Curtailed two-stage designs with bivariate binary endpoints in phase II clinical trials

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Outlines

- Background
- Motivation
- Goal
- Literature Review
- Extension
Background

Phase II clinical trials

**Goal:** to evaluate the clinical activity $p_r$ safety

**Response:** Binary responses

- Univariate activity $X_r$
- Bivariate
  - Activity $X_r$
  - Safety $X_t$

**Hypothesis:** Univariate

\[ H_0 : p_r = p_{r0} \text{ v.s. } H_1 : p_r = p_{r1} (> p_{r0}) \]

**Bivariate**

\[ H_0 : p_r \leq p_{r0} \text{ or } p_t \geq p_{t0} \text{ v.s. } H_1 : p_r > p_{r0} \text{ and } p_t < p_{t0} \]
Background

Data collection: Designs

Univariate binary responses

Simon (1989)

Herrmann/ Szatrowski (1985)

Chi/Chen (2008)
Background

\[ X_r < r \quad \text{Stop declare ineffective} \]

\[ X_r \geq r \quad \text{Stop declare effective} \]
Background

Simon's two-stage design

Stage 1

$X_{r_1} < r_1$

Stop declare ineffective

Stage 2

$X_{r_1} + X_{r_2} < r_2$

Stop declare ineffective

$X_{r_1} + X_{r_2} \geq r_2$

$X_{r_1} \geq r_1$
Example: Simon’s design parameter

\[(n_1, r_1, n_2, r_2) = (18, 5, 15, 11)\]

The need for a design to make a decision just based on currently recruited and treated patients with known results
Motivation

The need for a design to shorten the drug development process

if the investigator can stop the trial and claims the treatment to be effective or non-effective as early, as the number of responses based on currently recruited and treated patients with known results reaches the critical point before a predetermined number of patients have been treated.
However, the total number of items or subjects to be observed may be too large to be able to observe the required number of responses. Therefore, inverse binomial sampling was modified by setting an upper bound on the total number of subjects to be observed.
Review: Phatak and Bhatt (1967)
Curtailed sampling procedure

When the accrual rate is low, it can speed development of drug.
Review: Herrmann/ Szatrowski (1985)

Univariate

Recruit patient Therapy

Observe $r_1 + r_2$

$\mathrm{if} \ r_1 < \rho$ then observe $r_2$

$\mathrm{if} \ r_2 < \rho$ then stop and declare ineffective

$\mathrm{if} \ r_2 \geq \rho$ then stop and declare effective

no response response

Univariate Review: Herrmann/ Szatrowski (1985)

curtailed single-stage design
Review Chi/Chen (2008)

Univariate:

Stage 1 Therapy

Observe \( n_1 - r_1 + 1 \) non-responses

Stop and declare ineffective

Observe \( r_1 \) responses

Stage 2 Therapy

Observe \( n_1 + n_2 - r_2 + 1 \) non-responses

Observe \( r_2 \) responses

Stop and declare ineffective

Stop and declare effective

Univariate:

Review Chi/Chen (2008) curtailed two-stage design
Comparison results

\[ E_S(N \mid p) \quad \text{expected sample size of Simon} \]
\[ E_C(N \mid p) \quad \text{expected sample size of curtailed} \]

\[ RS(\%) = \frac{E_S(N \mid p) - E_C(N \mid p)}{E_S(N \mid p)} \times 100\% \]

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<th>( n_1 )</th>
<th>( r_1 )</th>
<th>( n )</th>
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Goal

Data collection: Designs
Bivariate binary responses

Single-stage design: Conaway and Petroni’s design (1995)
Two-stage design: Conaway and Petroni’s design (1995)
Curtailed single-stage designs: ?
Curtailed two-stage designs: ?
Conaway and Petroni’s design (1995)

Single-stage design: bivariate binary responses

\[ H_0 : p_r \leq p_{r_0} \text{ or } p_t \geq p_{t_0} \]
\[ H_1 : p_r > p_{r_0} \text{ and } p_t < p_{t_0} \]

The critical region is based on intersection union test:

\[ \{ (X_r, X_t) \mid X_r \geq r, X_t < t \} \]

**Single Stage**

\[ n \text{ patients fixed} \]

- \[ X_r < r \]
  - or \[ X_t \geq t \]
    - Stop declare ineffective

- \[ X_r \geq r \]
  - and \[ X_t < t \]
    - Stop declare effective
Review

Conaway and Petroni’s design (1995)

Single-stage design: bivariate binary responses

Error requirements

- Conaway and Petroni’s design (1995)
  
  (i) \( P(X_r \geq r, X_t < t \mid p_r = p_{r0}, p_t = p_{t0}, \phi) \leq \alpha \)
  
  (ii) \( \max_{p_r, p_t \in H_0} P(X_r \geq r, X_t < t \mid p_r, p_t, \phi) \leq \delta \)
  
  (iii) \( P(X_r \geq r, X_t < t \mid p_r = p_{r1}, p_t = p_{t1}, \phi) \geq 1 - \beta \)

- Jin’s design (2007)
  
  (i’) \( P(X_r \geq r, X_t < t \mid p_r = p_{r0}, p_t = 0) \leq \alpha_1 \)
  
  (ii’) \( P(X_r \geq r, X_t < t \mid p_r = 1, p_t = p_{t0}) \leq \alpha_2 \)
  
  (iii’) \( P(X_r \geq r, X_t < t \mid p_r = p_{r1}, p_t = p_{t1}, \phi) \geq 1 - \beta \)
Conaway and Petroni’s design (1995)

Two-stage design: bivariate binary responses

Stage 1
fixed $n_1$

$X_{r1} < r_1$

or $X_{t1} \geq t_1$

declare ineffective or unsafe

Stage 2
fixed $n_2$

$X_{r1} \geq r_1$

and $X_{t1} < t_1$

$X_{r1} + X_{r2} < r_2$

or $X_{t1} + X_{t2} \geq t_2$

declare ineffective or unsafe

$X_{r1} + X_{r2} \geq r_2$

and $X_{t1} + X_{t2} < t_2$

declare Effective and safe
Extension curtailed two-stage design bivariate binary responses

