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 p_t

Response: Binary responses

Univariate activity X_r

Bivariate { **activity** X_r ; **safety** X_t }

Hypothesis: Univariate

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

Bivariate

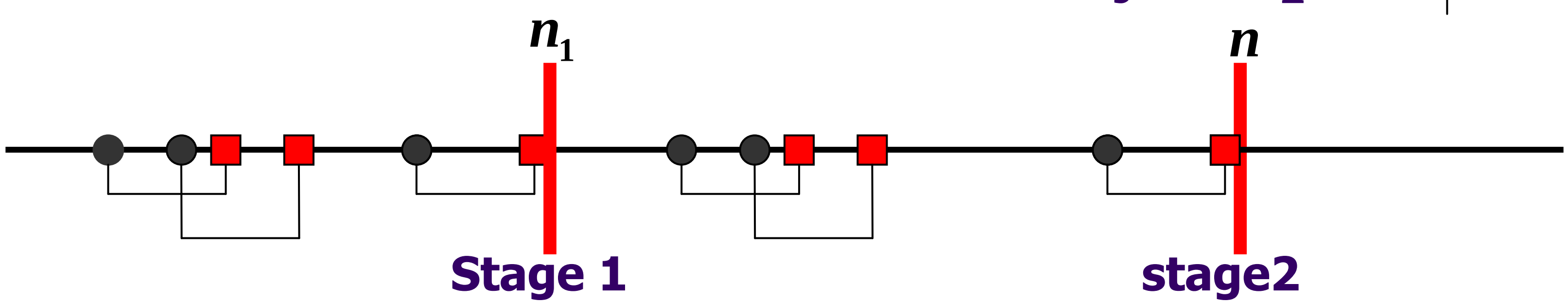
$$H_0 : p_r \le p_{r0} \ or \ \ p_t \ge p_{t0} \ v.s.$$

$$H_1 : p_r > p_{r0} \ and \ \ p_t < p_{t0}$$

Background

Data collection: Designs

Univariate binary responses



● entry time

■ evaluated time

: Simon (1989)

: Herrmann/ Szatrowski (1985)

hi/Chen (2008)

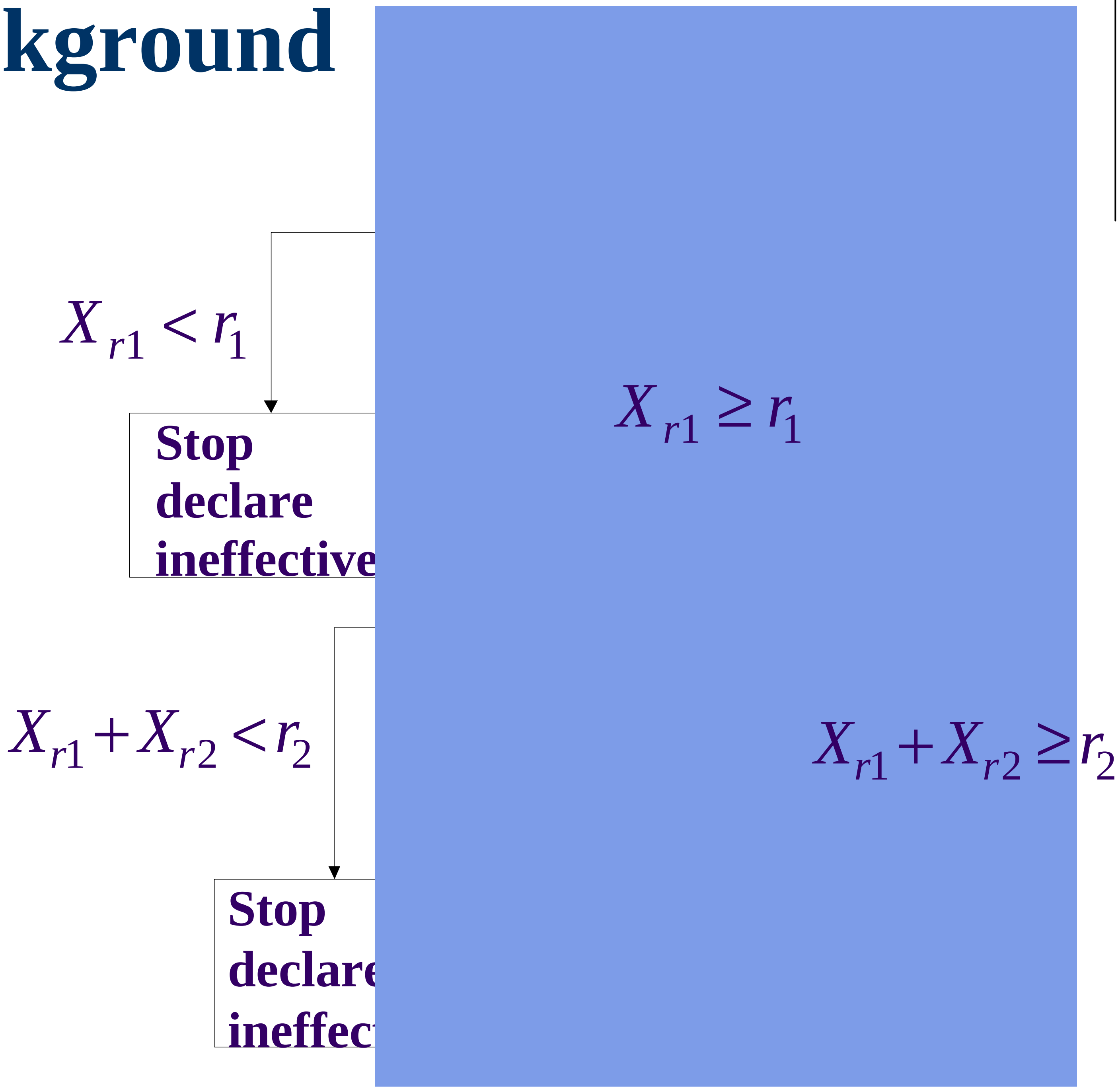
Background

$X_r < r$

$X_r \geq r$

Stop
decl **e**
ineff **ve**

Background



$X_{r1} < r_1$
$X_{r1} \geq r_1$
Stop declare ineffective
$X_{r1} + X_{r2} < r_2$
$X_{r1} + X_{r2} \geq r_2$
Stop declare ineffec

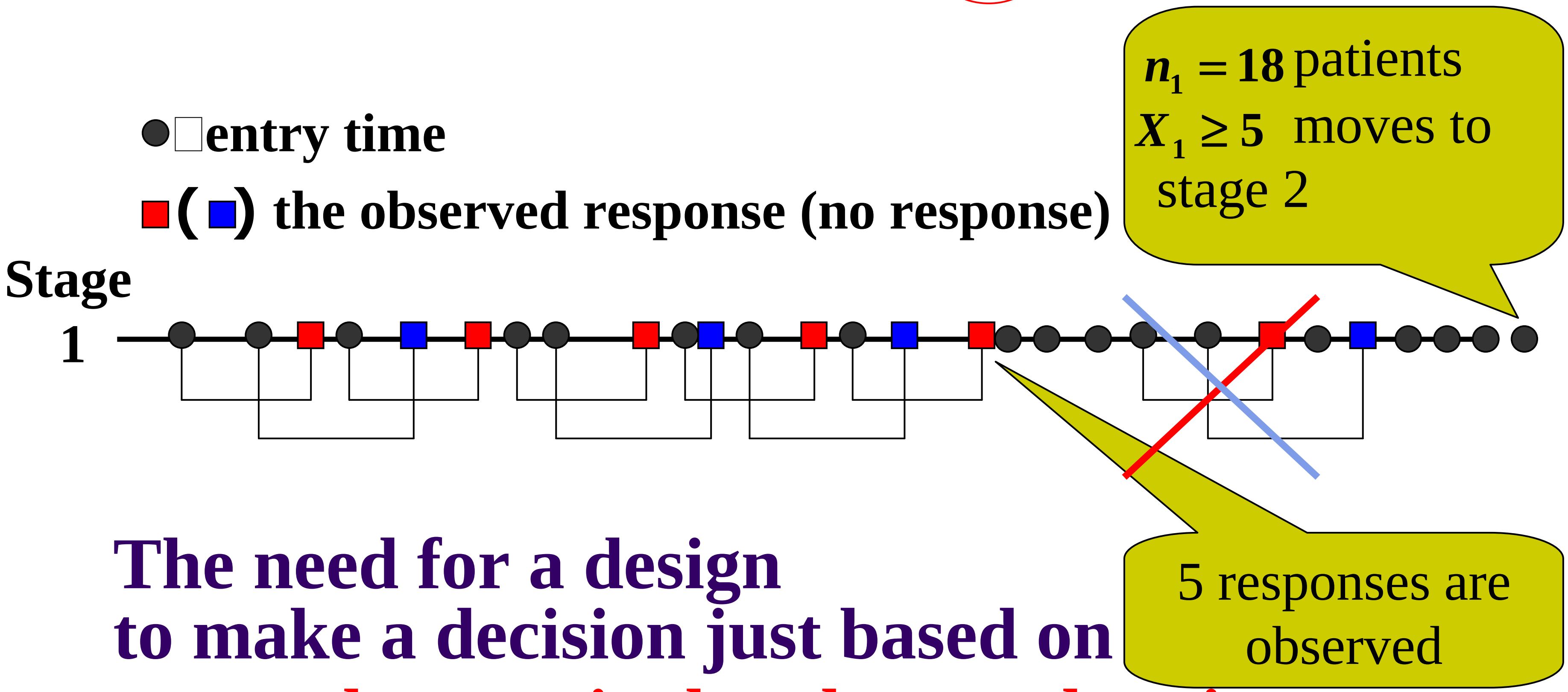
Background

Example: Simon's design parameter

$$(n_1, r_1, n_2, r_2) = (18, 5, 15, 11)$$

●□entry time

■(■) the observed response (no response)



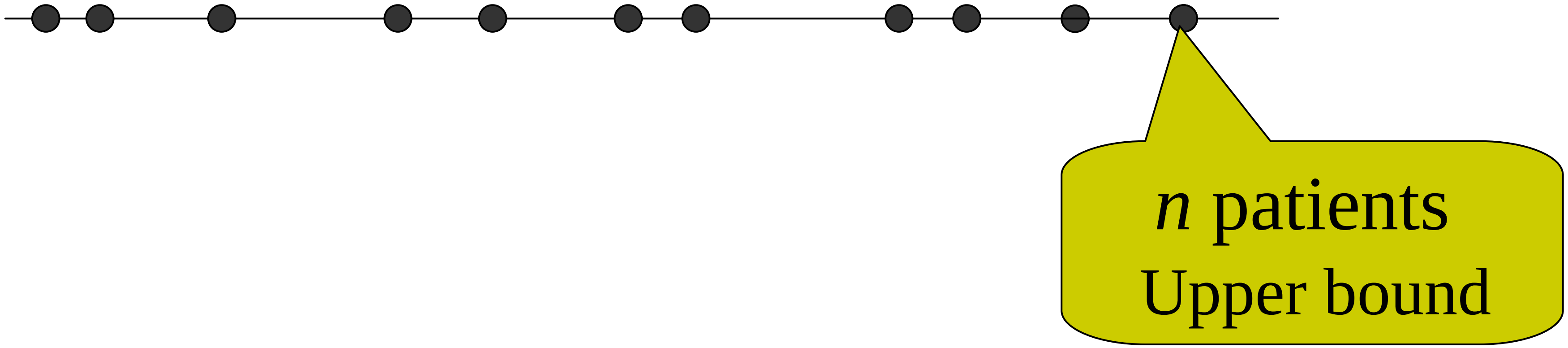
The need for a design to make a decision just based on currently recruited and treated patients with known results

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.

