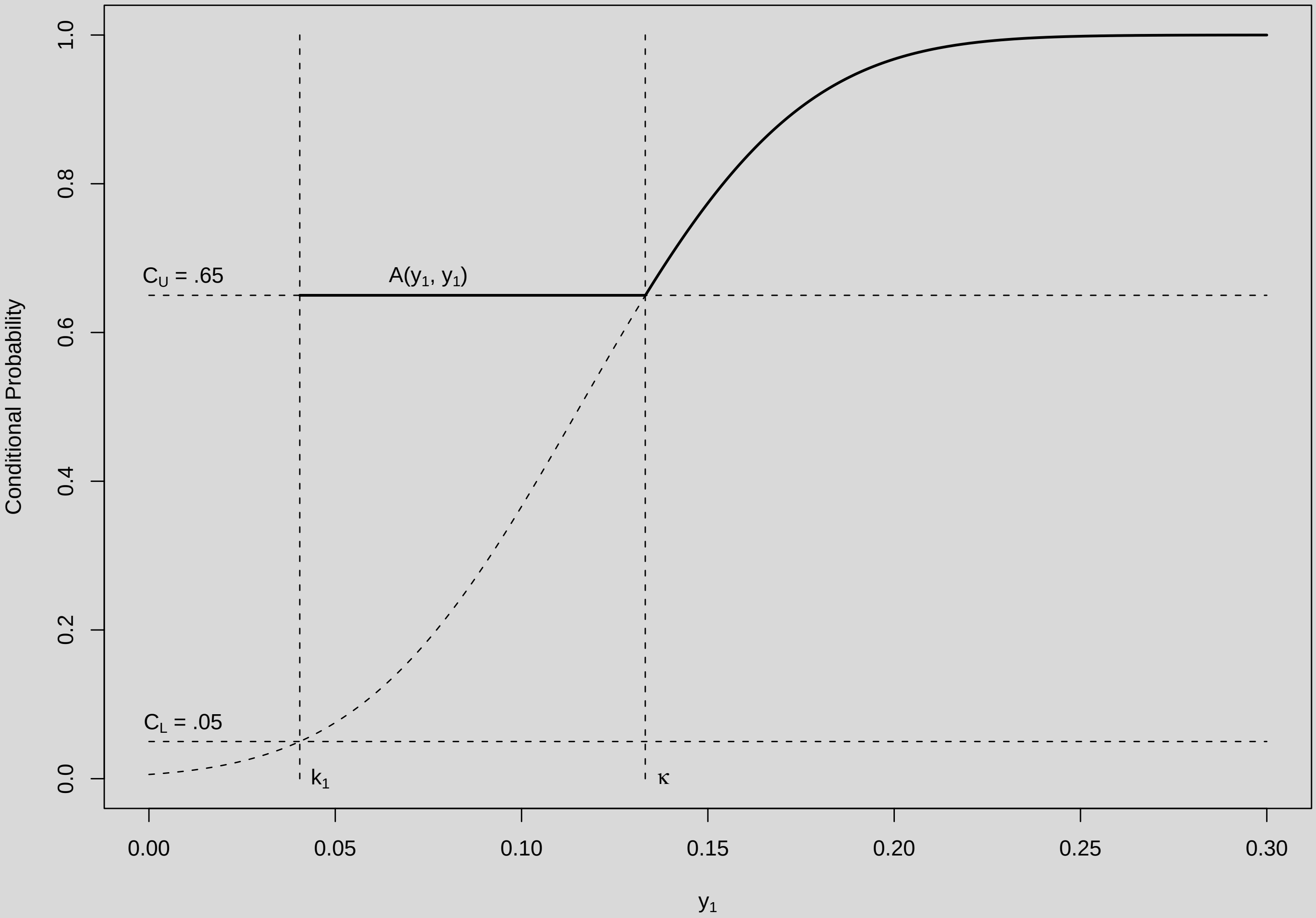
Stage II

Sample size = $n_2(y_1)$

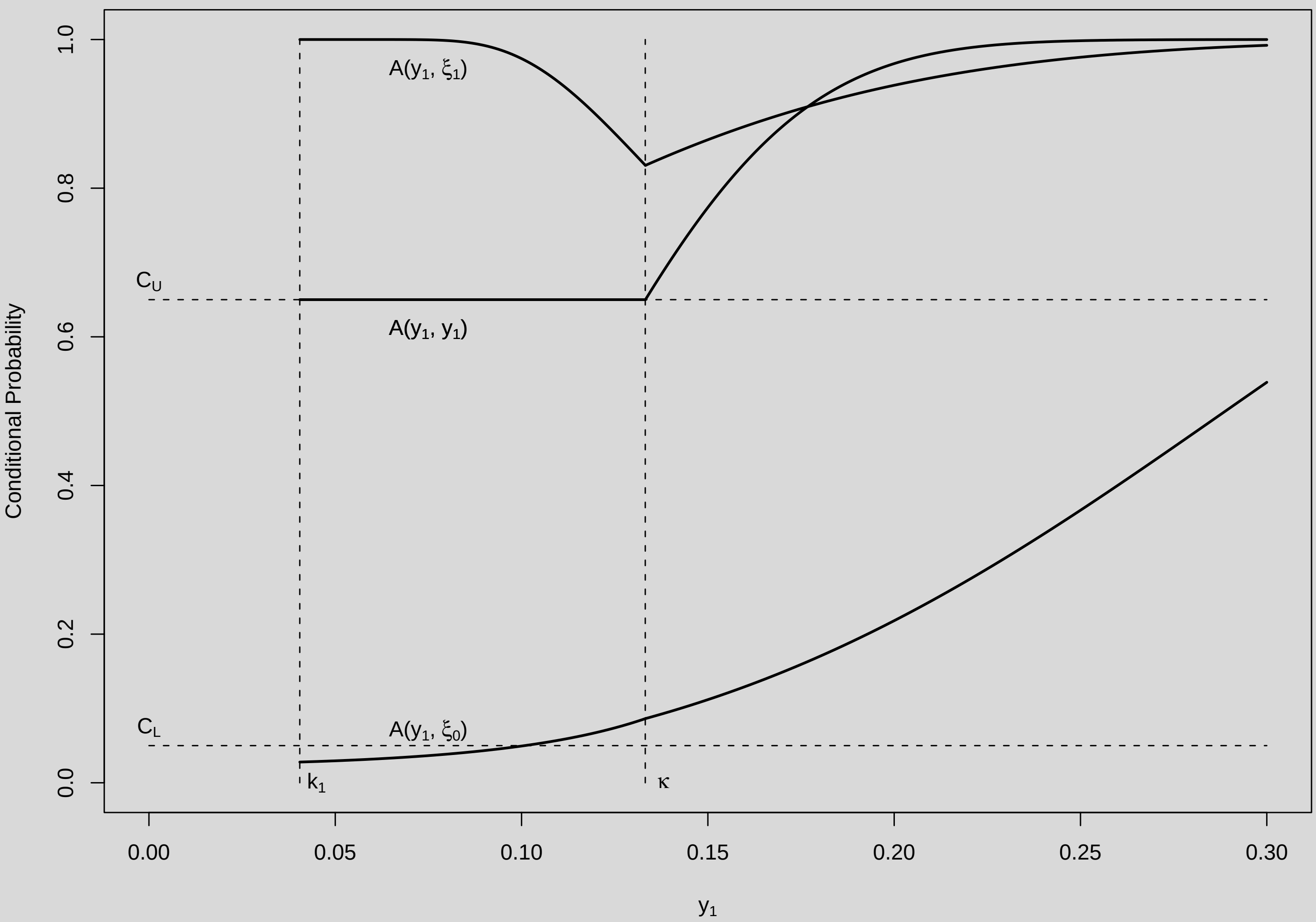
$w(y_1)$

Accept H_0	Reject H_0