Stage 1

therapy

The maximum Sample size is $n_1$

Stage 2

no

response toxicity
response no toxicity
no response toxicity
no response no toxicity

no

observe $n_1 - r_1 + 1$ non-responses or $t_1$ toxicity side effects

yes declared ineffective or unsafe

observe $\geq r_1$ responses and $\geq n_1 - t_1 + 1$ no toxicity side effects

yes
Extension curtailed two-stage design bivariate binary responses

Stage 2

therapy

The maximum Sample size is \( n = n_1 + n_2 \)

no

response toxicity

no response toxicity

response no toxicity

no response no toxicity

observe \( n - r_2 + 1 \) non-responses or \( t_2 \) toxicity side effects

yes

declared ineffective or unsafe

observe \( \geq r_2 \) responses and \( \geq n - t_2 + 1 \) no toxicity side effects

yes

declared effective and safe
Extension Comparison results

Conditions:

- maximum type I error rate = 0.05
- power = 0.8
- \( p_{to} = 0.30 \)
- \( p_{t1} = 0.15 \)
- \( \phi = 2 \)

\[ E_{BC}(N \mid p) \] expected sample size of curtailed

\[ E_{CP}(N \mid p) \] expected sample size of C/P

\[
RS(\%) = \frac{E_{CP}(N) - E_{BC}(N)}{E_{CP}(N)} \times 100\%
\]

relative percentage of expected sample size savings
## Extension

Comparison results

\( E_{CP}(N \mid p) \) expected sample size of C/P

\( E_{BC}(N \mid p) \) expected sample size of curtailed

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<th>( r_1 )</th>
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The curtailed two-stage design allows early termination of a trial when a treatment is either very effective or very ineffective.

The curtailed two-stage design is recommended to apply when the patient accrual rate is very slow.
The end

Thanks for your attention
**Review** Chi/Chen (2008)

Univariate:

Stage 1 Therapy

Observe $n_1 - r_1 + 1$ non-responses

- yes: Stop and declare ineffective
- no: Observe $r_1$ responses

Stage 2 Therapy

Observe $n_1 + n_2 - r_2 + 1$ non-responses

- yes: Stop and declare effective
- no: Observe $r_2$ responses

Univariate: Review Chi/Chen (2008) curtailed two-stage design
Background

Simon's two-stage design

- If $X_{r_1} < r_1$, stop and declare ineffective.
- If $X_{r_1} + X_{r_2} < r_2$, stop and declare ineffective.
- If $X_{r_1} \geq r_1$, continue to the next stage.
- If $X_{r_1} + X_{r_2} \geq r_2$, stop and declare effective.
Extension
Bivariate single-stage design

\[ H_0 : p_r \leq p_{r0} \text{ or } p_t \geq p_{t0} \quad H_1 : p_r > p_{r0} \text{ and } p_t < p_{t0} \]

Intersection union test

The critical region

\[ = \{ (X_r, X_t) | X_r \geq r, X_t < t \} \]

\[ P(X_r \geq r, X_t < t \mid p_r, p_t, \phi) \leq \min\{P(X_r \geq r \mid p_r), P(X_t < t \mid p_t)\} \]

since

\[ P(X_r \geq r \mid p_r) = P(X_r \geq r, X_t < t \mid p_r, p_t = 0) \]

\[ P(X_t < t \mid p_t) = P(X_r \geq r, X_t < t \mid p_r = 1, p_t) \]
Review

Comparison results

\[ E_S(N \mid p) \quad \text{expected sample size of Jin} \]
\[ E_C(N \mid p) \quad \text{expected sample size of curtailed} \]

\[ RS(\%) = \frac{E_S(N \mid p) - E_C(N \mid p)}{E_S(N \mid p)} \times 100 \% \]
two endpoints of interest as **response** and **toxicity side effect**.

\[
\begin{array}{c|c|c}
\text{Toxicity} & X_{11} = \min(0, X_r + X_t - n), K & \min(X_r, X_t) \\
\hline
\text{yes} & X_{11}(p_{11}) & X_{12}(p_{12}) \\
\hline
\text{no} & X_{21}(p_{21}) & X_{22}(p_{22}) \\
\end{array}
\]

\(X_r(p_r)\) is known.

\(X_t(p_t)\) is known.

\(X_{11} + X_{12} + X_{21} + X_{22} = n\)

\((X_{11}, X_{12}, X_{21}, X_{22}) \sim \text{Multinomial}(n, p_{11}, p_{12}, p_{21}, p_{22}), \quad p_{11} + p_{12} + p_{21} + p_{22} = 1\)

\(X_r \sim B(n, p_r)\) and \(X_t \sim B(n, p_t)\)
Bivariate single-stage design
Errors requirement

- Conaway and Petroni’s design (1995)
  (i) \( P(X_r \geq r, X_t < t \mid p_r = p_{r0}, p_t = p_{t0}, \phi) \leq \alpha \)
  (ii) \( \max_{p_r, p_t \in H_0} P(X_r \geq r, X < t \mid p_r, p_t, \phi) \leq \delta \)

- Jin’s design (2007)
  (i’) \( P(X_r \geq r, X_t < t \mid p_r = p_{r0}, p_t = 0) \leq \alpha_1 = \delta \)
  (ii’) \( P(X_r \geq r, X_t < t \mid p_r = 1, p_t = p_{t0}) \leq \alpha_2 = \delta \)

\[ \max_{p_r, p_t \in H_0} P(X_r \geq r, X_t < t \mid p_r, p_t, \phi) \leq \delta \]
\[ \max\{P(X_r \geq r \mid p_r = p_{r0}), P(X_t < t \mid \phi, p_t = p_{t0})\} \leq \delta \]
\[ P(X_r \geq r, X_t < t \mid p_r = p_{r1}, p_t = p_{t1}, \phi) \geq 1 - \beta \]
Motivation

Phase II clinical trials

- Goal: to evaluate the clinical activity and safety

Univariate \( \Rightarrow \) Simon’s design (1989)

\[ H_0 : p = p_0 \ v.s. \ H_1 : p = p_1 (> p_0) \]