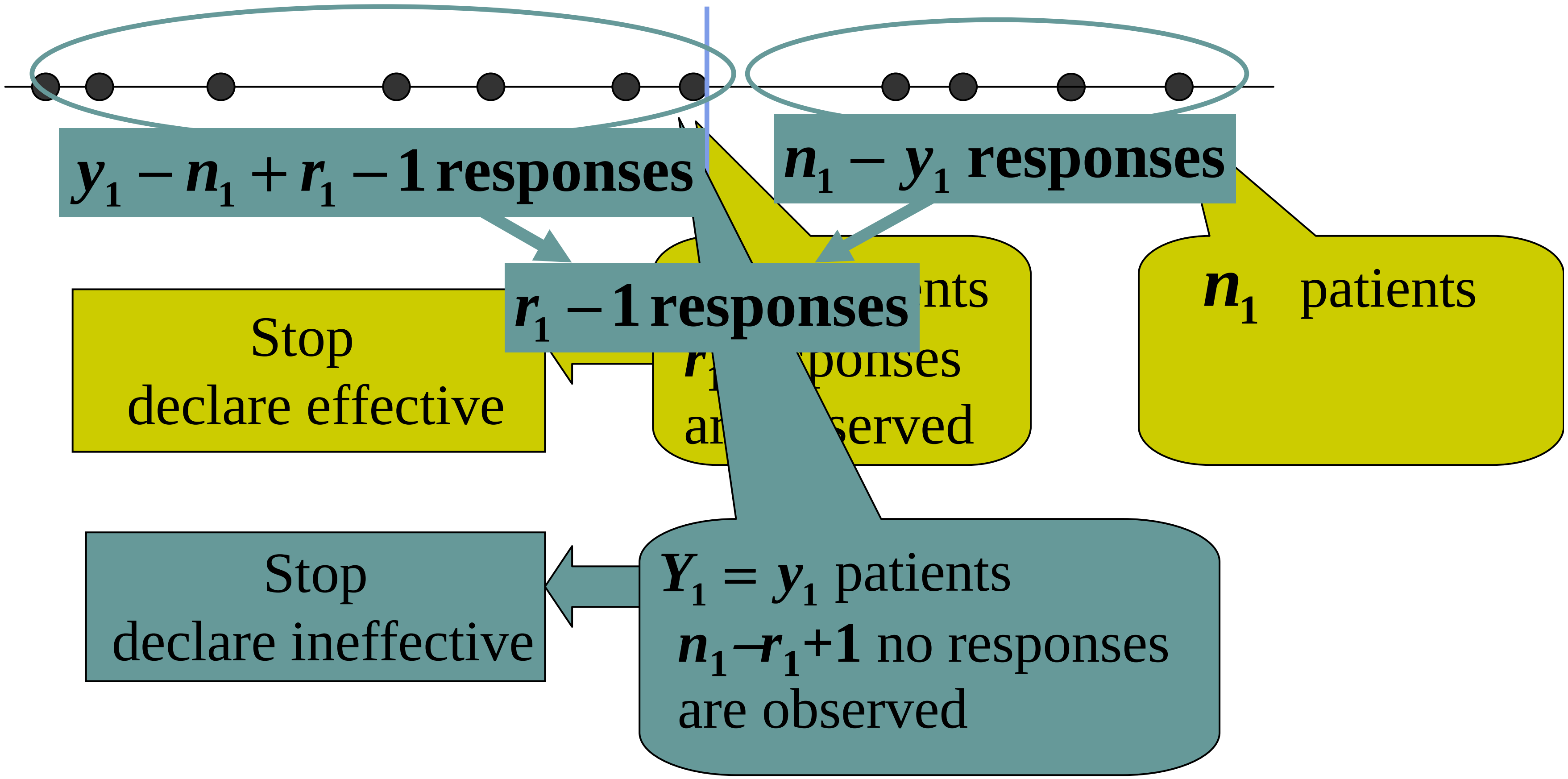
Review: Inverse binomial sampling



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)

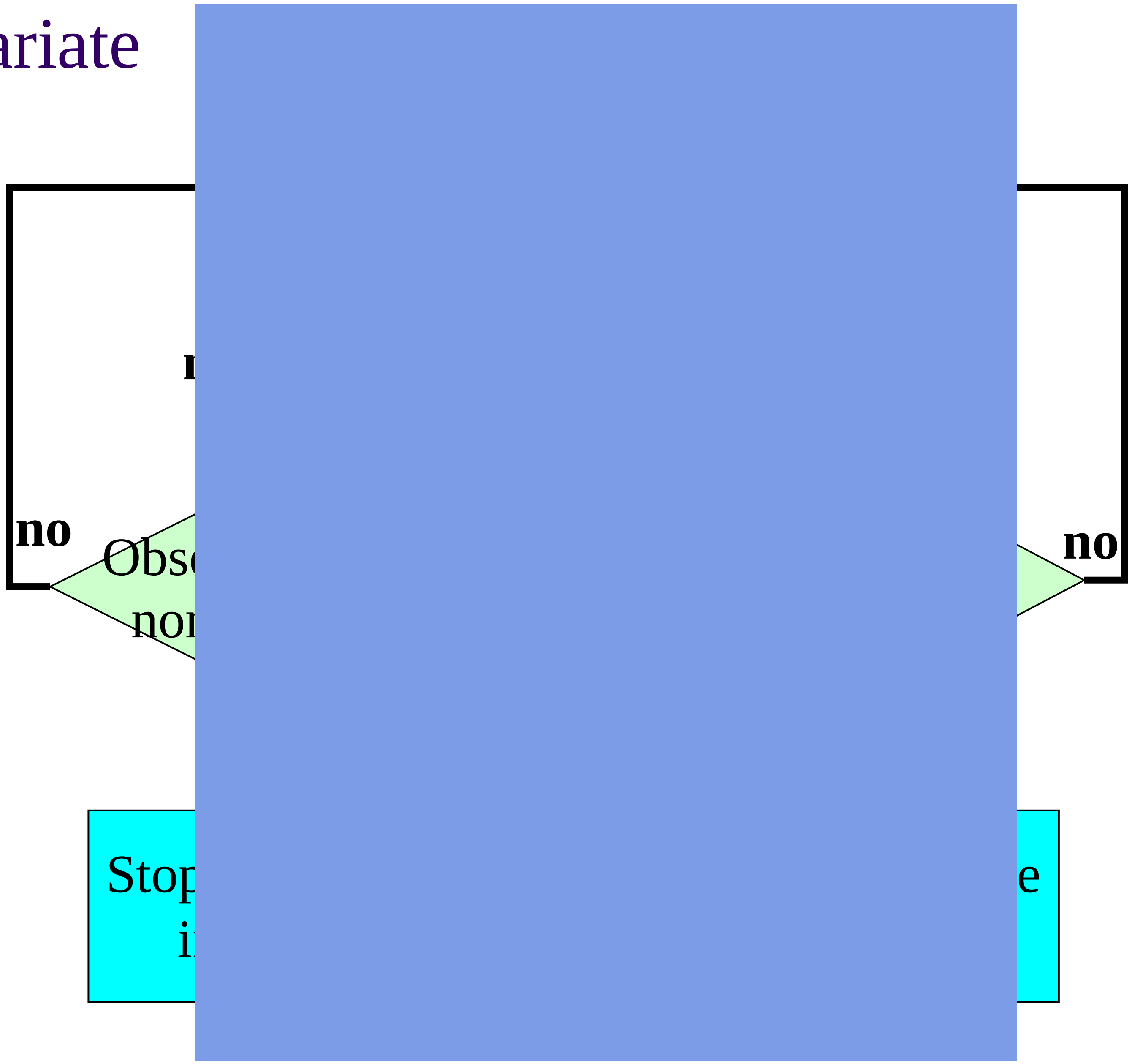
Curtailed sampling procedure



When the accrual rate is low, it can speed development of drug.

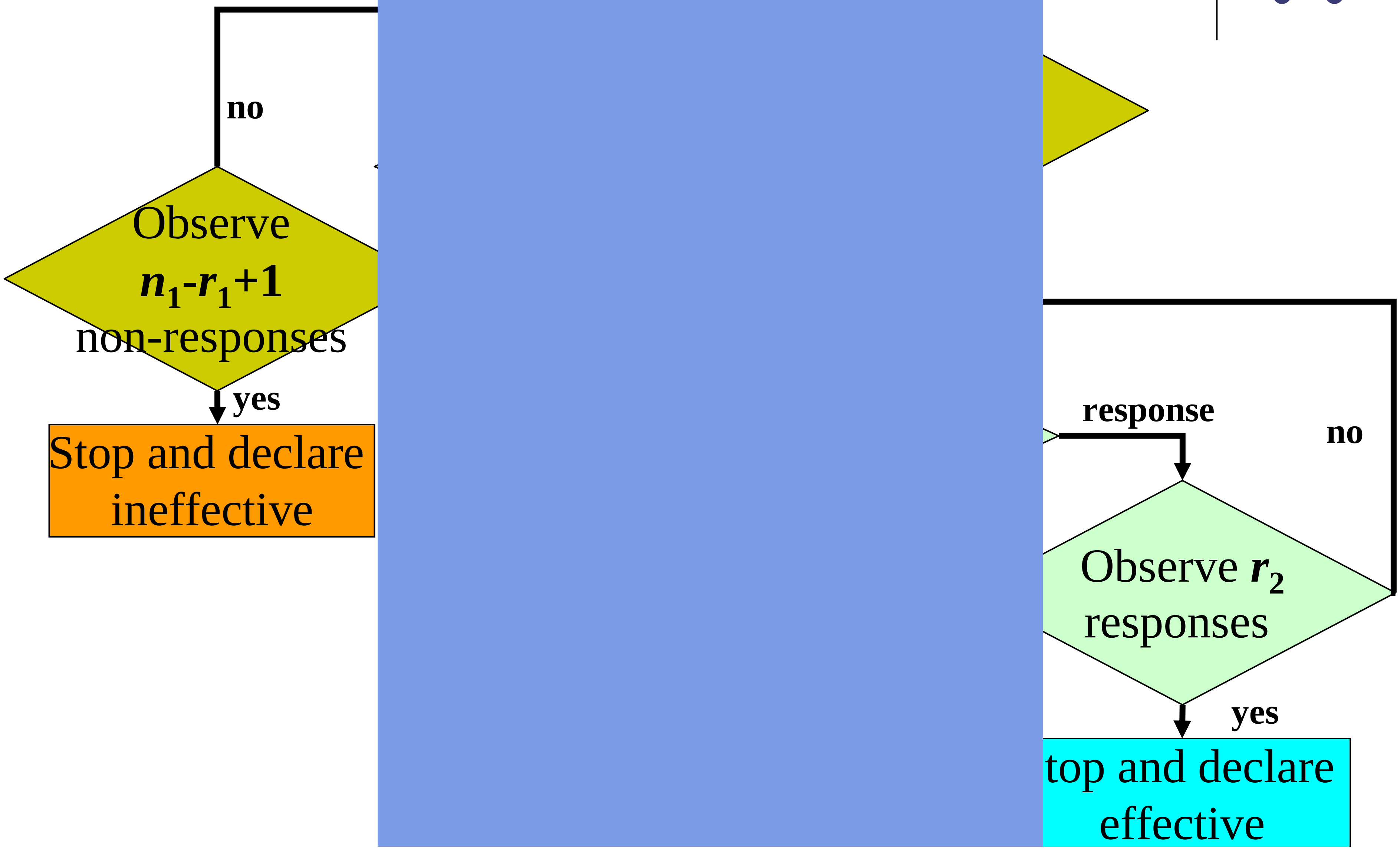
Review: Herrmann/ Szatrowski (1985)