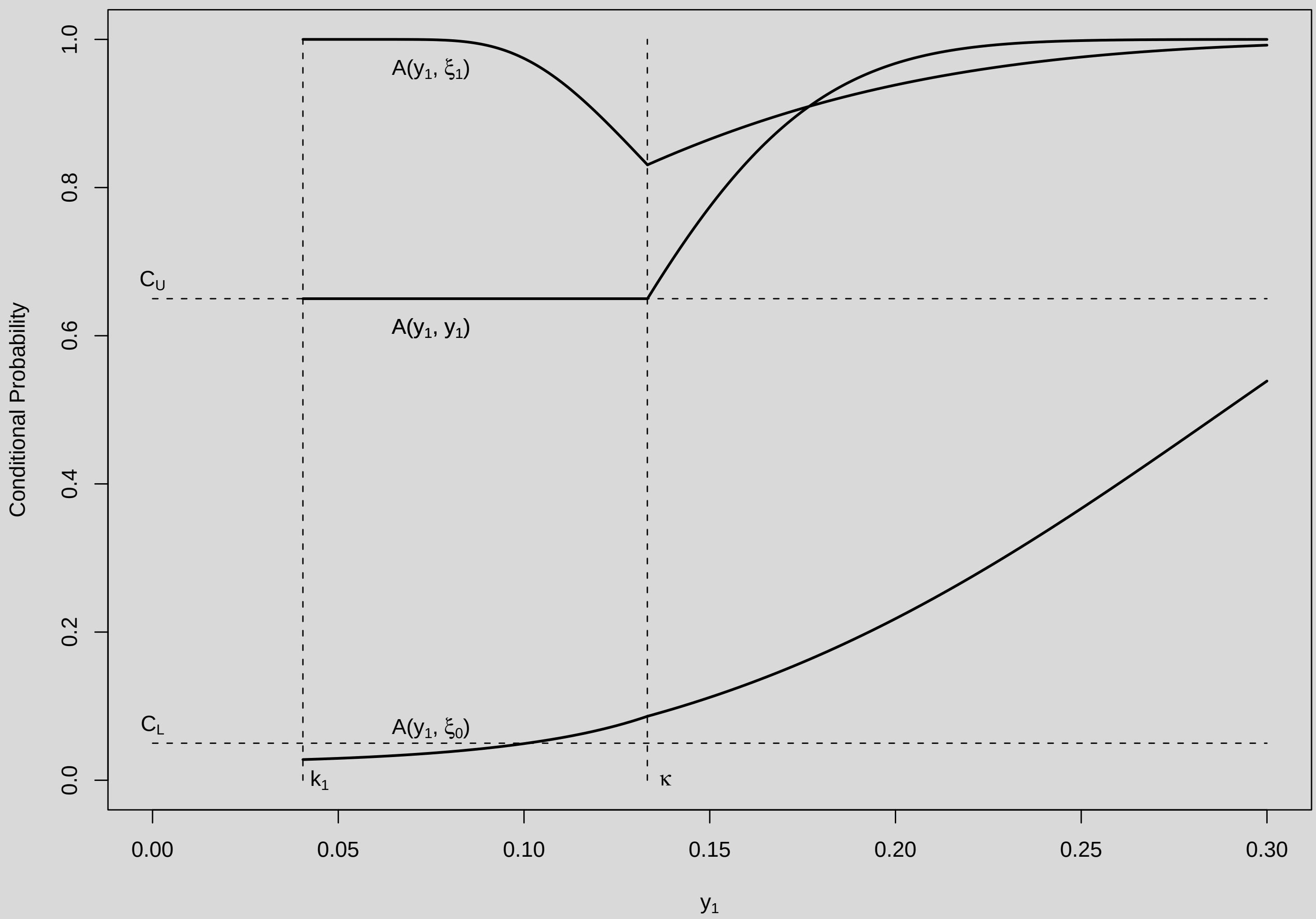
Lan and Trosts's $A(y_1, y_1)$



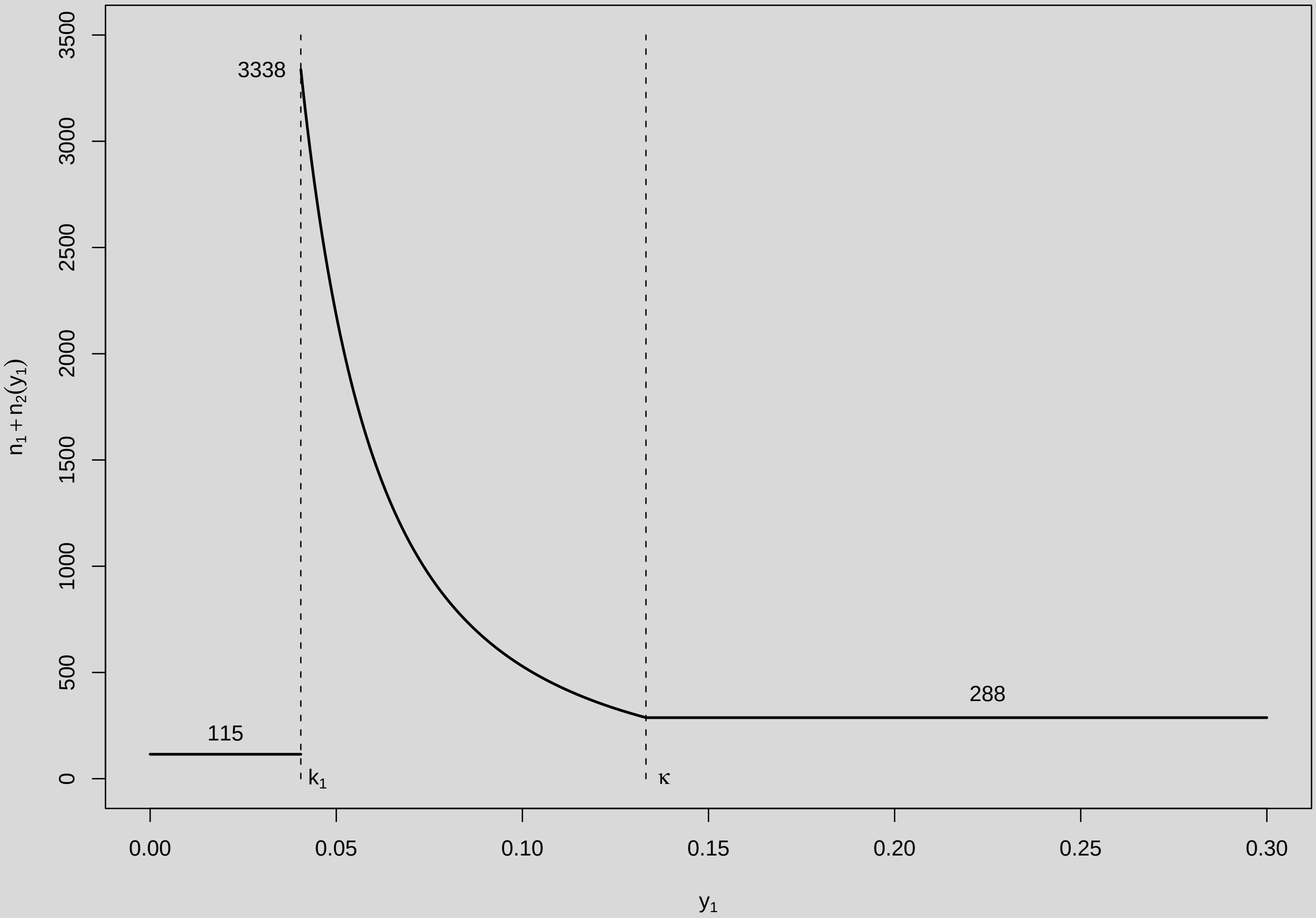
Lan and Trosts's $\boldsymbol{A(y_1, \xi)}$