Bivariate \( \Rightarrow \) Conaway and Petroni’s design (1995)

Jin’s design (2007)

\[ H_0 : p_r \leq p_{r0} \text{ or } p_t \geq p_{t0} \ v.s. \ H_1 : p_r > p_{r0} \text{ and } p_t < p_{t0} \]
Univariate curtailed two-stage design probability and expectation

Stage 1

Therapy

Observe \( n_1 - r_1 + 1 \) non-responses

\[ y_1 = n_1 - r_1 + 1, K, n_1 \]

Stop and declare ineffective

\[ P(Y_1 = y_1) = \binom{y_1 - 1}{n_1 - r_1} p^{y_1 - n_1 + r_1 - 1} (1 - p)^{n_1 - r_1 + 1} \]

\[ E_1(Y_1 = y_1) = \sum_{y_1 = r_1}^{n_1} y_1 \binom{y_1 - 1}{n_1 - r_1} p^{y_1 - n_1 + r_1 - 1} (1 - p)^{n_1 - r_1 + 1} \]

Observe \( r_1 \) responses

\[ y_1 = r_1, K, n_1 \]

Moves to stage 2

\[ P(Y_1 = y_1) = \binom{y_1 - 1}{r_1 - 1} p^{r_1 - 1} (1 - p)^{y_1 - r_1} \]

\[ E_\mu(Y_1 = y_1) = \sum_{y_1 = r_1}^{n_1} y_1 \binom{y_1 - 1}{r_1 - 1} p^{r_1 - 1} (1 - p)^{y_1 - r_1} \]
Univariate curtailed two-stage design probability and expectation

Given $y_1 = y_1$ and $r_1$ responses are observed in stage 1

$$m = n_1 + n_2 - y_1 - (r_2 - r_1) + 1$$

Stage 2

- **No** non-responses
  - **No** response
    - Observe $n_1 + n_2 - r_2 + 1$ non-responses
    - $y_2 = m, K, n_1 + n_2 - y_1$
    - $P(Y_2 = y_2 | Y_1 = y_1) = \binom{y_2 - 1}{m - 1} p^{n_2 - m} (1 - p)^m$
    - $E_{U,A}(Y_2) = \sum_{y_1 \neq y_1} \binom{y_1 - 1}{r_1 - 1} p^{n_1} (1 - p)^{y_1 - r_1} \sum_{y_2 \neq m} y_2 \binom{y_2 - 1}{m - 1} p^{n_2 - m} (1 - p)^m$

- **Response**
  - Observe $r_2$ responses
    - $y_2 = r_2 - r_1, K, n_1 + n_2 - y_1$
    - $P(Y_2 = y_2 | Y_1 = y_1) = \binom{y_2 - 1}{r_2 - r_1 - 1} p^{n_2 - r_2 + r_1} (1 - p)^{y_2 - r_2 + r_1}$
    - $E_{U,A}(Y_2) = \sum_{y_1 \neq y_1} \binom{y_1 - 1}{r_1 - 1} p^{n_1} (1 - p)^{y_1 - r_1} \sum_{y_2 \neq r_2 - r_1} y_2 \binom{y_2 - 1}{r_2 - r_1 - 1} p^{n_2 - r_2 + r_1} (1 - p)^{y_2 - r_2 + r_1}$

- **Stop and declare ineffective**
Univariate curtailed two-stage design

design parameter

\[ R_C(n_1, r_1, n_2, r_2 \mid p) = \sum_{y_1=r_1}^{n_1} \left\{ \frac{y_1 - 1}{r_1 - 1} p^{r_1} (1 - p)^{y_1 - r_1} \sum_{y_2=r_2-r_1}^{n_1+n_2-r_1} \left( \frac{y_2 - 1}{r_2 - r_1 - 1} p^{r_2-r_1} (1 - p)^{y_2-r_2+r_1} \right) \right\} \]

\[ \Psi = \{ (n_1, r_1, n_2, r_2) \mid R(n_1, r_1, n_2, r_2 \mid p_0) \leq \alpha, R(n_1, r_1, n_2, r_2 \mid p_1) \geq 1 - \beta \} \]

(1) Minimax design

Minimim total sample size \( \phi = \{ (n_1, r_1, n_2, r_2) \mid \min_{\Psi}(n_1 + n_2) \} \)

Minimim expected total sample size \( \min_{\phi} E_C(N \mid p_0) \)

(2) Optimal design

Minimim expected total sample size \( \min_{\Psi} E_C(N \mid p_0) \)

The expected total number of patients

\[ E_C(N \mid p) = E_I(Y_1) + E_{II}(Y_1) + E_{IIR}(Y_2) + E_{IIA}(Y_2) \]
Univariate curtailed two-stage design comparison

**Simon’s two-stage design**

\[
R_S(n_1,r_1,n_2,r_2 \mid p) = \sum_{x_1=r_1}^{n_1} \left( \begin{pmatrix} n_1 \\ x_1 \end{pmatrix} p^{x_1} (1 - p)^{n_1-x_1} \right) \sum_{x_2=\max(r_2-x_1,0)}^{n_2} \left( \begin{pmatrix} n_2 \\ x_2 \end{pmatrix} p^{x_2} (1 - p)^{n_2-x_2} \right)
\]

\[
E_S(N \mid p) = n_1 + n_2 \sum_{x_1=r_1}^{n_1} \left( \begin{pmatrix} n_1 \\ x_1 \end{pmatrix} p^{x_1} (1 - p)^{n_1-x_1} \right)
\]

Under the same design parameters \((n_1,r_1,n_2,r_2)\)