Univariate



Review Chi/Chen (2008)

Univariate:



Review Comparison results

$E_S(N \mid p)$ expected sample size of Simon

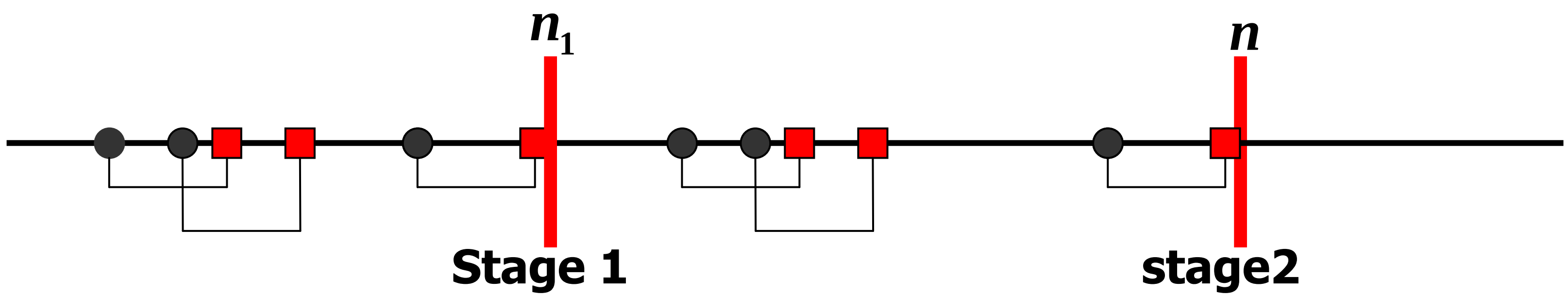
$E_C(N \mid p)$ expected sample size of curtailed

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

		Minimax Design							Optimal Design						
p_0	p_1	n_1	$\mathbf{r_1}$	n	r_2	$E_C(N \mid p_0)$	$E_S(N \mid p_0)$	$RS(\%)$	n_1	$\mathbf{r_1}$	n	r_2	$E_C(N \mid p_0)$	$E_S(N \mid p_0)$	$RS(\%)$
0.1	0.3	15	2	25	6	18.39	19.51	5.7	10	2	29	6	14.07	15.01	6.3
0.2	0.4	18	5	33	11	20.43	22.26	8.2	13	4	43	13	18.77	20.58	8.8
0.3	0.5	19	7	39	17	23.10	25.69	10.1	15	6	46	19	21.11	23.63	10.7
0.4	0.6	34	18	39	21	28.34 <	34.44	17.7	16	8	46	24	21.31 <	24.52	13.1
0.5	0.7	23	13	37	24	23.78	27.74	14.3	15	9	43	27	19.76	23.50	15.9
0.6	0.8	13	9	35	26	16.63	20.77	19.9	11	8	43	31	16.34	20.48	20.2
0.7	0.9	23	20	26	22	13.20	23.16	43.0	6	5	27	23	10.59	14.82	28.6

Goal

Data collection: Designs
Bivariate binary responses



● entry time

■ evaluated time

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: ?

Review Conaway and Petroni's design (1995)

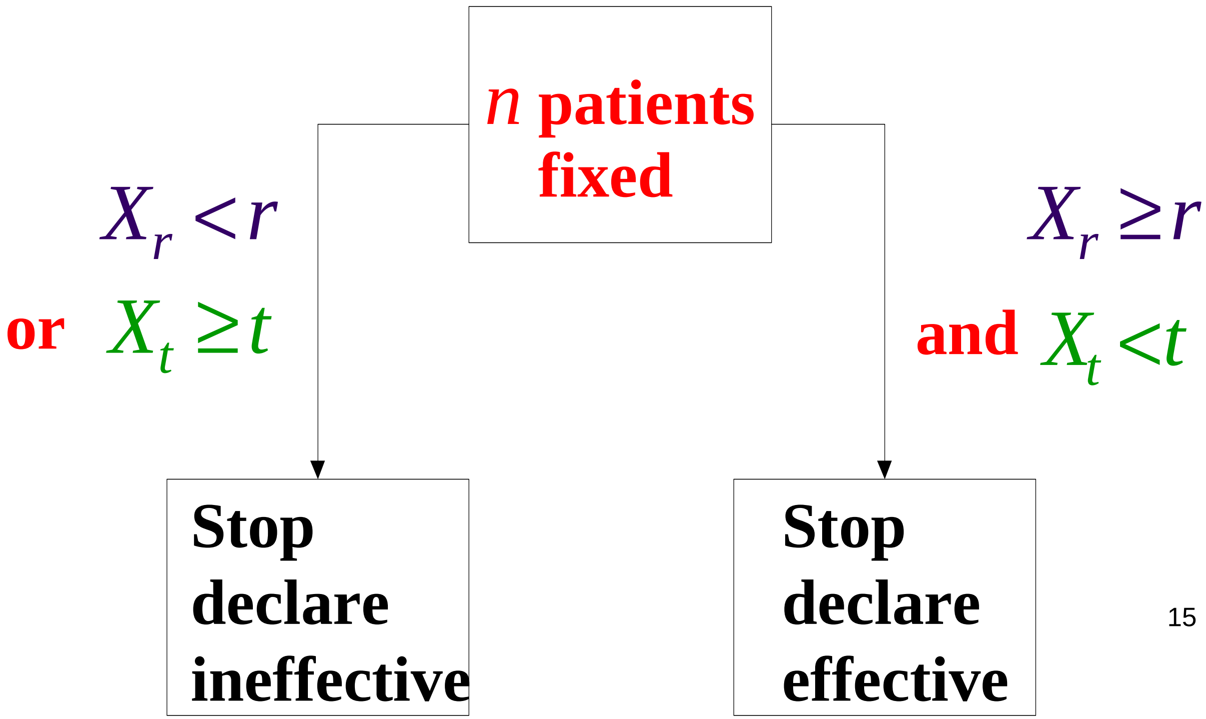
Single-stage design: bivariate binary responses

$$H_0 : p_r \le p_{r0} \text{ or } p_t \ge p_{t0}$$

$$H_1 : p_r > p_{r0} \text{ and } p_t < p_{t0}$$

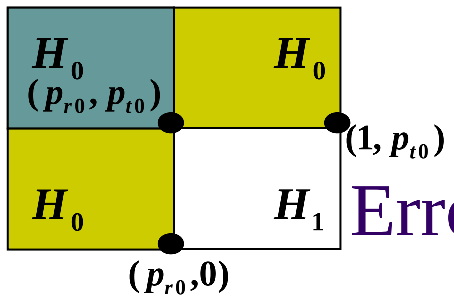
The critical region is based on intersection union test $= \{(X_r, X_t) \mid X_r \ge r, X_t < t\}$

Single Stage



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)

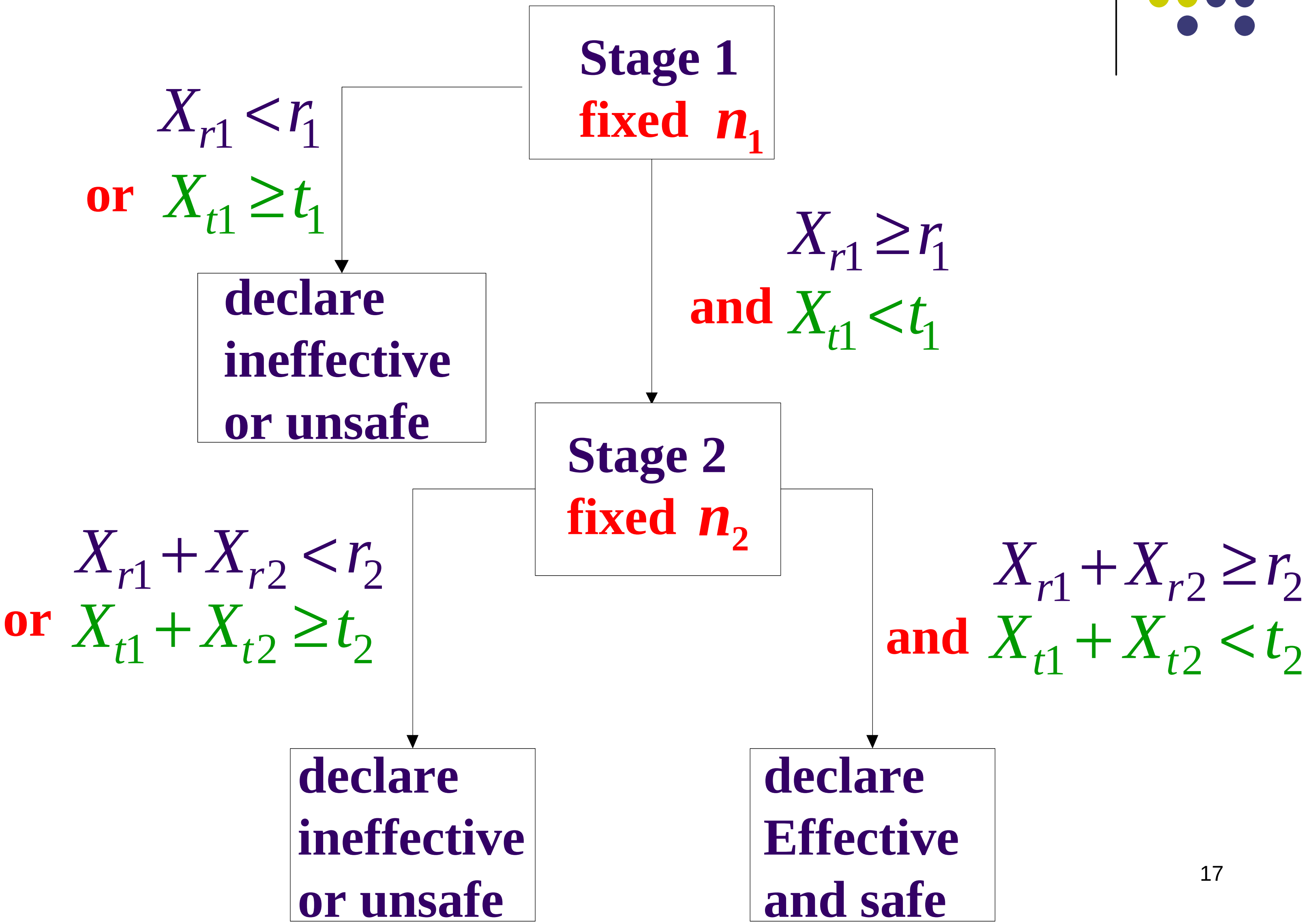
(i') $P(X_r \geq r, X_t < t \mid p_r = p_{r0}, p_t = 0) \leq \alpha_1$