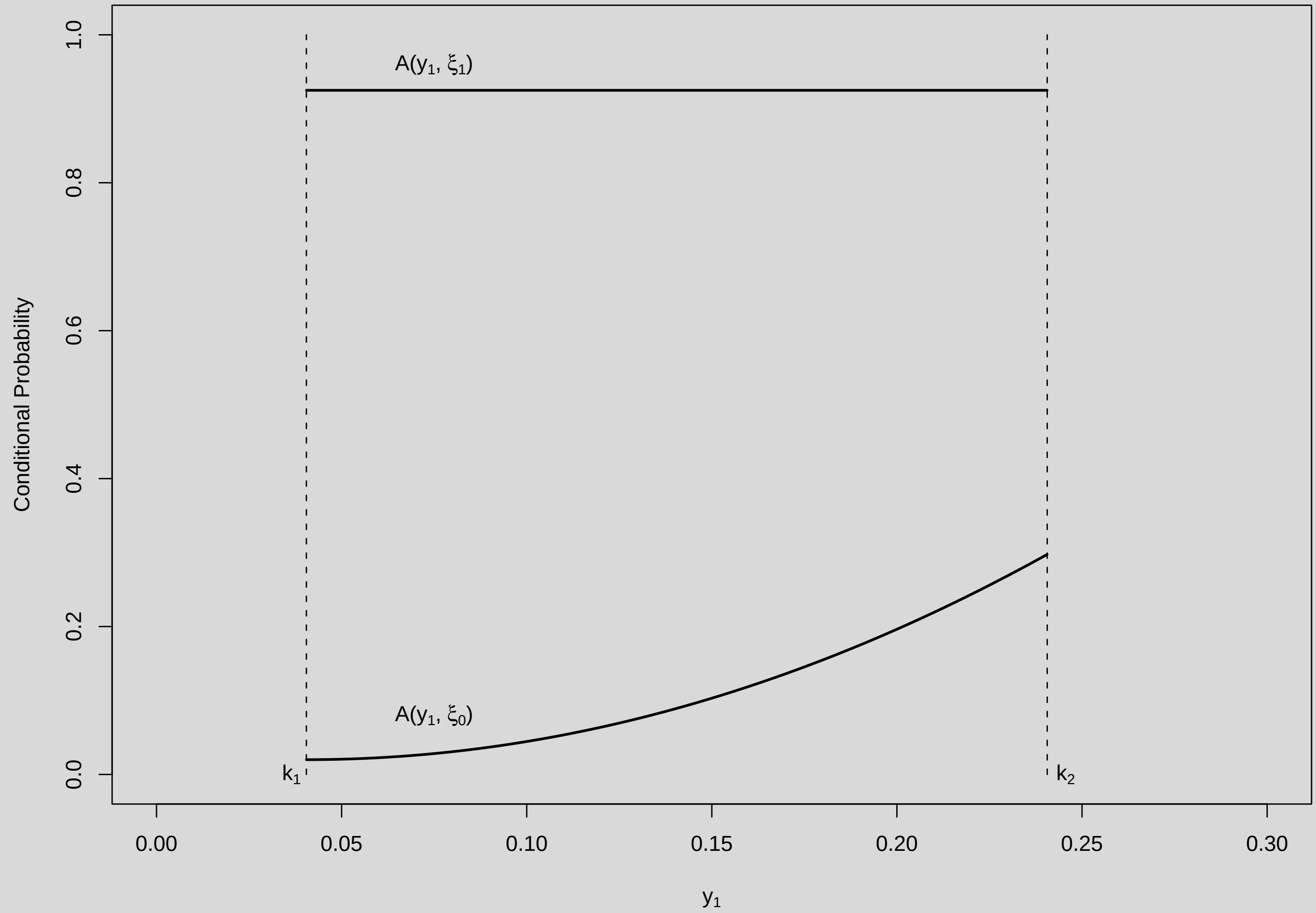
Lan and Trosts's $A(y_1, \xi)$



Total Sample Size

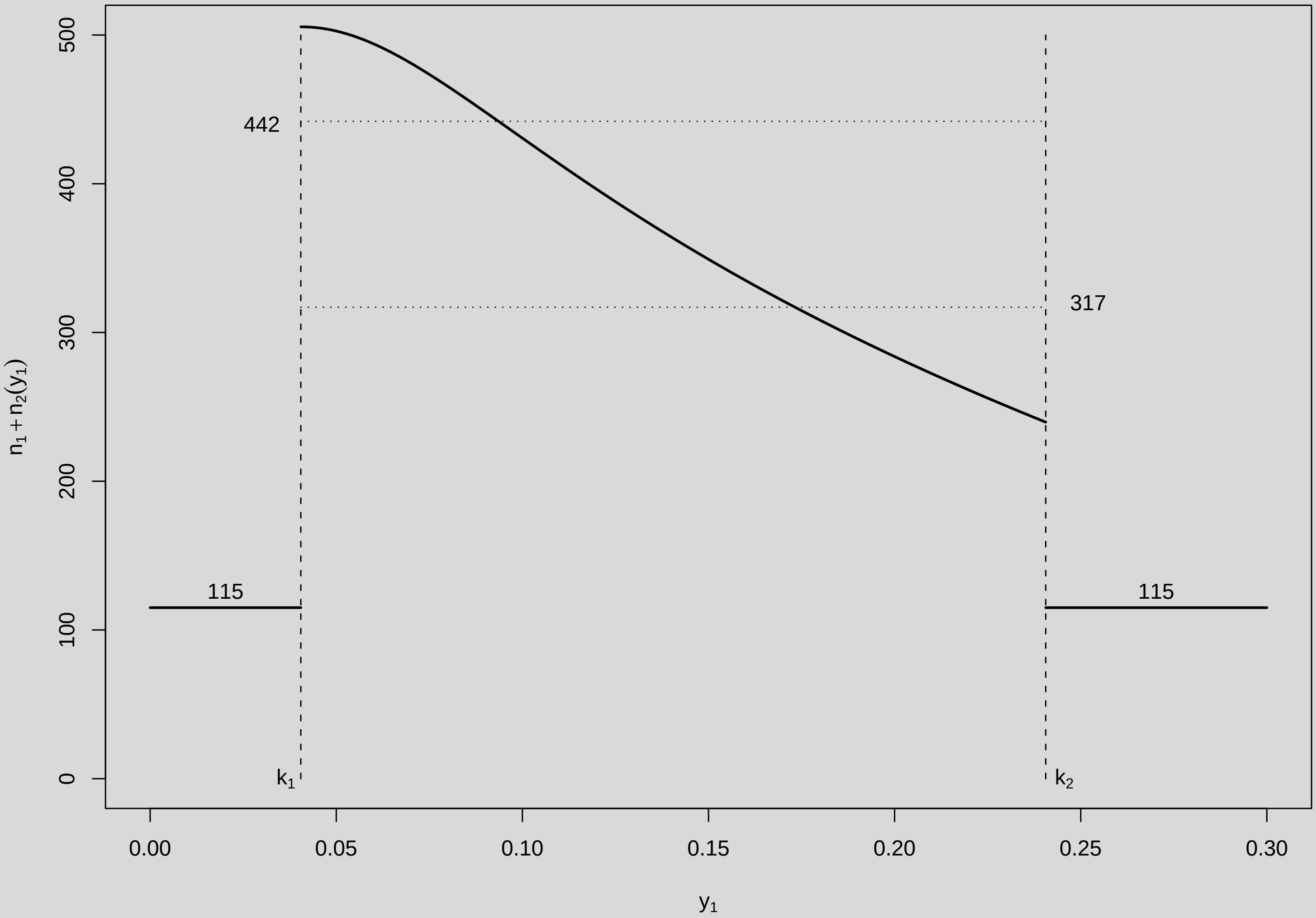


$A(y_1, \xi)$