- \(E_C(N \mid p) \leq E_S(N \mid p)\)
- \(R_C(n_1,r_1,n_2,r_2 \mid p) = R_S(n_1,r_1,n_2,r_2 \mid p)\)
Univariate curtailed two-stage design
design parameter (optimal design)

| $P_0$ | $P_1$ | $n_1$ | $r_1$ | $n$ | $r_2$ | $E_c(M|p)$ | $E_c(N|p)$ | $E_c(N|p)$ | $E_c(N|p)$ |
|-------|-------|-------|-------|-----|-------|-------------|-------------|-------------|-------------|
| 0.05  | 0.25  | 9     | 1     | 24  | 3     | 13.74       | 14.55       | 10.99       | 22.87       |
| 0.1   | 0.3   | 12    | 2     | 35  | 6     | 18.53       | 19.84       | 18.45       | 33.04       |
| 0.2   | 0.4   | 22(17)| 6(4)  | 38(37)| 11(11)| 24.17       | 26.02       | 26.15       | 36.07       |
| 0.3   | 0.5   | 22    | 8     | 46  | 18    | 27.27       | 29.89       | 34.25       | 44.39       |
| 0.4   | 0.6   | 18    | 8     | 46  | 23    | 27.13       | 30.22       | 36.47       | 44.39       |
| 0.5   | 0.7   | 21    | 12    | 45  | 27    | 25.29       | 28.96       | 36.71       | 43.38       |
| 0.6   | 0.8   | 11    | 7     | 38  | 27    | 21.19       | 25.38       | 32.10       | 36.64       |
| 0.7   | 0.9   | 9     | 7     | 28  | 23    | 13.99       | 17.79       | 24.27       | 26.99       |
| 0.8   | 0.9   | 6     | 5     | 27  | 23    | 10.59       | 14.82       | 22.48       | 24.60       |

$\alpha, \beta = (0.1,0.1)$

$\alpha, \beta = (0.05,0.2)$

$\alpha, \beta = (0.05,0.1)$
### Univariate curtailed two-stage design design parameter (minimax design)

| $P_0$ | $P_1$ | $n_1$ | $r_1$ | $n_2$ | $r_2$ | $E_c(N|p)$ | $E(N|p)$ | $E_c(N|p)$ | $E(N|p)$ |
|-------|-------|-------|-------|-------|-------|------------|--------|------------|--------|
| 0.05  | 0.25  | 13    | 1     | 20    | 3     | 15.77      | 16.41  | 11.35      | 19.83  |
|       |       | 12    | 1     | 16    | 3     | 13.39      | 13.84  | 10.74      | 15.87  |
|       |       | 15    | 1     | 25    | 4     | 19.53      | 20.37  | 15.29      | 24.87  |
| 0.1   | 0.3   | 11(16)| 1(2)  | 25(25)| 5(5)  | 19.24      | 20.37  | 15.92      | 24.76  |
|       |       | 15    | 2     | 25    | 6     | 18.39      | 19.51  | 18.43      | 24.65  |
|       |       | 18(22)| 2(3)  | 33(33)| 7(7)  | 24.73      | 26.18  | 22.54      | 32.77  |
| 0.2   | 0.4   | 19    | 4     | 36    | 11    | 26.26      | 28.26  | 26.62      | 35.61  |
|       |       | 18    | 5     | 33    | 11    | 20.43      | 22.25  | 25.14      | 31.59  |
|       |       | 24    | 6     | 45    | 14    | 29.02      | 31.23  | 33.70      | 44.16  |
| 0.3   | 0.5   | 26(28)| 7(8)  | 39(39)| 16(16)| 32.02      | 34.99  | 31.36      | 38.93  |
|       |       | 19    | 7     | 39    | 17    | 23.09      | 25.69  | 31.37      | 37.33  |
|       |       | 24    | 8     | 53    | 22    | 33.31      | 36.62  | 42.59      | 52.07  |
| 0.4   | 0.6   | 19(28)| 7(12) | 41(41)| 21(21)| 30.31      | 33.84  | 34.2       | 40.72  |
|       |       | 34    | 18    | 39    | 21    | 28.34      | 34.44  | 33.16      | 38.22  |
|       |       | 29    | 13    | 54    | 28    | 34.06      | 38.06  | 45.33      | 53.18  |
| 0.5   | 0.7   | 15(23)| 7(12) | 39(39)| 24(24)| 27.16      | 31.00  | 33.4       | 38.66  |
|       |       | 16(23)| 8(13) | 37(37)| 24(24)| 23.73      | 27.74  | 32.54      | 36.24  |
|       |       | 24(27)| 13(15)| 53(53)| 33(33)| 31.26      | 36.11  | 45.72      | 52.07  |
| 0.6   | 0.8   | 27    | 19    | 35    | 25    | 22.78      | 28.47  | 30.24      | 34.41  |
|       |       | 13    | 9     | 35    | 26    | 16.63      | 20.77  | 29.52      | 32.82  |
|       |       | 26    | 16    | 45    | 33    | 29.84      | 35.90  | 40.46      | 44.85  |
| 0.7   | 0.9   | 29(16)| 6(12) | 25(25)| 21(21)| 15.26      | 20.05  | 22.65      | 24.85  |
|       |       | 23    | 20    | 26    | 22    | 13.20      | 23.16  | 22.65      | 25.42  |
|       |       | 18    | 14    | 32    | 27    | 17.49      | 22.66  | 29.09      | 31.61  |

For the design parameter $(\alpha, \beta)$:
- $(0.1,0.1)$
- $(0.05,0.2)$
- $(0.05,0.1)$
Univariate curtailed two-stage design comparison

<table>
<thead>
<tr>
<th></th>
<th>Simon</th>
<th>Curtail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sample size</td>
<td>Minimax: Simon’s design equal to Curtailed design.</td>
<td>Minimax: Eight sets from curtailed design are different from Simon’s design.</td>
</tr>
<tr>
<td></td>
<td>Optimal: Simon’s design less than or equal to Curtailed design.</td>
<td>Optimal: Two sets from curtailed design are different from Simon’s design.</td>
</tr>
<tr>
<td>Design parameter</td>
<td>Minimax: Eight sets from curtailed design are different from Simon’s design.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Optimal: Two sets from curtailed design are different from Simon’s design.</td>
<td></td>
</tr>
<tr>
<td>Expected sample size</td>
<td>large</td>
<td>small</td>
</tr>
</tbody>
</table>
Bivariate single-stage design