(ii') $P(X_r \geq r, X_t < t \mid p_r = 1, p_t = p_{t0}) \leq \alpha_2$

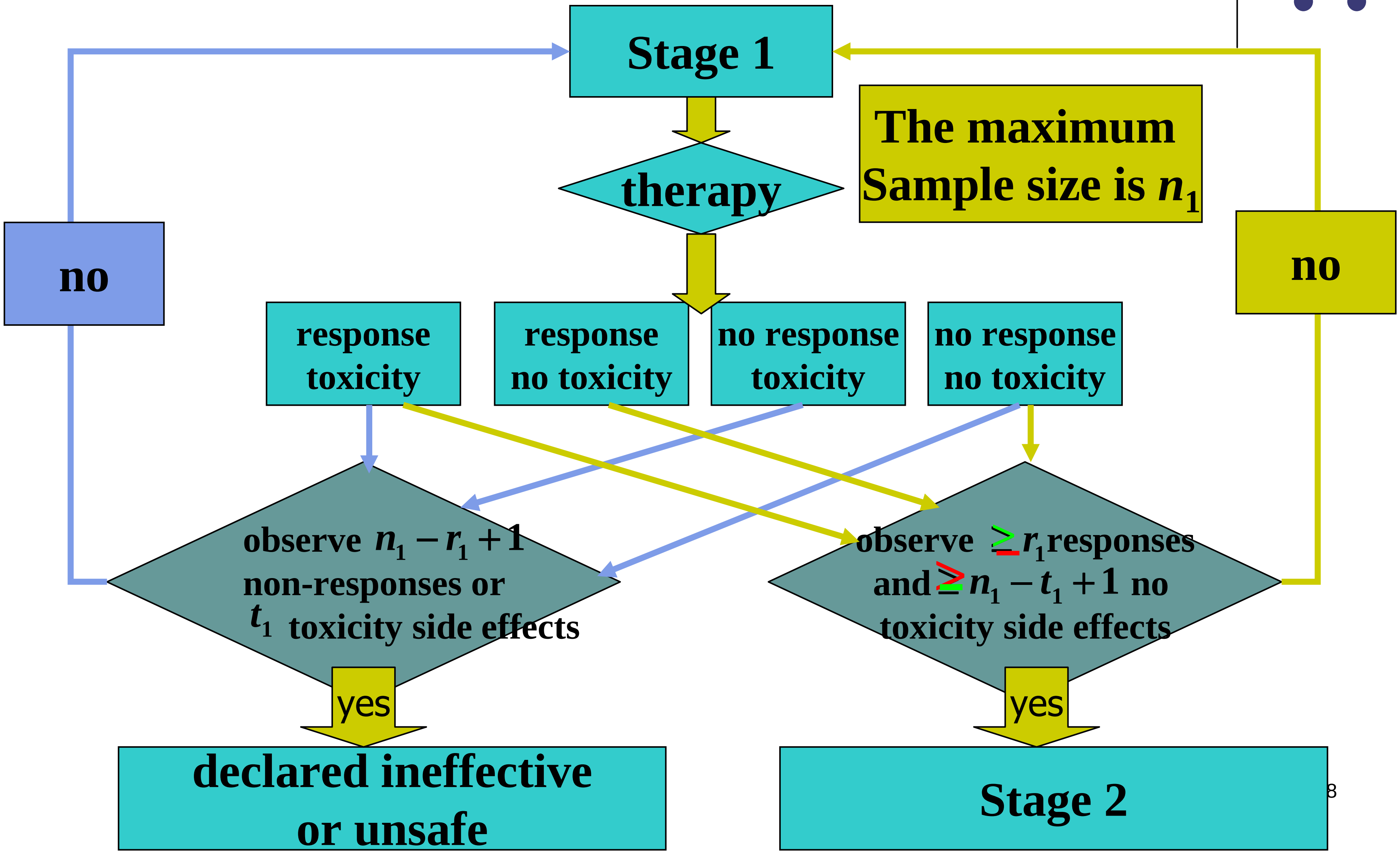
(iii') $P(X_r \geq r, X_t < t \mid p_r = p_{r1}, p_t = p_{t1}, \phi) \geq 1 - \beta$

Review

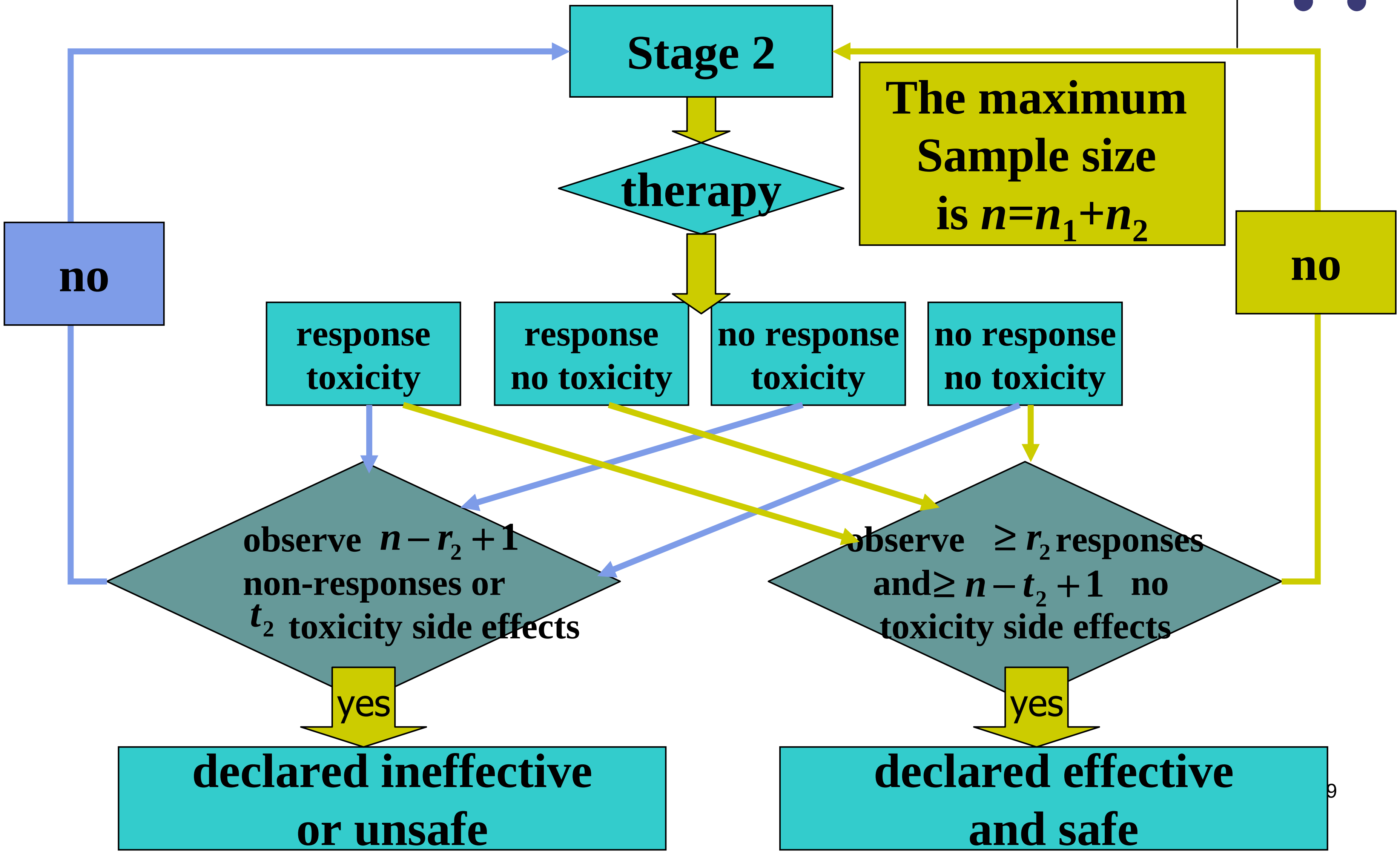
Conaway and Petroni's design (1995)
Two-stage design: bivariate binary responses



Extension curtailed two-stage design bivariate binary responses



Extension curtailed two-stage design bivariate binary responses



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

								$p_r = p_{r0}, p_t = p_{t0}$			$p_r = p_{r1}, p_t = p_{t1}$		
p_{r0}	p_{r1}	n_1	r_1	t_1	n	r_2	t_2	$E_{CP}(N)$	$E_{BC}(N)$	$RS(\%)$	$E_{CP}(N)$	$E_{BC}(N)$	$RS(\%)$
0.1	0.35	21	2	8	49	10	10	33.4953	26.6052	20.57	48.7264	45.1255	7.39
0.2	0.45	20	5	7	53	17	11	26.7435	21.9691	17.85	51.6590	48.0531	6.98
0.3	0.55	20	7	7	53	22	11	27.0905	21.9129	19.11	51.5757	47.9775	6.98
0.4	0.65	18	8	7	53	28	11	28.2553	21.9863	22.19	51.8466	48.2448	6.95
0.5	0.75	19	11	7	53	33	11	25.5917	19.7578	22.80	51.4748	47.8817	6.98
0.6	0.85	16	11	6	53	39	11	23.2581	16.9807	26.99	51.2686	47.7316	6.90
0.7	0.95	17	14	7	49	40	10	21.6190	14.4360	33.23	48.4547	44.8540	7.43