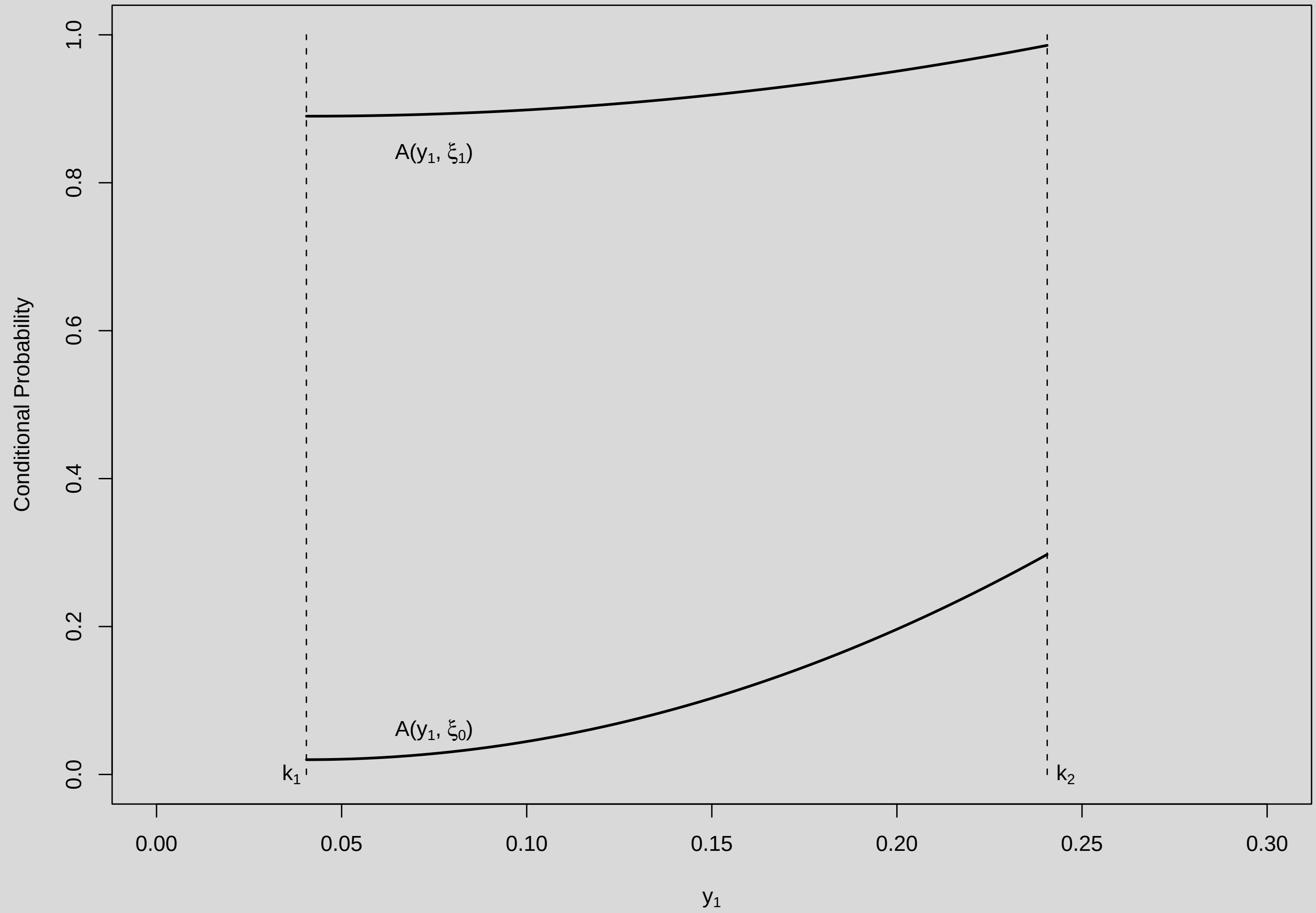
A(y1, ξ1)
A(y1, ξ0)
k1
k2
Conditional Probability
0.0
0.2
0.4
0.6
0.8
1.0
0.00
0.05
0.10
0.15
0.20
0.25
0.30
y1