The joint probability mass function of $X_r$ and $X_t$ is

$$P(X_r = x_r, X_t = x_t) = \sum_{i=\max(0,x_r+x_t-n)}^{\min(x_r,x_t)} \binom{n}{i, x_r-i, x_t-i, n-x_r-x_t+i} p_1^i p_2^{x_r-i} p_2^{x_t-i} p_2^{n-x_r-x_t+i}$$

Dale (1986)

$p_r$ and $p_t$ are known + odds ratio $\phi (\neq 1)$

$$p_{11} = \frac{a - \sqrt{a^2 + b}}{a(\phi - 1)} \quad a = 1 + (\phi - 1)(p_r + p_t)$$

$$b = -4\phi(\phi - 1)p_r p_t$$
Bivariate single-stage design
Decision rules and power function

Decision rules

- if $X_r < r$ or $X_t \geq t$, then the trial is stopped and the drug is declared ineffective or unsafe.
- if $X_r \geq r$ and $X_t < t$, then the trial is stopped and the drug is declared effective and safe.

The power function can be derived

$$P(X_r \geq r, X_t < t \mid p_r, p_t, \phi)$$

$$= \sum_{x_r=r}^{n} \sum_{x_t=0}^{t-1} \sum_{i=\max(0, x_r + x_t - n)}^{\min(x_r, x_t)} \binom{n}{i} x_r - i \quad x_t - i \quad n - x_r - x_t + i \quad p_{11} x_r - i \quad p_{12} x_t - i \quad p_{22}^{n-x_r-x_t+i}$$
Bivariate two-stage design
power function and errors requirement

\[ P(X_{r1} \geq r_1, X_{t1} < t_1, X_{r1} + X_{r2} \geq r_2, X_{t1} + X_{t2} < t_2) \]

\[
= \sum_{x_{r1} = r_1}^{n_1} \sum_{x_{r2} = 0}^{t_1 - 1} \left\{ \min(x_{r1}, x_{t1}) \left( \sum_{i = \max(0, x_{r1} + x_{r2} - n_1)}^{n_1} \left( n_1 x_{r1} - i \right)^{x_{r1} - i} \right) p_{11}^{x_{r1} - i} p_{12}^{x_{r1} - i} p_{21}^{x_{t1} - i} p_{22}^{x_{t1} - i} \right\} \\
\times \sum_{x_{r2} = \max(0, r_2 - x_{r1})}^{n_2} \sum_{x_{t2} = 0}^{t_2 - x_{t1} - 1} \left( \min(x_{r2}, x_{t2}) \left( \sum_{j = \max(0, x_{r2} + x_{t2} - n)}^{n_2} \left( n_2 x_{r2} - j \right)^{x_{r2} - j} \right) p_{11}^{x_{r2} - j} p_{12}^{x_{r2} - j} p_{21}^{x_{t2} - j} p_{22}^{x_{t2} - j} \right) \}
\times p_{11}^{x_{r2} - j} p_{12}^{x_{r2} - j} p_{21}^{x_{t2} - j} p_{22}^{x_{t2} - j + 1} \}
\]

Errors requirement

\[ \max \{ P(X_{r1} \geq r_1, X_{r1} + X_{r2} \geq r_2 \mid p_r = p_r_1, p_t = p_{t1}, \phi) \} \geq 1 - \beta \]
Bivariate curtailed sampling procedure

How to shorten the experiment duration?

Bivariate curtailed sampling procedure

- response and toxicity \((p_{11})\)
- response and no toxicity \((p_{12})\)
- no response and toxicity \((p_{21})\)
- no response and no toxicity \((p_{22})\)

\[
\begin{align*}
Y & \text{ patients} \\
n & \text{ patients} \\
\text{ineffective or unsafe} & \text{ observe } X_r < r \text{ or } X_i \geq t \\
\text{effective and safe} & \text{ observe } X_r \geq r \text{ and } X_i < t
\end{align*}
\]
Individual (the drug is declared effective and safe)

Effective: The trial is stopped if $r$ responses are observed

Safe: The trial is stopped if $n-t+1$ no toxicity are observed

The required numbers of patients are difference

(A) There are exactly $r$ responses and $n-t+1$ no toxicity

(B) There are more than $r$ responses and exactly $n-t+1$ no toxicity

(C) There are exactly $r$ responses and more than $n-t+1$ no toxicity

◆ the drug is declared effective and safe
Individual (the drug is declared ineffective or unsafe)

Ineffective: The trial is stopped if \( n-r+1 \) no responses are observed

Unsafe: The trial is stopped if \( t \) toxicity are observed

(D) There are exactly \( n-r+1 \) no responses and \( t \) toxicity

(E) There are exactly \( n-r+1 \) no responses and less than \( t \) toxicity

(F) There are less than \( n-r+1 \) no responses and exactly \( t \) toxicity

\( \text{the drug is declared ineffective or unsafe} \)
Bivariate curtailed single-stage design probability derivation

Among \(y\) currently enrolled patients

\(U(y)\): the number of response \(y - U(y)\): the number of no response

\(V(y)\): the number of toxicity \(y - V(y)\): the number of no toxicity

\[P_y(U(y) = u, V(y) = v)\]

\[
= \sum_{i=\max(0,u+v-y)}^{\min(u,v)} \binom{y}{u-i, v-i, y-u-v+i} p_{11}^i p_{12}^{u-i} p_{21}^{v-i} p_{22}^{y-u-v+i}
\]

To derive probabilities of event (A) to event (F)

- \(P(A) + P(B) + P(C) = P_{\text{reject}}(Y = y)\)
- \(P(D) + P(E) + P(F) = P_{\text{accept}}(Y = y)\)

effective and safe

ineffective or unsafe
Bivariate curtailed single-stage design probability (A)

(A) There are exactly \( r \) responses and \( n-t+1 \) no toxicity

\[
y = \max(r, n-t+1), \ldots, n
\]