Concluding Remark

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

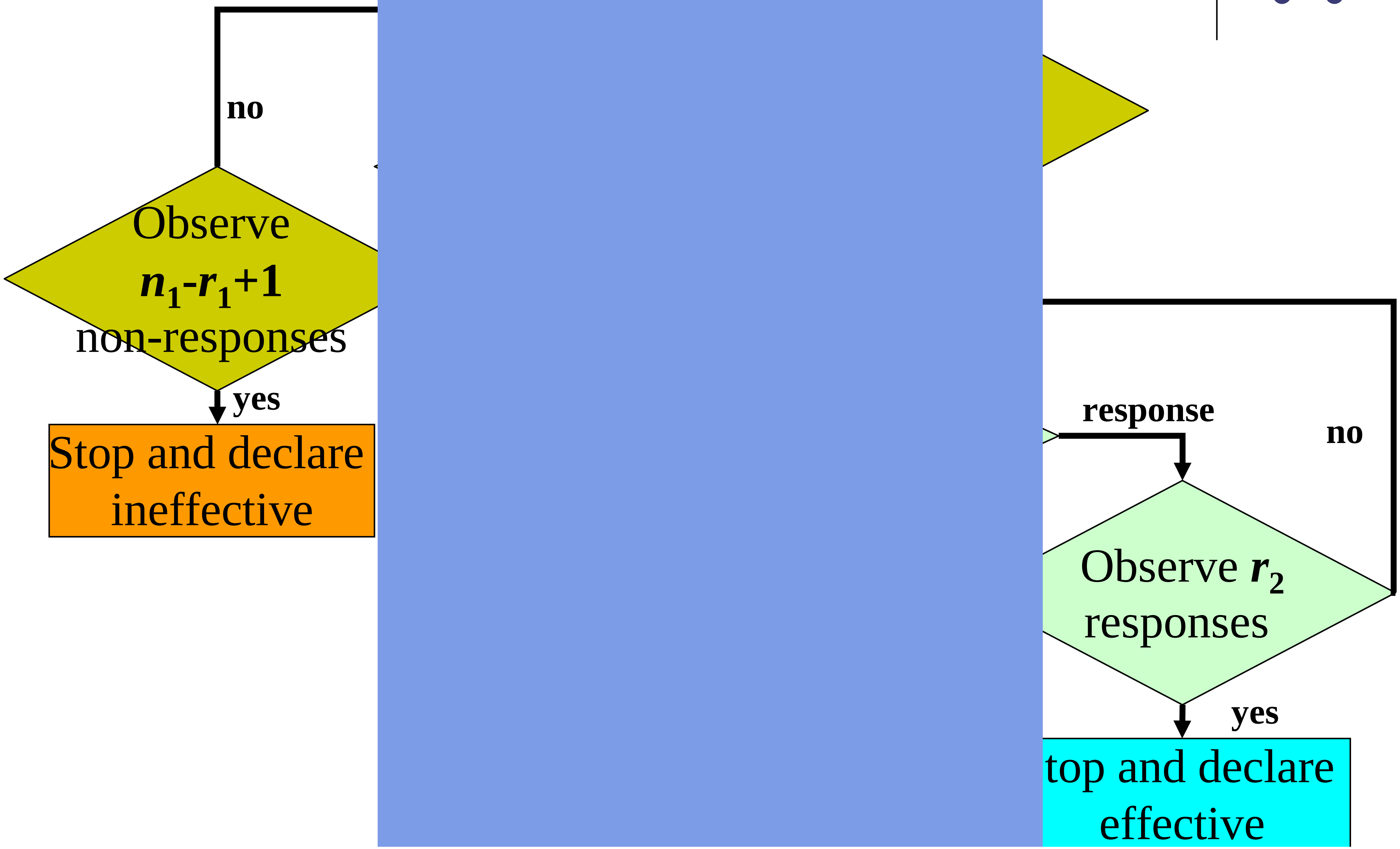
The curtailed two-stage design is recommended to apply when the patient accrual rate is very slow.

The end

Thanks for your attention

Review Chi/Chen (2008)

Univariate:



Background

$X_{r1} < r_1$

Stop
declare
ineffective

$X_{r1} \geq r_1$

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

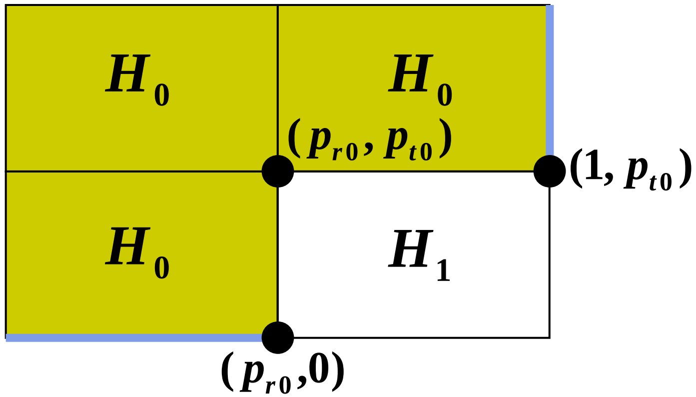
$X_{r1} + X_{r2} \geq r_2$

Stop
declare
ineffec

Extension

Bivariate single-stage design

$H_0: p_r \le p_{r0}$ or $p_t \ge p_{t0}$ $\qquad H_1: p_r > p_{r0}$ and $p_t < p_{t0}$



Intersection union test

The critical region

$$= \{(X_r, X_t) \mid X_r \ge r, X_t < t\}$$

$$P(X_r \ge r, X_t < t \mid p_r, p_t, \phi) \le \min\{P(X_r \ge r \mid p_r), P(X_t < t \mid p_t)\}$$

since $P(X_r \ge r \mid p_r) = P(X_r \ge r, X_t < t \mid p_r, p_t = 0)$ — Increasing function of p_r

$P(X_t < t \mid p_t) = P(X_r \ge r, X_t < t \mid p_r = 1, p_t)$ — decreasing function of p_t

Review Comparison results

$E_S(N \mid p)$ expected sample size of Jin

$E_C(N \mid p)$ expected sample size of curtailed

$$\boldsymbol{RS\,(\%) = \frac{E_S(N \mid p) - E_C(N \mid p)}{E_S(N \mid p)} \times 100\,\%}$$

Data collection: Designs

Bivariate

two endpoints of interest as **response** and **toxicity side effect**.

$X_{11} = \min(0, X_r + X_t - n), \ldots, \min(X_r, X_t)$

Response \ Toxicity	yes	no	
yes	$X_{11}(p_{11})$	$X_{12}(p_{12})$	$X_r(p_r)$ — known
no	$X_{21}(p_{21})$	$X_{22}(p_{22})$	
	$X_t(p_t)$ — known		

unknown

$X_{11} + X_{12} + X_{21} + X_{22} = n$

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

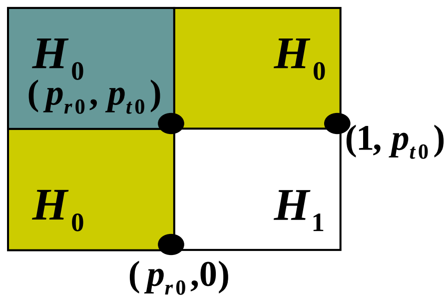
$X_r \sim B(n, p_r)$ and $X_t \sim B(n, p_t)$

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') $P(X_r \geq r, X_t < t \mid p_r = p_{r0}, p_t = 0) \leq \alpha_1 \quad = \delta$

(ii') $P(X_r \geq r, X_t < t \mid p_r = 1, p_t = p_{t0}) \leq \alpha_2 \quad = \delta$

$\Rightarrow \max_{p_r, p_t \in H_0} P(X_r \geq r, X_t < t \mid p_r, p_t, \phi) \leq \delta$

$\Rightarrow \max\{P(X_r \geq r \mid p_r = p_{r0}, \quad), P(X_t < t \mid \quad , p_t = p_{t0})\} \leq \delta$

$P(X_r \geq r, X_t < t \mid p_r = p_{r1}, p_t = p_{t1}, \phi) \geq 1 - \beta$

Motivation

Phase II clinical trials

- **Goal□to evaluate the clinical activity and safety**

Univariate ➔ Simon's design (1989)

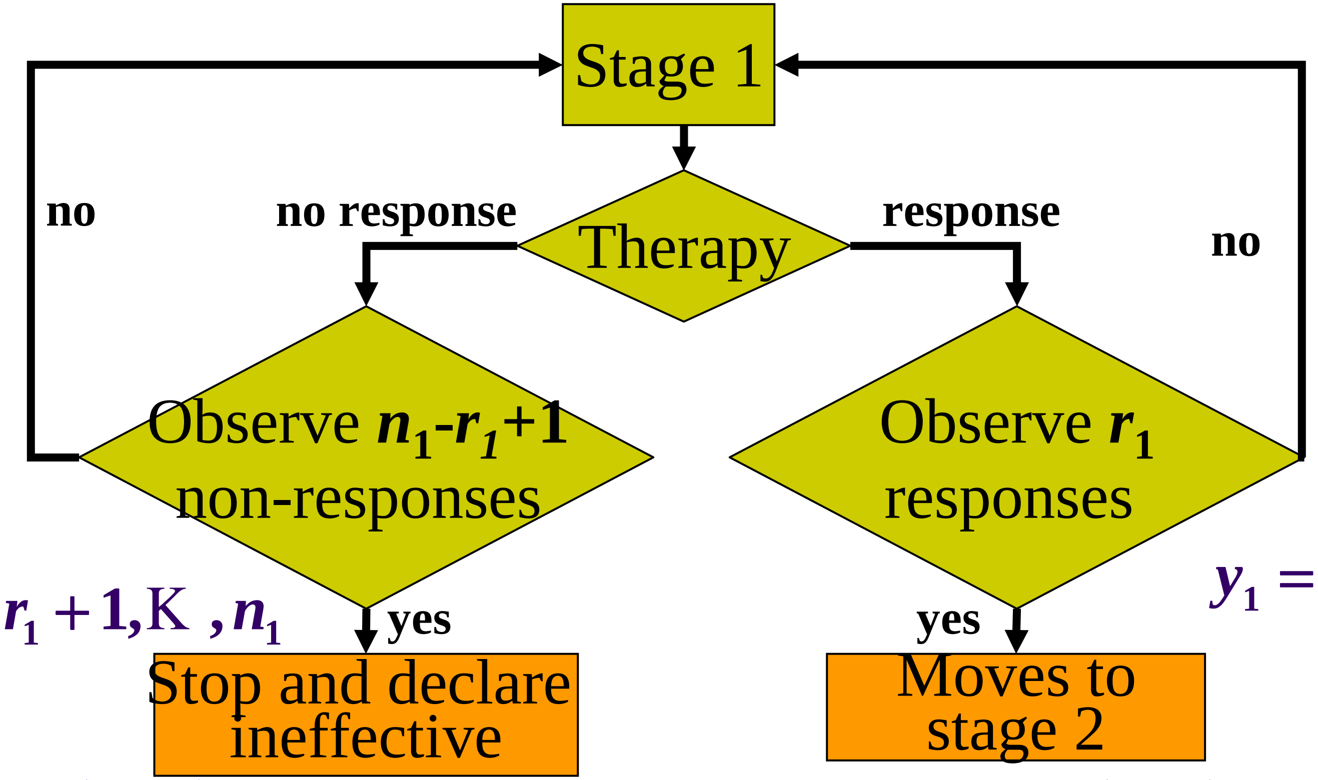
$$H_0 : p = p_0 \ \ v.s. \ \ H_1 : p = p_1 (> p_0)$$