$n_1 + n_2(y_1)$



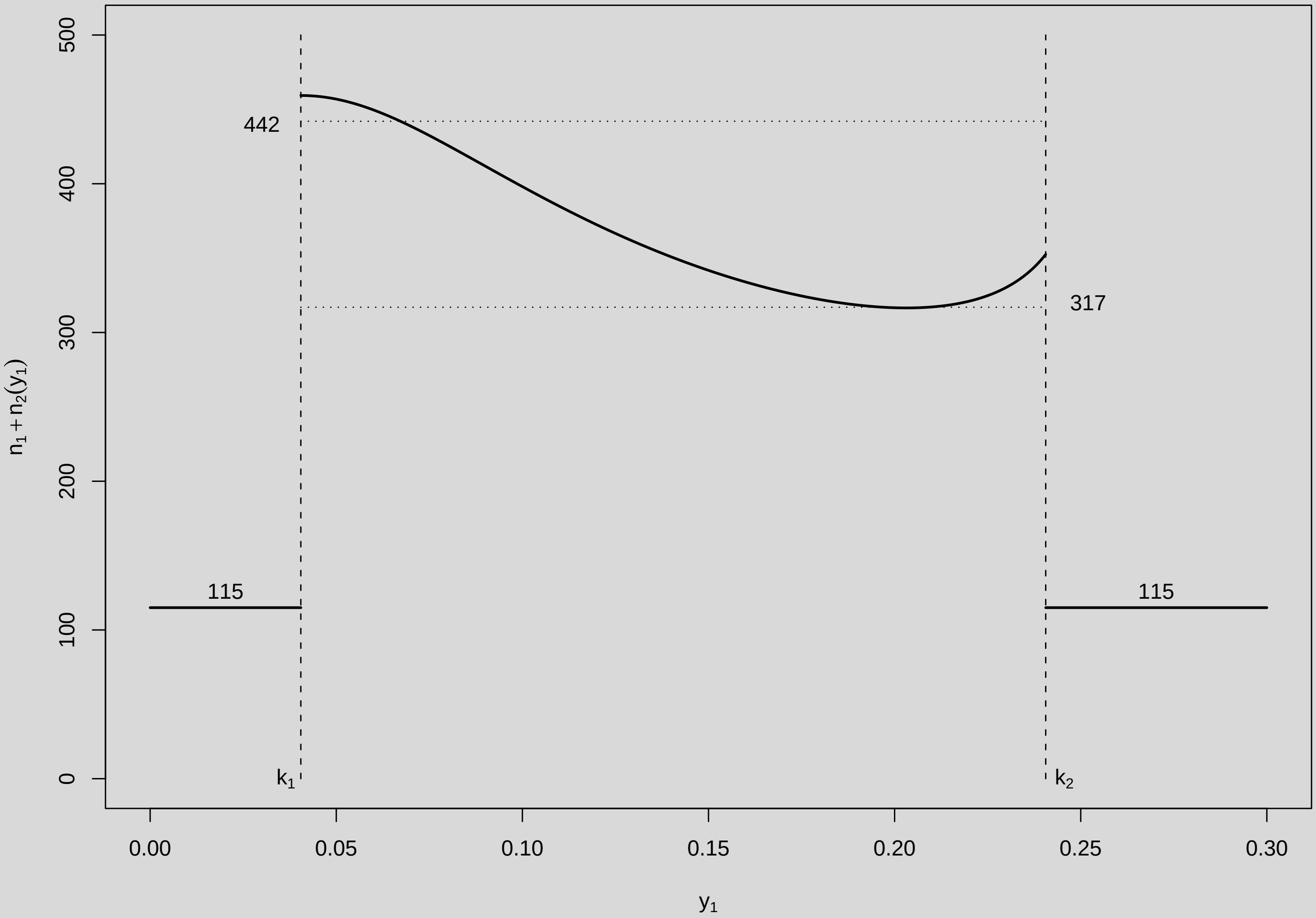
500
400
300
200
100
0
442
317
115
115
k_1
k_2
0.00
0.05
0.10
0.15
0.20
0.25
0.30
$n_1+n_2(y_1)$
y_1

$A(y_1, \xi)$



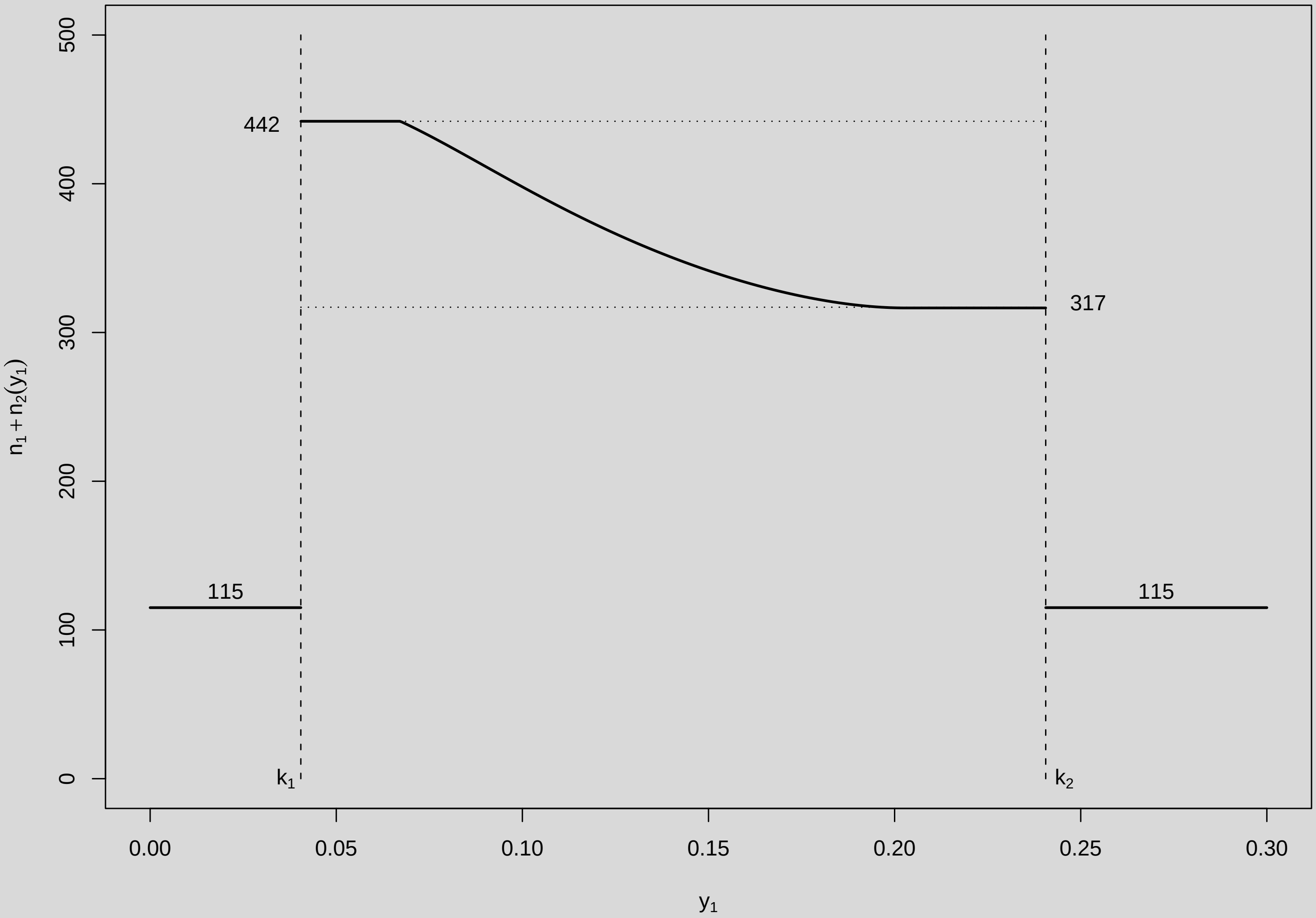
Conditional Probability
1.0
0.8
0.6
0.4
0.2
0.0
A(y1, ξ1)
A(y1, ξ0)
k1
k2
0.00
0.05
0.10
0.15
0.20
0.25
0.30
y1