\( \begin{align*}
\text{\( r-1 \) responses and \( n-t \) no toxicity} & \quad + \\
\text{\( r \) responses and \( n-t \) no toxicity} & \quad + \\
\text{\( r-1 \) responses and \( n-t+1 \) no toxicity} & \quad + \\
\end{align*} \]

\[
\begin{align*}
&\text{\( P_{Y-1}(U(y-1) = r-1, (y-1) - V(y-1) = n-t) \)} \\
&\text{\( P_{Y-1}(U(y-1) = r-1, V(y-1) = y-n+t-1) \)} \\
&\text{\( P_{Y-1}(U(y-1) = r, (y-1) - V(y-1) = n-t) \)} \\
&\text{\( P_{Y-1}(U(y-1) = r, V(y-1) = y-n+t-1) \)} \\
&\text{\( P_{Y-1}(U(y-1) = r-1, (y-1) - V(y-1) = n-t+1) \)} \\
&\text{\( P_{Y-1}(U(y-1) = r-1, V(y-1) = y-n+t-2) \)} \\
\end{align*}
\]
Bivariate curtailed single-stage design probability (B)

(B) There are more than \( r \) responses and exactly \( n-t+1 \) no toxicity

\[
\begin{align*}
\text{\( y \)} & = \max (r + 1, n - t + 1), K, n \\
\text{(response, no toxicity)} & = p_{12} \\
\text{(any, no toxicity)} & = p_{12} + p_{22} \\
\end{align*}
\]
(C) Bivariate curtailed single-stage design probability (C)

(C) There are exactly \( r \) responses and more than \( n-t+1 \) no toxicity

\[
\begin{align*}
\text{y} & = \max(r, n - t + 2), K, n \\
\sum_{v=0}^{y-n+t-3} P_{Y_{-1}}(U(y-1) = r - 1, V(y-1) = v) & + P_{12} \\
\text{P}_{Y_{-1}}(U(y-1) = r - 1, V(y-1) = y - n + t - 2) & + P_{12} \\
\text{P}_{Y_{-1}}(U(y-1) = r - 1, V(y-1) = y - n + t - 2) & + P_{12} \\
\end{align*}
\]
Bivariate curtailed single-stage design

\[ P_{\text{reject}}(Y = y) \]

The probability of a trial stopping early at \( Y = y \) due to the new therapy being sufficiently effective and safe

\[
P_{\text{reject}}(Y = y) = P(A) + P(B) + P(C)
\]

\[
= P_{Y-1}(U(y-1) = r - 1, V(y-1) = y - n + t - 1)p_{12}
\]

\[
+ \sum_{u=r}^{y-1} P_{Y-1}(U(y-1) = u, V(y-1) = y - n + t - 1)(1 - p_t)I[Y \geq r + 1]
\]

\[
+ \sum_{v=0}^{y-n+t-2} P_{Y-1}(U(y-1) = r - 1, V(y-1) = v)p_r I[Y \geq n - t + 2]
\]

\[ y = \max(r, n - t + 1), K, n \]

\[
P_Y(U(y) = u, V(y) = v) = \sum_{i=\max(0, u+v-y)}^{\min(u,v)} \left( u - i \quad v - i \quad y - u - v + i \right) p_i^{u-i} p_{12}^{v-i} p_{21}^{y-u-v+i} \]
Bivariate curtailed single-stage design probability (D)

(D) There are exactly \( n-r+1 \) no responses and \( t \) toxicity

- \( n-r \) no responses and \( t-1 \) toxicity
  
  \[
  P_{Y-1}((y-1) - U(y-1) = n-r, V(y-1) = t-1) \\
  P_{Y-1}(U(y-1) = y-n+r-1, V(y-1) = t-1)
  \]

\[
y = \max(r, n-t+1), K, n
\]

+ (no response, toxicity)

\[
p_{21}
\]

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Bivariate curtailed single-stage design probability (E)

(E) There are exactly \( n-r+1 \) no responses and less than \( t \) toxicity

\[
\begin{align*}
\text{(y - 1)} \\
\text{n-r no responses and t-1 toxicity} & \quad + \text{(no response, no toxicity)} \\
\mathbb{P}_{Y-1}((y-1) - U(y-1) = n-r, V(y-1) = t-1) & \quad \mathbb{P}_{22} I[Y \geq t] \\
\mathbb{P}_{Y-1}(U(y-1) = y-n+r-1, V(y-1) = t-1) & \quad \mathbb{P}_{22} \\
\text{n-r no responses and less than t-2 toxicity} & + \text{(no response, any)} \\
\min(t-2, y-1) \sum_{y=0}^{\min(t-2, y-1)} \mathbb{P}_{Y-1}(U(y-1) = y-n+r-1, V(y-1) = y) & \quad p_{21} + p_{22} \\
1 - p_r & \quad 1 - p_r \\
y = n - r + 1, K, n
\end{align*}
\]
**Bivariate curtailed single-stage design probability (F)**

(F) There are less than $n-r+1$ no responses and exactly $t$ toxicity

- **$n-r$** no responses and **$t-1$** toxicity: $P_{Y-1}((y-1)-U(y-1)=n-r,V(y-1)=t-1)$
- less than **$n-r-1$** no responses and **$t-1$** toxicity: $P_{Y-1}((y-1)-U(y-1)\leq n-r-1,V(y-1)=t-1)$

$$y = t, K, n$$
The probability of a trial stopping early at $Y = y$ due to the new therapy being not sufficiently effective or safe

$$P_{\text{accept}}(Y = y) = P(D) + P(E) + P(F)$$

$$= P_{Y-1}(U(y - 1) = y - n + r - 1, V(y - 1) = t - 1)(1 - p_{12})I[Y \geq \max(n - r + 1, t)]$$

$$+ \sum_{y=0}^{\min(t-2, y-1)} P_{Y-1}(U(y - 1) = y - n + r - 1, V(y - 1) = v)(1 - p_r)I[Y \geq n - r + 1]$$

$$+ \sum_{u=\max(0, y-r+n)}^{y-1} P_{Y-1}(U(y - 1) = u, V(y - 1) = t - 1)p_iI[Y \geq t]$$

$$y = \min(n - r + 1, t), K , n$$

$$P_Y(U(y) = u, V(y) = v) = \sum_{i=\max(0, u+\gamma-v)}^{\min(u, v)} \binom{y}{u-i, v-i, y-u-v+i} p_{11}^{i} p_{12}^{u-i} p_{21}^{v-i} p_{22}^{y-u-v+i}$$
Bivariate curtailed two-stage design probability and expected sample size