Bivariate ➔ Conaway and Petroni's design (1995)

Jin's design (2007)

$$H_0 : p_r \le p_{r0} \text{ or } p_t \ge p_{t0} \ \text{ v.s. } \ H_1 : p_r > p_{r0} \text{ and } p_t < p_{t0}$$

Univariate curtailed two-stage design probability and expectation



$$y_1 = n_1 - r_1 + 1, \ldots, n_1$$

$$y_1 = r_1, \ldots, n_1$$

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

$$E_I(Y_1 = y_1) = \sum_{y_1 = r_1}^{n_1} y_1 \binom{y_1 - 1}{n_1 - r_1} p^{y_1 - n_1 + r_1 - 1} (1 - p)^{n_1 - r_1 + 1}$$

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

$$E_{II}(Y_1 = y_1) = \sum_{y_1 = r_1}^{n_1} y_1 \binom{y_1 - 1}{r_1 - 1} p^{r_1} (1 - p)^{y_1 - r_1}$$

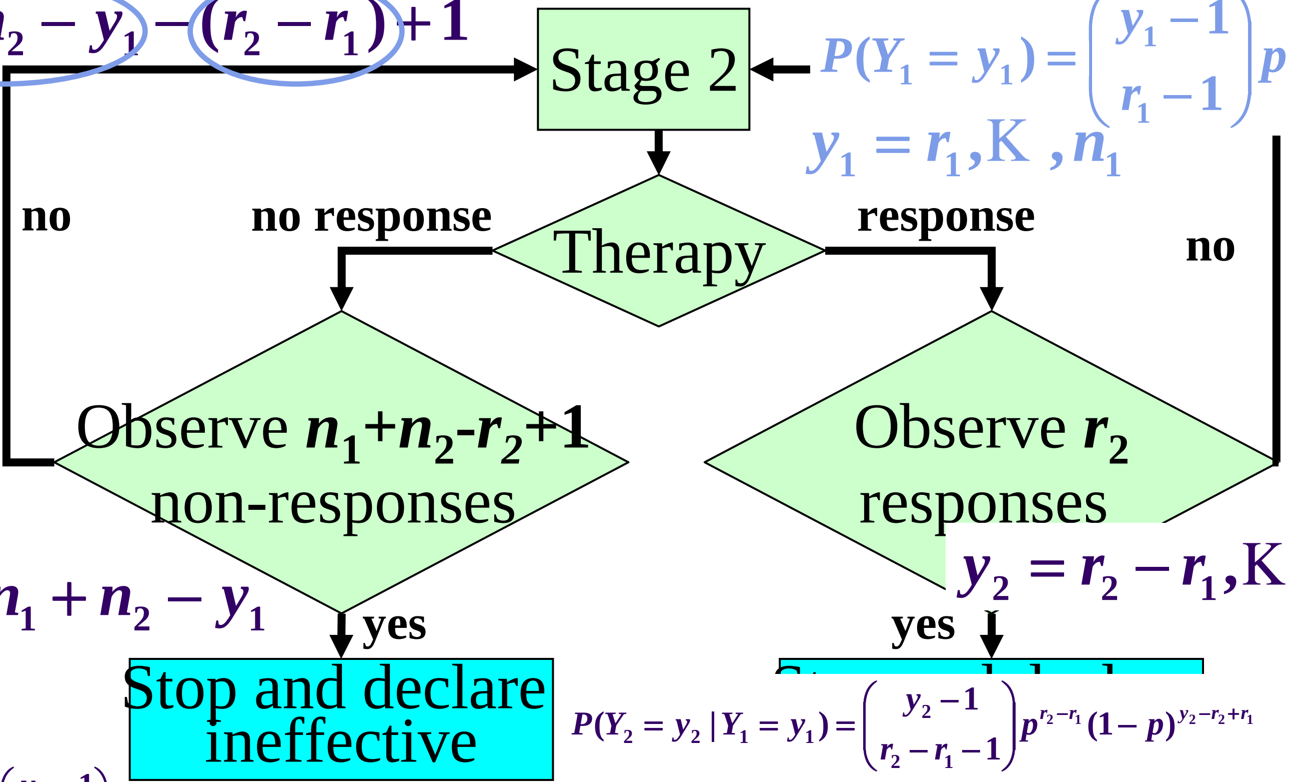
Univariate curtailed two-stage design probability and expectation

Given $Y_1 = y_1$ and r_1 responses are observed in stage 1

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

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

$$y_1 = r_1, \ldots, n_1$$



$$y_2 = m, \ldots, n_1 + n_2 - y_1$$

$$y_2 = r_2 - r_1, \ldots, n_1 + n_2 - y_1$$

$$P(Y_2 = y_2 \mid Y_1 = y_1) = \binom{y_2 - 1}{r_2 - r_1 - 1} p^{r_2 - r_1}(1-p)^{y_2 - r_2 + r_1}$$

$$E_{II,A}(Y_2) = \sum_{y_1 = r_1}^{n_1} \left\{ \binom{y_1 - 1}{r_1 - 1} p^{r_1}(1-p)^{y_1 - r_1} \sum_{y_2 = r_2 - r_1}^{n_1 + n_2 - y_1} y_2 \binom{y_2 - 1}{r_2 - r_1 - 1} p^{r_2 - r_1}(1-p)^{y_2 - r_2 + r_1} \right\}$$

$$P(Y_2 = y_2 \mid Y_1 = y_1) = \binom{y_2 - 1}{m - 1} p^{y_2 - m}(1-p)^{m}$$

$$E_{II,A}(Y_2) = \sum_{y_1 = r_1}^{n_1} \left\{ \binom{y_1 - 1}{r_1 - 1} p^{r_1}(1-p)^{y_1 - r_1} \sum_{y_2 = m}^{n_1 + n_2 - y_1} y_2 \binom{y_2 - 1}{m - 1} p^{y_2 - m}(1-p)^{m} \right\}$$

Univariate curtailed two-stage design design parameter

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

$$\Psi = \{(n_1,r_1,n_2,r_2) \mid R(n_1,r_1,n_2,r_2 \mid p_0) \le \alpha, R(n_1,r_1,n_2,r_2 \mid p_1) \ge 1-\beta\}$$

(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

$$R_S(n_1,r_1,n_2,r_2 \mid p) = \sum_{x_1=r_1}^{n_1} \left\{ \binom{n_1}{x_1} p^{x_1}(1-p)^{n_1-x_1} \sum_{x_2=\max(r_2-x_1,0)}^{n_2} \binom{n_2}{x_2} p^{x_2}(1-p)^{n_2-x_2} \right\}$$

$$E_S(N \mid p) = n_1 + n_2 \sum_{x_1=r_1}^{n_1} \binom{n_1}{x_1} p^{x_1}(1-p)^{n_1-x_1}$$

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

- $E_C(N \mid p) \le E_S(N \mid p)$
- $R_C(n_1,r_1,n_2,r_2 \mid p) = R_S(n_1,r_1,n_2,r_2 \mid p)$

Univariate curtailed two-stage design design parameter (optimal design)

		Design parameter				$p = p_0$		$p = p_1$	
p_0	p_1	n_1	r_1	n	r_2	$E_C(N\|p)$	$E_S(N\|p)$	$E_C(N\|p)$	$E_S(N\|p)$
0.05	0.25	9	1	24	3	13.74	14.55	10.99	22.87
		9	1	17	3	11.55	11.96	10.53	16.40
		9	1	30	4	16.07	16.76	14.68	28.42
0.1	0.3	12	2	35	6	18.53	19.84	18.45	33.04
		10	2	29	6	14.07	15.01	17.14	26.16
		18	3	35	7	21.27	22.53	22.06	33.98
0.2	0.4	22(17)	6(4)	38(37)	11(11)	24.17	26.02	26.15	36.07
		13	4	43	13	18.76	20.58	27.83	37.94
		19	5	54	16	28.18	30.43	37.65	51.56
0.3	0.5	22	8	46	18	27.27	29.89	34.25	44.39
		15	6	46	19	21.11	23.63	33.21	41.32
		24	9	63	25	31.50	34.72	47.12	60.04
0.4	0.6	18	8	46	23	27.13	30.22	36.47	44.39
		16	8	46	24	21.31	24.52	35.32	41.73
		25	12	66	33	31.88	35.98	51.81	62.81
0.5	0.7	21	12	45	27	25.29	28.96	36.71	43.38
		15	9	43	27	19.76	23.50	34.34	39.33
		24	14	61	37	29.22	34.01	49.95	58.25
0.6	0.8	11	7	38	27	21.19	25.38	32.10	36.64
		11	8	43	31	16.34	20.48	33.31	37.84
		19	13	53	38	24.13	29.47	44.92	50.70
0.7	0.9	9	7	28	23	13.99	17.79	24.27	26.99
		6	5	27	23	10.59	14.82	22.48	24.60
		17(15)	14(12)	39(36)	32(30)	15.68	21.23	33.42	34.83

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

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

$(\alpha, \beta) = (0.05, 0.1)$

Univariate curtailed two-stage design design parameter (minimax design)

		Design parameter				$p = p_0$		$p = p_1$	
p_0	p_1	n_1	r_1	n	r_2	$E_C(N\|p)$	$E_S(N\|p)$	$E_C(N\|p)$	$E_S(N\|p)$
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	9(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

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

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

$(\alpha, \beta) = (0.05, 0.1)$

Univariate curtailed two-stage design comparison

	Simon	Curtail
Total sample size	Minimax: Simon's design equal to Curtailed design. Optimal: Simon's design less than or equal to Curtailed design.	
Design parameter	Minimax: Eight sets from curtailed design are different from Simon's design. Optimal: Two sets from curtailed design are different from Simon's design.	
Expected sample size	large	small

Bivariate single-stage design

The joint probability mass function of X_r and X_t is

$$P(X_r = x_r, X_t = x_t)$$

$$= \sum_{i=\max(0, x_r + x_t - n)}^{\min(x_r, x_t)} \binom{n}{i \quad x_r - i \quad x_t - i \quad n - x_r - x_t + i} p_{11}^{i} p_{12}^{x_r - i} p_{21}^{x_t - i} p_{22}^{n - x_r - x_t + i}$$