$n_1 + n_2(y_1)$



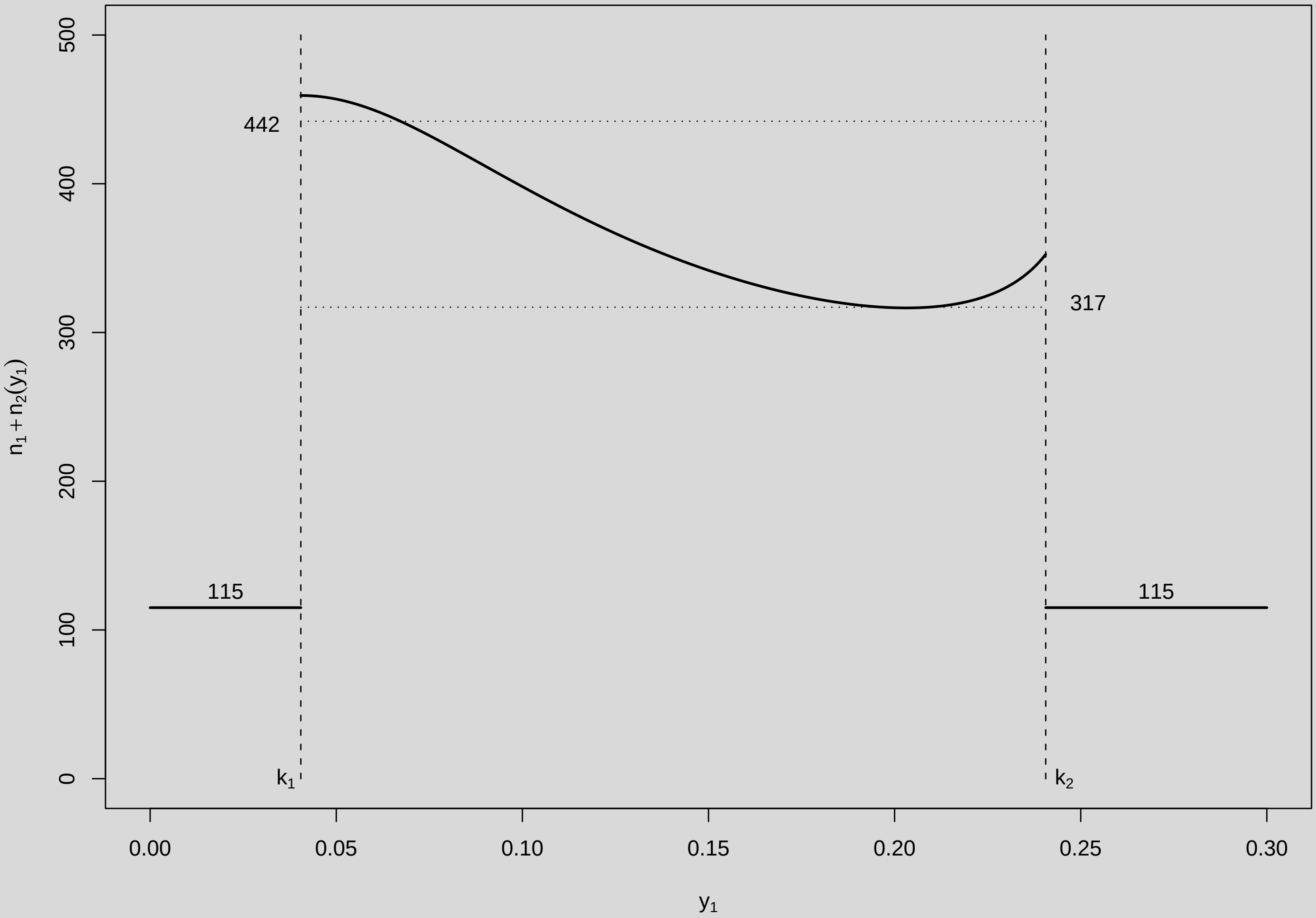
500
400
300
200
100
0
$n_1+n_2(y_1)$
442
317
115
115
k_1
k_2
0.00
0.05
0.10
0.15
0.20
0.25
0.30
y_1

$n_1 + n_2(y_1)$



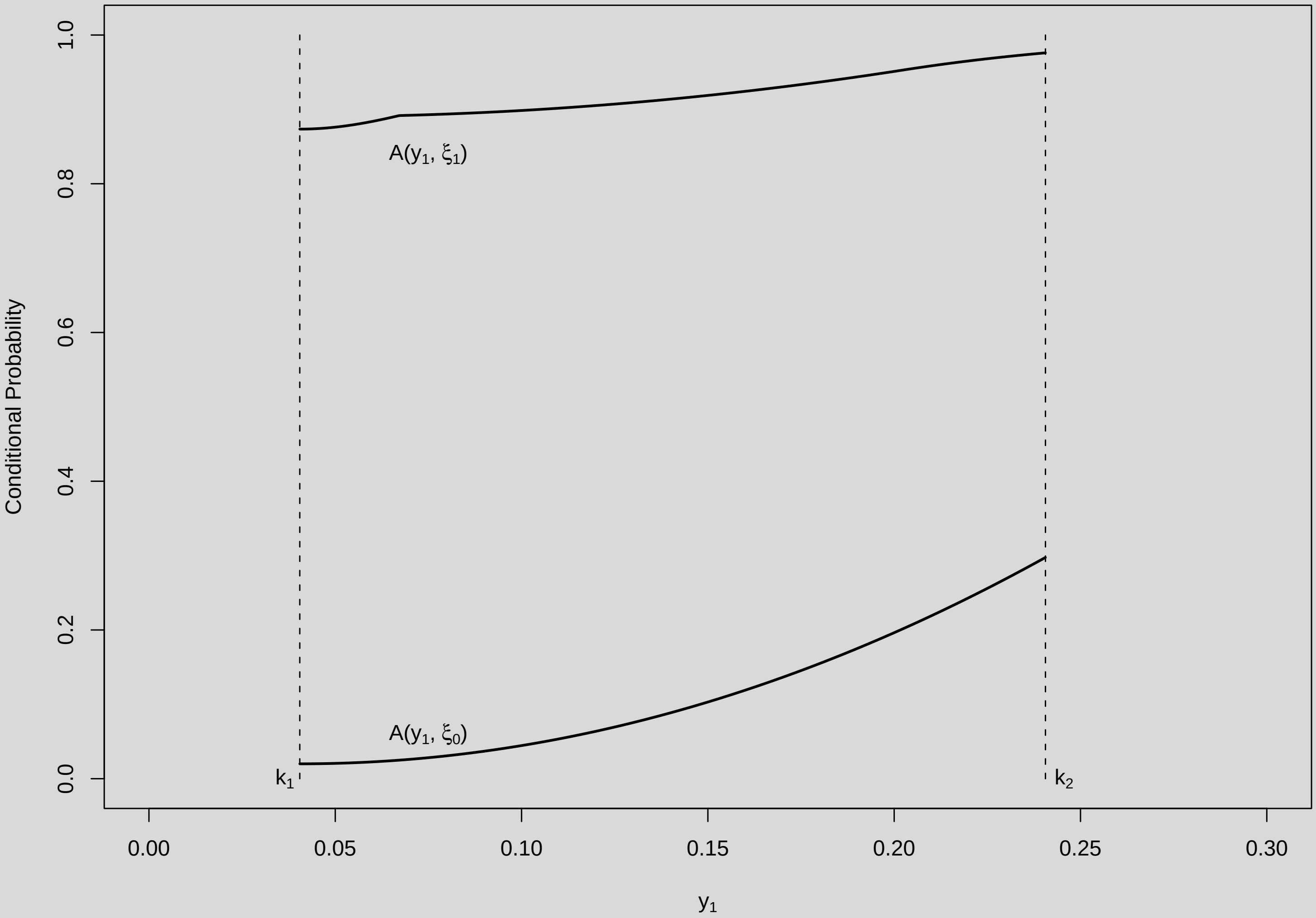
442
317
115
115
k1
k2
0
100
200
300
400
500
0.00
0.05
0.10
0.15
0.20
0.25
0.30
n1+n2(y1)
y1