- **Notation:**

  - Among $y_1$ currently enrolled patients at the first stage
    $U_1(y_1)$: the number of response at the first stage
    $V_1(y_1)$: the number of toxicity at the first stage

  - Among $y_2$ currently enrolled patients at the first stage
    $U_2(y_2)$: the number of response at the second stage
    $V_2(y_2)$: the number of toxicity at the second stage
Bivariate curtailed two-stage design probability and expected sample size

◆ Stop at the first stage (declared ineffective or unsafe)

\[ P_1(Y_1 = y_1) \]

\[ = P_{Y_1^{-1}}(U_1(y_1 - 1) = y_1 - n_1 + r_1 - 1, V_1(y_1 - 1) = t_1 - 1)(1 - p_{12})I[Y_1 \geq \max(n_1 - r_1 + 1, t_1)] \]

\[ + \sum_{y_1=0}^{\min(t_1-2,y_1-1)} P_{Y_1^{-1}}(U_1(y_1 - 1) = y_1 - n_1 + r_1 - 1, V_1(y_1 - 1) = v_1)(1 - p_r)I[Y_1 \geq n_1 - r_1 + 1] \]

\[ + \sum_{u_1 = \max(0, y_1 - n_1 + r_1)}^{y_1-1} P_{Y_1^{-1}}(U_1(y_1 - 1) = u_1, V_1(y_1 - 1) = t_1 - 1)p_tI[Y_1 \geq t_1] \]

\[ y_1 = \min(n_1 - r_1 + 1, t_1), K, n_1 \]

\[ E_{BC^{-1}}(Y_1) = \sum_{y_1 = \min(n_1 - r_1 + 1, t_1)}^{n_1} y_1 P_1(Y_1 = y_1) \]

\[ \Rightarrow U_1, V_1, Y_1, n_1, r_1, t_1 \]
Bivariate curtailed two-stage design probability and expected sample size

◆ Continue to the second stage

\[ P_{II}(Y_1 = y_1) = P_{Y_1-1}(U_1(y_1 - 1) = r_1 - 1, V_1(y_1 - 1) = y_1 - n_1 + t_1 - 1)p_{12} \]

\[ + \sum_{u_1 = r_1}^{y_1 - n_1 + t_1 - 2} P_{Y_1-1}(U_1(y_1 - 1) = u_1, V_1(y_1 - 1) = y_1 - n_1 + t_1 - 1)(1 - p_y)I[Y_1 \geq r_1 + 1] \]

\[ + \sum_{v_1 = 0}^{y_1 - n_1 + t_1 - 2} P_{Y_1-1}(U_1(y_1 - 1) = r_1 - 1, V_1(y_1 - 1) = v_1)p_rI[Y_1 \geq n_1 - t_1 + 2] \]

\[ y_1 = \max(r_1, n_1 - t_1 + 1), K, n_1 \]

\[ E_{BC_{-II}}(Y_1) = \sum_{y_1 = \max(r_1, n_1 - t_1 + 1)}^{n_1} y_1 P_{II}(Y_1 = y_1) \]

\[ \Rightarrow U_1, V_1, Y_1, n_1, r, t, Y = y \]

\[ P_{\text{reject}}(Y = y) \]

\[ U, V, Y, n, r, t \]

\[ \Rightarrow U_1, V_1, Y_1, n_1, r_1, t_1 \]
Bivariate curtailed two-stage design probability and expected sample size

Given $Y_1 = y_1, U_1 = u_1$ and $V_1 = v_1$ that observed at the first stage

The maximum sample size is $n_1 + n_2 - y_1$

Required response $m_1 = \max(0, r_2 - u_1)$ and toxicity $m_2 = \max(0, t_2 - v_1)$

◆ Stop at the second stage (declared ineffective or unsafe)

$$P_{II,A}(Y_2 = y_2 | Y_1 = y_1, U_1(y_1) = u_1, V_1(y_1) = v_1) = P_{accept}(Y = y), U, V, Y \Rightarrow U_2, V_2, Y_2$$

$$= P_{Y_2-1}(U_2(y_2 - 1) = y_1 + y_2 - n + m_1 - 1, V_2(y_2 - 1) = m_2 - 1)(1 - p_{12})I[Y_2 \geq \max(n - y_1 - m_1 + 1, m_2)]$$

$$+ \sum_{y_2=0}^{\min(m_1-2, y_2-1)} P_{Y_2-1}(U_2(y_2 - 1) = y_1 + y_2 - n + m_1 - 1, V_2(y_2 - 1) = v_2)(1 - p_r)I[Y_2 \geq n - y_1 - m_1 + 1]$$

$$+ \sum_{u_2=\max(0, y_1 + y_2 - n + m_1)} P_{Y_2-1}(U_2(y_2 - 1) = u_2, V_2(y_2 - 1) = m_2 - 1) p_r I[Y_2 \geq m_2]$$

$$y_2 = \min(n - y_1 - m_1 + 1, m_2), K, n - y_1$$

$$E_{BC_{II,A}}(Y_2) = \sum_{y_1=\max(r_1, m_1 - 1, +1)}^{n_1} \left\{ P_{II}(Y_1 = y_1) \times \sum_{y_2=\min(n - y_1 - m_1 + 1, m_2)}^{n-y_1} y_2 P_{II,A}(Y_2 = y_2 | Y_1 = y_1, U_1(y_1) = u_1, V_1(y_1) = v_1) \right\}^{56}$$
Bivariate curtailed two-stage design probability and expected sample size

Given \( Y_1 = y_1, U_1 = u_1 \) and \( V_1 = v_1 \) that observed at the first stage

The maximum sample size = \( n_1 + n_2 - y_1 \)