Dale (1986)

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

$$p_{11} = \frac{a - \sqrt{a^2 + b}}{a(\phi - 1)} \qquad a = 1 + (\phi - 1)(p_r + p_t) \qquad b = -4\phi(\phi - 1)\,p_r p_t$$

$\Rightarrow$ p_{12}, p_{21}, p_{22}

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

$$P(X_r \geq r, X_t < t \mid p_r, p_t, \phi)$$
$$= \sum_{x_r=r}^{n} \sum_{x_t=0}^{t-1} \sum_{i=\max(0, x_r+x_t-n)}^{\min(x_r, x_t)} \binom{n}{i \quad x_r - i \quad x_t - i \quad n - x_r - x_t + i} p_{11}^{i} p_{12}^{x_r-i} p_{21}^{x_t-i} p_{22}^{n-x_r-x_t+i}$$

Bivariate two-stage design

power function and errors requirement

$$P(X_{r1} \ge r_1, X_{t1} < t_1, X_{r1} + X_{r2} \ge r_2, X_{t1} + X_{t2} < t_2)$$

$$= \sum_{x_{r1}=r_1}^{n_1} \sum_{x_{t1}=0}^{t_1-1} \left\{ \sum_{i=\max(0, x_{r1}+x_{t1}-n_1)}^{\min(x_{r1}, x_{t1})} \binom{n_1}{i \quad x_{r1}-i \quad x_{t1}-i \quad n_1 - x_{r1} - x_{t1} + i} p_{11}^{i} p_{12}^{x_{r1}-i} p_{21}^{x_{t1}-i} p_{22}^{n_1 - x_{r1} - x_{t1} + i} \right.$$

$$\times \sum_{x_{r2}=\max(0, r_2 - x_{r1})}^{n_2} \sum_{x_{t2}=0}^{t_2 - x_{t1} - 1} \sum_{j=\max(0, x_{r2}+x_{t2}-n)}^{\min(x_{r2}, x_{t2})} \binom{n_2}{j \quad x_{r2}-j \quad x_{t2}-j \quad n_2 - x_{r2} - x_{t2} + j}$$

$$\left. \times p_{11}^{j} p_{12}^{x_{r2}-j} p_{21}^{x_{t2}-j} p_{22}^{n_2 - x_{r2} - x_{t2} + j} \right\}$$

The probability of the second stage is allowed to continue $P(X_{r1} \ge r_1, X_{t1} < t_1)$

$E_{CP}(N) = n_1 + n_2 P(X_{r1} \ge r_1, X_{t1} < t_1)$

Errors requirement

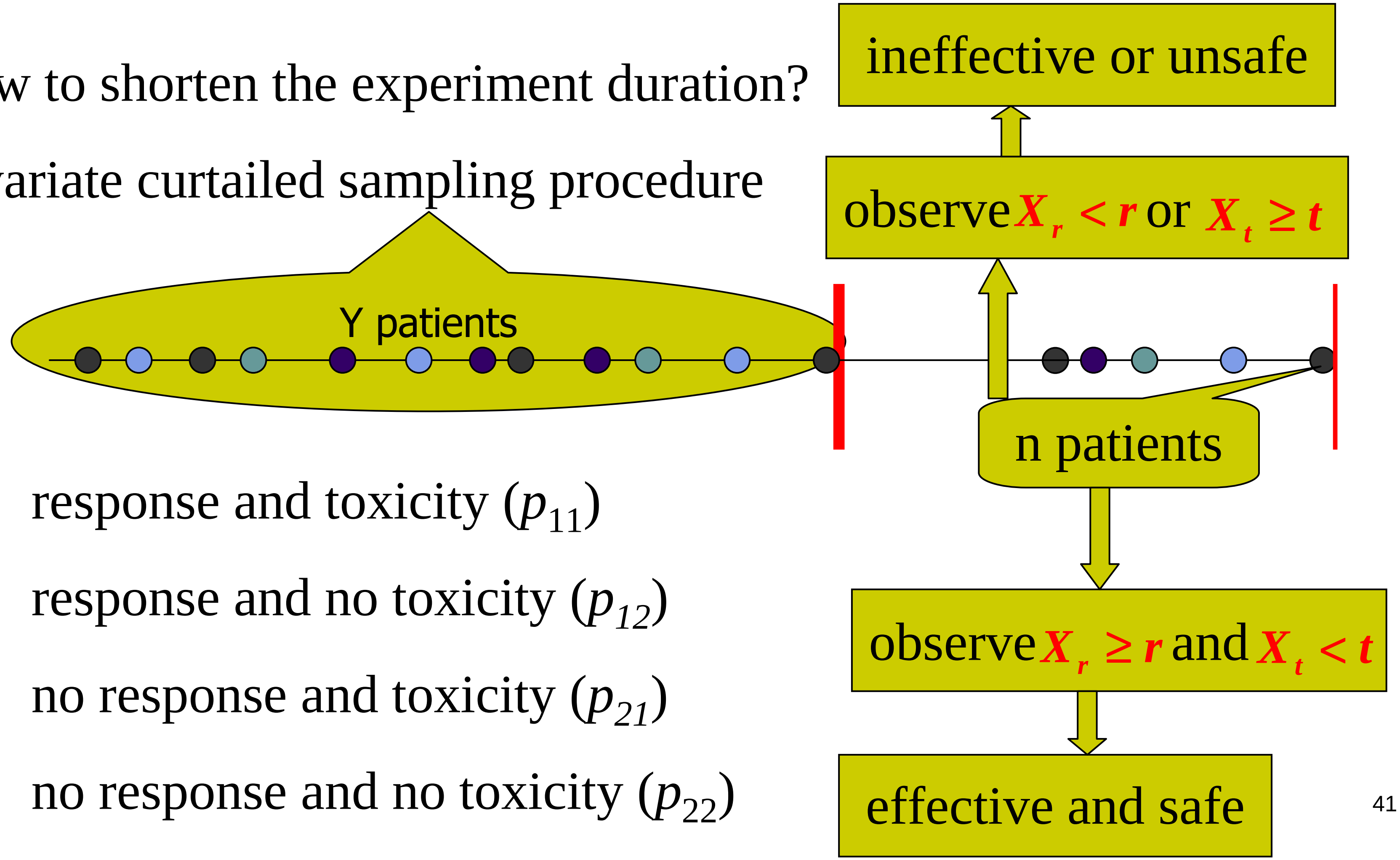
$\max\{P(X_{r1} \ge r_1, X_{r1} + X_{r2} \ge r_2 \mid p_r = p_{r\ldots}$

$P(X_{r1} \ge r_1, X_{t1} < t_1, X_{r1} + X_{r2} \ge r_2, X_{t1} + X_{t2} < t_2 \mid p_r = p_{r1}, p_t = p_{t1}, \phi) \ge 1 - \beta$

Bivariate curtailed sampling procedure

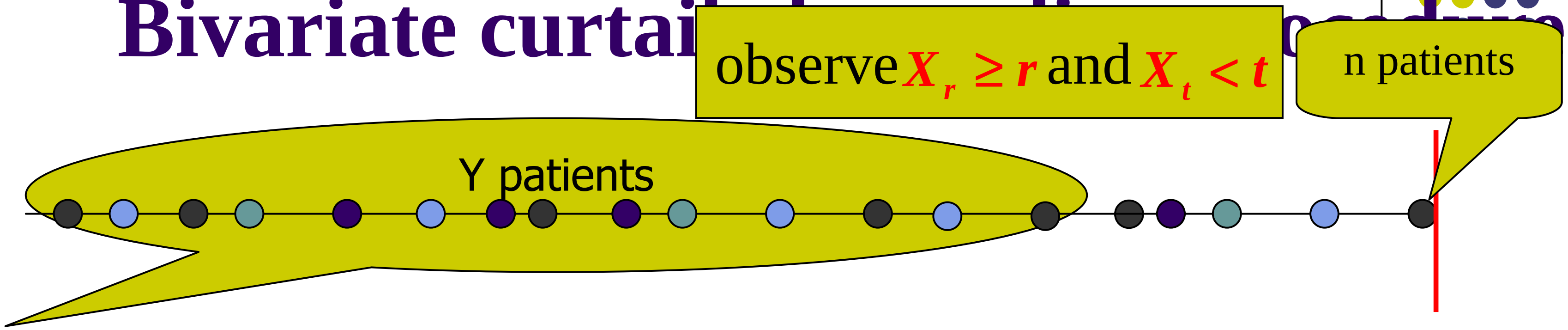
How to shorten the experiment duration?

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})

Bivariate curtai



- **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

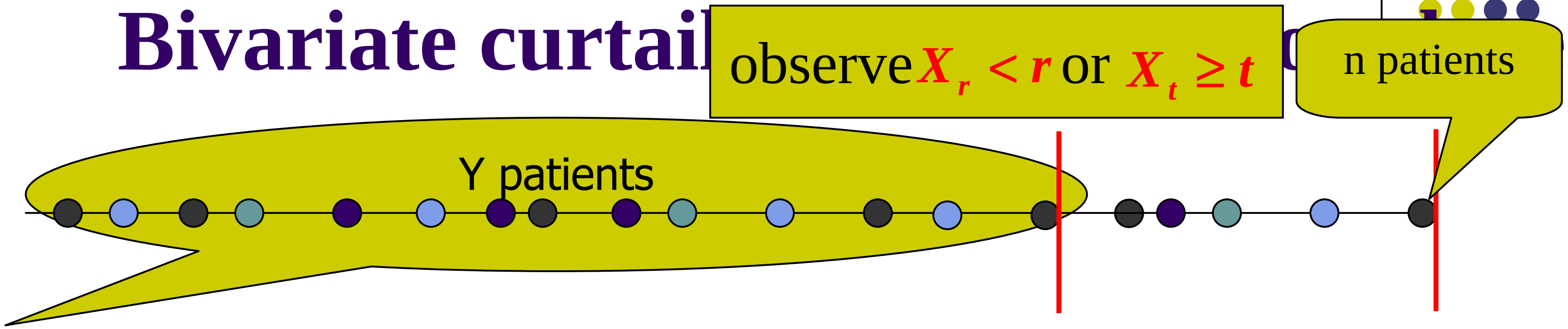
(A) There are exactly ***r*** responses and ***n-t*+1** no toxicity

(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**

Bivariate curtail...