$n_1 + n_2(y_1)$



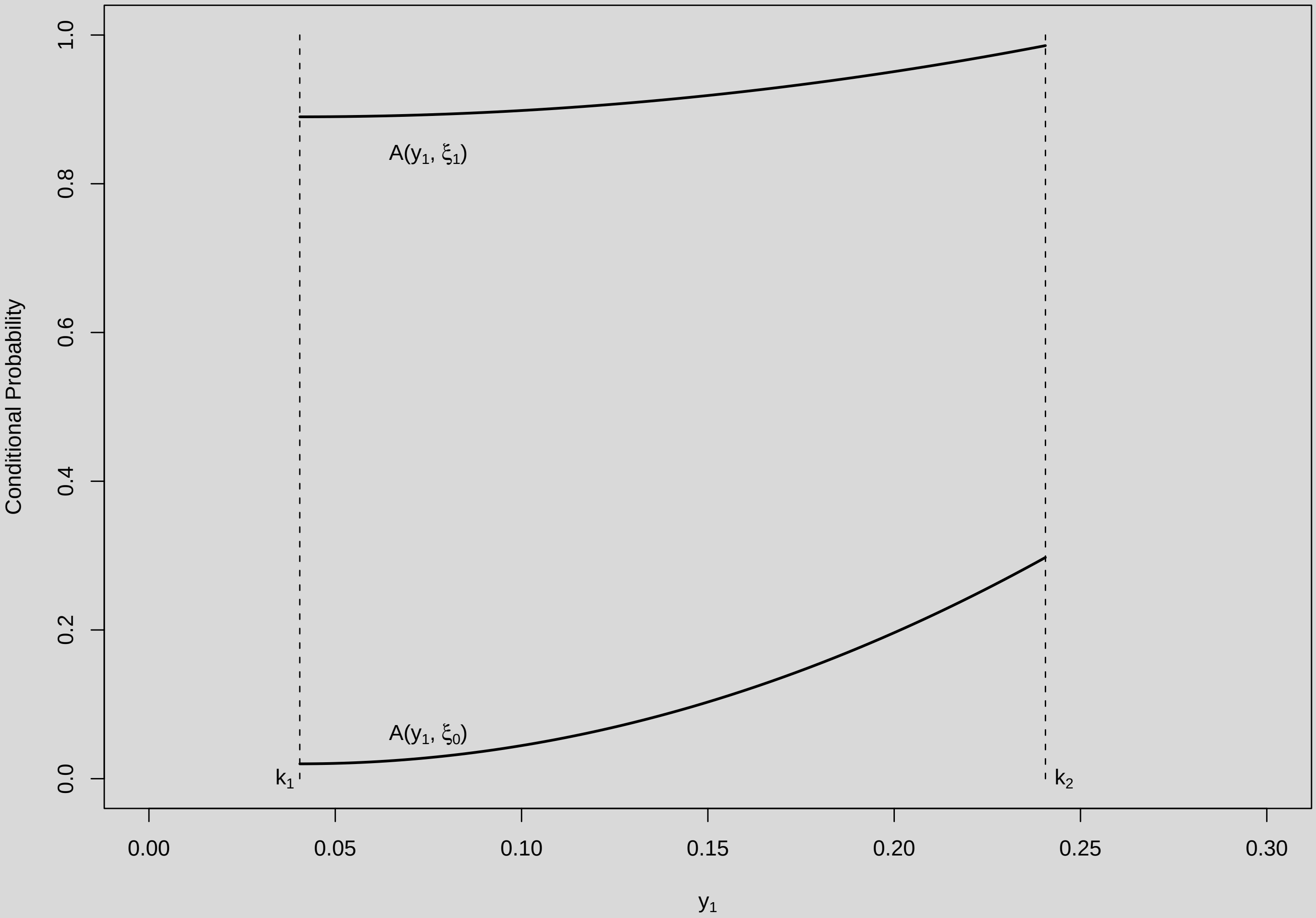
500
400
300
200
100
0
$n_1+n_2(y_1)$
442
317
115
115
k_1
k_2
0.00
0.05
0.10
0.15
0.20
0.25
0.30
y_1