Required response \( m_1 = \max(0, r_2 - u_1) \) and toxicity \( m_2 = \max(0, t_2 - v_1) \)

◆ Stop at the second stage (declared effective and safe)

\[
P_{\text{II,R}}(Y_2 = y_2 \mid Y_1 = y_1, U_1(y_1) = u_1, V_1(y_1) = v_1) = P_{\text{accept}}(Y = y), U, V, Y \Rightarrow U_2, V_2, Y_2
\]

\[
P_{Y_2\mid Y_1}(y_2 = m_1 - 1, V_2(y_2 - 1) = y_1 + y_2 - n + m_2 - 1)p_{12}
\]

\[
+ \sum_{u_2 = m_1}^{y_1 + y_2 - n + m_2 - 2} P_{Y_2\mid Y_1}(y_2 = m_1 - 1, V_2(y_2 - 1) = v_2)p_r I[Y_2 \geq m_1 + 1]
\]

\[
y_2 = \max(m_1, n - y_1 - m_2 + 1), K, n - y_1
\]

\[
E_{\text{BC-II,R}}(Y_2) = \sum_{y_1 = \max(r_1, n_1 - r_1 + 1)}^{n_1} \left\{ P_{\text{II}}(Y_1 = y_1) \times \sum_{y_2 = \max(m_1, n - y_1 - m_2 + 1)}^{n_1 - y_1} y_2 P_{\text{II,R}}(Y_2 = y_2 \mid Y_1 = y_1, U_1(y_1) = u_1, V_1(y_1) = v_1) \right\}
\]
Bivariate curtailed two-stage design

The probability of rejecting the null hypothesis

\[ R_{BC}(n_1, r_1, t_1, n_2, r_2, t_2 \mid p_r, p_t, \phi) \]

\[
= \sum_{y_1 = \max(r_1, n_1 - t_1 + 1)}^{n_1} \left\{ \sum_{n-y_1}^{y_1-1} P_{Y_{1,-1}}(U_1(y_1 - 1) = r_1 - 1, V_1(y_1 - 1) = y_1 - n_1 + t_1 - 1) p_{12} \right. \\
\times \left. \sum_{y_2 = \max(m_1, n-y_1 - m_2 + 1)}^{n-y_1} P_{II,R}(Y_2 = y_2 \mid Y_1 = y_1, U_1(y_1) = r_1 - 1, V_1(y_1) = y_1 - n_1 + t_1 - 1) \right\}
\]

\[
+ \sum_{y_1 = \max(r_1 + 1, n_1 - t_1 + 1)}^{n_1} \sum_{u_1 = r_1}^{n-y_1} \left\{ \sum_{y_2 = \max(m_1, n-y_1 - m_2 + 1)}^{n-y_1} P_{Y_{1,-1}}(U_1(y_1 - 1) = u_1, V_1(y_1 - 1) = y_1 - n_1 + t_1 - 1)(1 - p_t) \right. \\
\times \left. \sum_{y_2 = \max(m_1, n-y_1 - m_2 + 1)}^{n-y_1} P_{II,R}(Y_2 = y_2 \mid Y_1 = y_1, U_1(y_1) = u_1, V_1(y_1) = y_1 - n_1 + t_1 - 1) \right\}
\]

\[
+ \sum_{y_1 = \max(r_1, n_1 - t_1 + 2)}^{n_1} \sum_{y_1 - t_1 + 2}^{n-y_1} \left\{ \sum_{v_1 = 0}^{n-y_1} P_{Y_{1,-1}}(U_1(y_1 - 1) = r_1 - 1, V_1(y_1 - 1) = v_1) p_r \right. \\
\times \left. \sum_{y_2 = \max(m_1, n-y_1 - m_2 + 1)}^{n-y_1} P_{II,R}(Y_2 = y_2 \mid Y_1 = y_1, U_1(y_1) = r_1 - 1, V_1(y_1) = v_1) \right\}
\]

\[ E_{BC}(N \mid p) = E_{BC-I}(Y_1) + E_{BC-II}(Y_1) + E_{BC-IIR}(Y_2) + E_{BC-IIA}(Y_2) \]
Bivariate curtailed two-stage design
design parameters

Errors requirement

1. \( R_{BC}(n_1,r_1,t_1,n_2,r_2,t_2 \mid p_r = p_{r0}, p_t = 0) \leq \alpha \)
2. \( R_{BC}(n_1,r_1,t_1,n_2,r_2,t_2 \mid p_r = 1, p_t = p_{t0}) \leq \alpha \)
3. \( R_{BC}(n_1,r_1,t_1,n_2,r_2,t_2 \mid p_r = p_{r1}, p_t = p_{t1}) \geq 1 - \beta \)

Minimax design

Minimim total sample size \( \Phi_{BC} = \{(n_1,r_1,t_1,n_2,r_2,t_2) \mid \min_{\Psi_{BC}}(n_1 + n_2)\} \)

Minimim expected total sample size \( \min_{\Phi_{BC}} E_{C}(N \mid p_0) \)
Bivariate curtailed two-stage design

Design parameters

\[ (p_{r0}, p_{t0}) \]

\[ (1, p_{t0}) \]

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<th>Design parameters</th>
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The maximum type I error rate is specified as 0.05 and the power is specified as 0.8.
Concluding remarks

- The curtailed two-stage design allow early termination of a trial when a treatment is either very effective or very ineffective.

- The curtailed two-stage design is recommended to apply when the patient accrual rate is very slow.

- The curtailed two-stage design is easy to implement in practice since it offers fixed stopping rules at each stage.
Future work

- If there is sufficient evidence of efficacy and safety to make it worth further studying in a phase III clinical trials, how to estimate the treatment effects (efficacy and safety)?

- It is interesting and important to extend the curtailed sampling procedure to a two-stage design with continuous endpoints.

- This dissertation focus on the marginal total numbers of patients observed responses and toxicity side effects to evaluate the efficacy and safety for the bivariate two-stage design. A reasonable inference has to be developed based on the individual cell counts.
The end

Thanks for your attention