$A(y_1, \xi)$



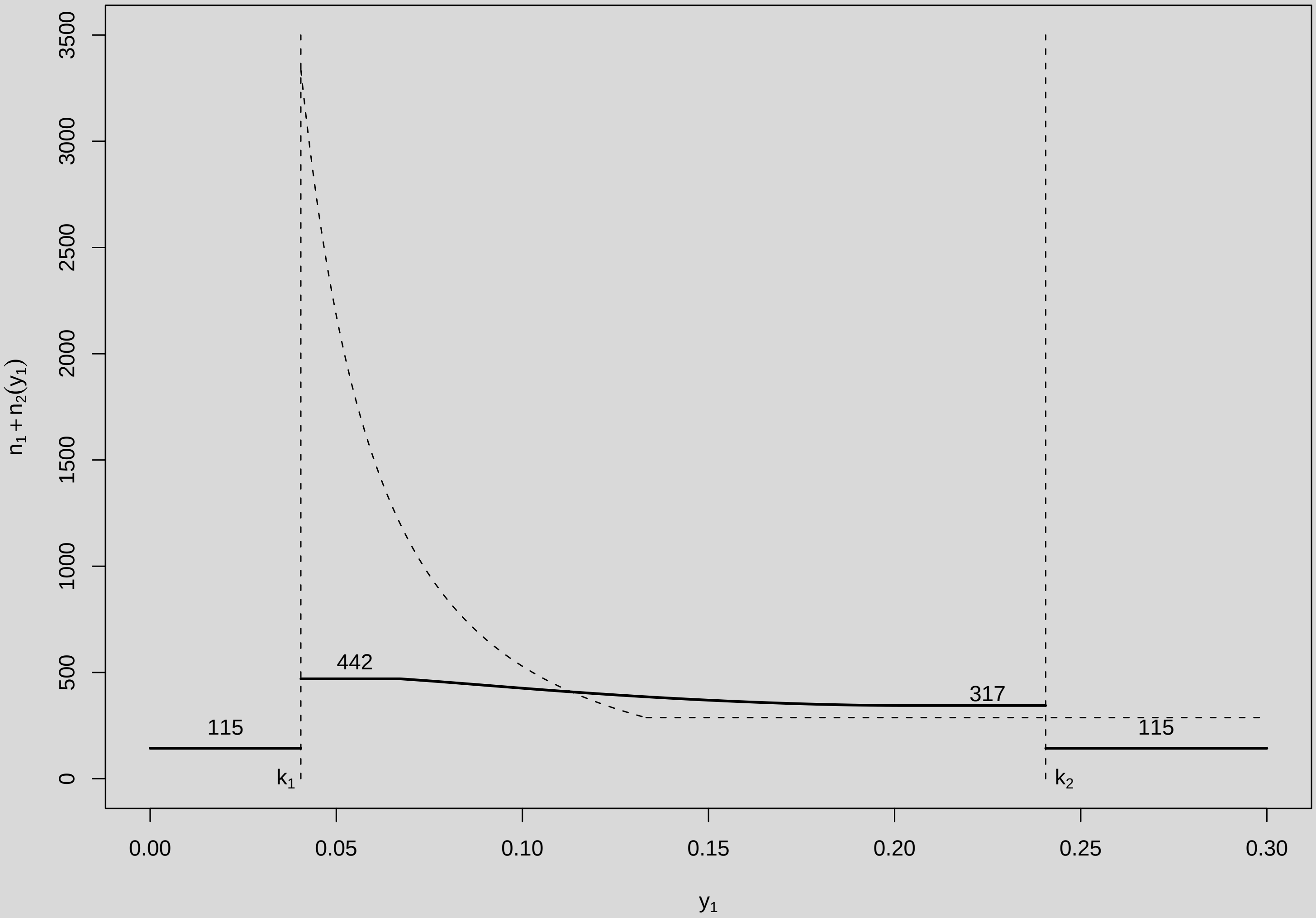
Conditional Probability
0.0
0.2
0.4
0.6
0.8
1.0
A(y1, ξ1)
A(y1, ξ0)
k1
k2
0.00
0.05
0.10
0.15
0.20
0.25
0.30
y1

$A(y_1, \xi)$



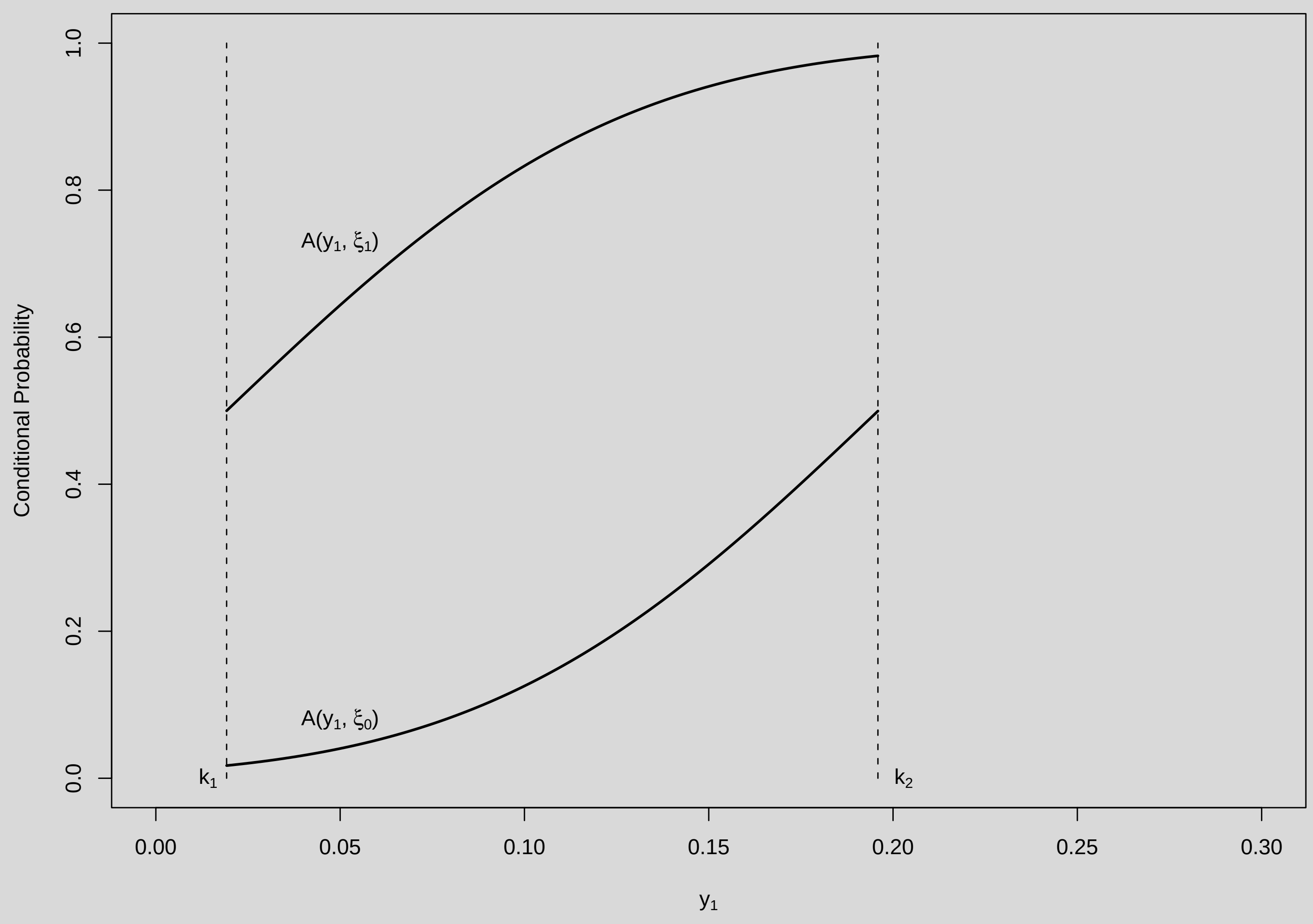
Conditional Probability
0.0
0.2
0.4
0.6
0.8
1.0
A(y1, ξ1)
A(y1, ξ0)
k1
k2
0.00
0.05
0.10
0.15
0.20
0.25
0.30
y1

$n_1 + n_2(y_1)$



$n_1+n_2(y_1)$
0
500
1000
1500
2000
2500
3000
3500
0.00
0.05
0.10
0.15
0.20
0.25
0.30
y_1
115
442
317
115
k_1
k_2

$A(y_1, \xi)$


1.0
0.8
0.6
0.4
0.2
0.0
Conditional Probability
A(y1, ξ1)
A(y1, ξ0)
k1
k2
0.00
0.05
0.10
0.15
0.20
0.25
0.30
y1