■ **Individual (the drug is declared ineffective or unsafe)**

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

$$y-(n-r+1)+(n-y)=r-1$$

Unsafe: The trial is stopped if ***t*** toxicity are observed

⇨ The required numbers of patients are difference

(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

◆**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

$$P_Y(U(y)=u, V(y)=v)$$

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

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

- P(A)+P(B)+P(C)= $P_{\text{reject}}(Y = y)$ — effective and safe
- P(D)+P(E)+P(F)= $P_{\text{accept}}(Y = y)$ — ineffective or unsafe

Bivariate curtailed single-stage design probability (A)

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

$(y-1)$		y
r*-1** responses and ***n-t no toxicity	+	(response, no toxicity)
$P_{Y-1}(U(y-1)=r-1,(y-1)-V(y-1)=n-t)$		p_{12}
$P_{Y-1}(U(y-1)=r-1,V(y-1)=y-n+t-1)$		p_{12}
r responses and ***n-t*** no toxicity	+	(no response, no toxicity)
$P_{Y-1}(U(y-1)=r,(y-1)-V(y-1)=n-t)$		p_{22} $I[Y\geq r+1]$
$P_{Y-1}(U(y-1)=r,V(y-1)=y-n+t-1)$		p_{22}
***r*-1** responses and ***n-t*+1** no toxicity	+	(response, toxicity)
$P_{Y-1}(U(y-1)=r-1,(y-1)-V(y-1)=n-t+1)$		p_{11} $I[Y\geq n-t+2]$
$P_{Y-1}(U(y-1)=r-1,V(y-1)=y-n+t-2)$		p_{11}

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

Bivariate curtailed single-stage design probability (B)

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

$(y-1)$ $\quad$ y

- ***r*** responses and ***n-t*** no toxicity + (response, no toxicity)

$P_{Y-1}(U(y-1)=r,(y-1)-V(y-1)=n-t)$ $\quad p_{12}$

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

- more than ***r*+1** responses and ***n-t*** no toxicity+(any, no toxicity)

$P_{Y-1}(U(y-1)\geq r+1,(y-1)-V(y-1)=n-t)$ $\quad p_{12}+p_{22}$

$I[Y\geq r+2]$

$\sum_{u=r+1}^{y-1} P_{Y-1}(U(y-1)=u,V(y-1)=y-n+t-1)$ $\quad 1-p_t$

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

Bivariate curtailed single-stage design probability (C)

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

$(y-1)$	y
● ***r*-1** responses and ***n-t*+1** no toxicity +	(response, no toxicity)
$P_{Y-1}(U(y-1)=r-1,(y-1)-V(y-1)=n-t+1)$	p_{12}
$P_{Y-1}(U(y-1)=r-1,V(y-1)=y-n+t-2)$	p_{12}
● ***r*-1** responses and more than ***n-t*+1** no toxicity+	(response, any)
$P_{Y-1}(U(y-1)=r-1,(y-1)-V(y-1)\geq n-t+2)$	$p_{11}+p_{12}$ $I[Y\geq n-t+3]$
$\sum_{v=0}^{y-n+t-3} P_{Y-1}(U(y-1)=r-1,V(y-1)=v)$	p_r

$$y=\max(r,n-t+2),\ldots,n$$

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

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

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

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

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

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

$$P_Y(U(y) = u, V(y) = v) = \sum_{i=\max(0,u+v-y)}^{\min(u,v)} \binom{y}{i \quad u-i \quad v-i \quad y-u-v+i} p_{11}^{i}\, p_{12}^{u-i}\, p_{21}^{v-i}\, p_{22}^{y-u-v+i}$$

Bivariate curtailed single-stage design probability (D)

(D) There are exactly n-$\boldsymbol{r}$**+1** no responses and $\boldsymbol{t}$ toxicity

- $(y-1)$ **n-r** no responses and **t-1** toxicity + y (no response, toxicity)

$P_{Y-1}((y-1)-U(y-1)=n-r, V(y-1)=t-1)$ p_{21}

$P_{Y-1}(U(y-1)=y-n+r-1, V(y-1)=t-1)$ p_{21}

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

Bivariate curtailed single-stage design probability (E)

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

$(y-1)$	y
● ***n*-*r*** no responses and ***t*-1** toxicity	+ (no response, no toxicity)
$P_{Y-1}((y-1)-U(y-1)=n-r, V(y-1)=t-1)$	p_{22} $I[Y \geq t]$
$P_{Y-1}(U(y-1)=y-n+r-1, V(y-1)=t-1)$	p_{22}
● ***n*-*r*** no responses and less than ***t*-2** toxicity	+(no response, any)
$P_{Y-1}((y-1)-U(y-1)=n-r, V(y-1)\leq t-2)$	$p_{21}+p_{22}$
$\sum_{v=0}^{\min(t-2,y-1)} P_{Y-1}(U(y-1)=y-n+r-1, V(y-1)=v)$	$1-p_r$

$$y = n-r+1, \ldots, n$$

Bivariate curtailed single-stage design probability (F)

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

$(y-1)$	y
n-r no responses and ***t*-1** toxicity +	(response, toxicity)
$P_{Y-1}((y-1)-U(y-1)=n-r, V(y-1)=t-1)$	p_{11}
	$I[Y \geq n-r+1]$
$P_{Y-1}(U(y-1)=y-n+r-1, V(y-1)=t-1)$	p_{11}
less than ***n-r*-1** no responses and ***t*-1** toxicity+	(any, toxicity)
$P_{Y-1}((y-1)-U(y-1)\leq n-r-1, V(y-1)=t-1)$	$p_{11}+p_{21}$
$\sum_{u=\min(0,y-n+r)}^{y-1} P_{Y-1}(U(y-1)=u, V(y-1)=v)$	p_t

$$y=t,\ldots,n$$

Bivariate curtailed single-stage design

$P_{\text{accept}}(Y = y)$

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

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

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

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

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

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

$$P_Y(U(y) = u, V(y) = v) = \sum_{i=\max(0,u+v-y)}^{\min(u,v)} \binom{y}{i \quad u-i \quad v-i \quad y-u-v+i} p_{11}^{i} p_{12}^{u-i} p_{21}^{v-i} p_{22}^{y-u-v+i}$$

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)

$$P_{\mathrm{I}}(Y_1 = y_1)$$

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

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

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

$$y_1 = \min(n_1 - r_1 + 1, t_1), \ldots, n_1$$

$$E_{BC\_I}(Y_1) = \sum_{y_1=\min(n_1-r_1+1, t_1)}^{n_1} y_1 P_{\mathrm{I}}(Y_1 = y_1)$$

$$P_{\text{accept}}(Y = y)$$

$$U, V, Y, n, r, t$$

$$\Rightarrow U_1, V_1, Y_1, n_1, r_1, t_1$$

Bivariate curtailed two-stage design probability and expected sample size

◆Continue to the second stage

$$P_{\mathrm{II}}(Y_1 = y_1)$$

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

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

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

$$y_1 = \max(r_1, n_1 - t_1 + 1), \ldots, n_1$$

$$E_{BC\_II}(Y_1) = \sum_{y_1=\max(r_1, n_1-t_1+1)}^{n_1} y_1 P_{\mathrm{II}}(Y_1 = y_1)$$

$$P_{\mathrm{reject}}(Y = y)$$

$$U, V, Y, n, r, t$$

$$\Rightarrow U_1, V_1, Y_1, n_1, r_1, t_1$$

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 $= n_1 + n_2 - y_1 \rightarrow n$

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

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

$$P_{accept}(Y = y), U, V, Y \Rightarrow U_2, V_2, Y_2$$

$$P_{II,A}(Y_2 = y_2 \mid Y_1 = y_1, U_1(y_1) = u_1, V_1(y_1) = v_1)$$

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

$$+ \sum_{v_2=0}^{\min(m_2-2, y_2-1)} P_{Y_2-1}(U_2(y_2-1) = y_1 + y_2 - n + m_1 - 1, V_2(y_2-1) = v_2)(1 - p_r) I[Y_2 \geq n - y_1 - m_1 + 1]$$

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

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

$$E_{BC\_II,A}(Y_2) = \sum_{y_1=\max(r_1, n_1-t_1+1)}^{n_1} \left\{ P_{II}(Y_1 = y_1) \times \sum_{y_2=\min(n-y_1-m_1+1, m_2)}^{n-y_1} y_2 P_{II,A}(Y_2 = y_2 \mid Y_1 = y_1, U_1(y_1) = u_1, V_1(y_1) = v_1) \right\}$$

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 $= n_1 + n_2 - y_1$ → n r t

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)

$P_{accept}(Y = y), U, V, Y \Rightarrow U_2, V_2, Y_2$

$$P_{\text{II,R}}(Y_2 = y_2 \mid Y_1 = y_1, U_1(y_1) = u_1, V_1(y_1) = v_1)$$

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

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

$$+ \sum_{v_2=0}^{y_1+y_2-n+m_2-2} P_{Y_2-1}(U_2(y_2-1) = m_1 - 1, V_2(y_2-1) = v_2)\, p_r I[Y_2 \geq n - y_1 - m_2 + 2]$$

$$y_2 = \max(m_1, n - y_1 - m_2 + 1), \ldots, n - y_1$$

$$E_{\text{BC\_II,R}}(Y_2) = \sum_{y_1=\max(r_1, n_1-t_1+1)}^{n_1} \left\{ P_{\text{II}}(Y_1 = y_1) \times \sum_{y_2=\max(m_1, n-y_1-m_2+1)}^{n-y_1} y_2 P_{\text{II,R}}(Y_2 = y_2 \mid Y_1 = y_1, U_1(y_1) = u_1, V_1(y_1) = v_1) \right\}$$

Bivariate curtailed two-stage design

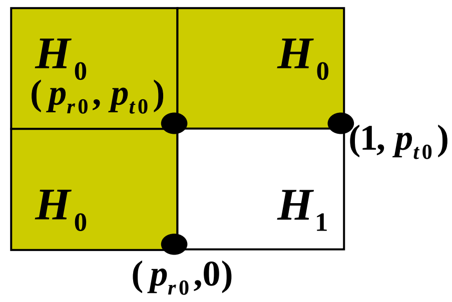
The probability of rejecting the null hypothesis

$$
\begin{aligned}
&R_{BC}(n_1,r_1,t_1,n_2,r_2,t_2 \mid p_r, p_t, \phi) \\
&= \sum_{y_1=\max(r_1,n_1-t_1+1)}^{n_1} \Big\{ P_{Y_1-1}(U_1(y_1-1)=r_1-1, V_1(y_1-1)=y_1-n_1+t_1-1)\, p_{12} \\
&\qquad \times \sum_{y_2=\max(m_1,n-y_1-m_2+1)}^{n-y_1} P_{\mathrm{II,R}}(Y_2=y_2 \mid Y_1=y_1, U_1(y_1)=r_1-1, V_1(y_1)=y_1-n_1+t_1-1) \Big\} \\
&\quad + \sum_{y_1=\max(r_1+1,n_1-t_1+1)}^{n_1} \sum_{u_1=r_1}^{y_1-1} \Big\{ P_{Y_1-1}(U_1(y_1-1)=u_1, V_1(y_1-1)=y_1-n_1+t_1-1)(1-p_t) \\
&\qquad \times \sum_{y_2=\max(m_1,n-y_1-m_2+1)}^{n-y_1} P_{\mathrm{II,R}}(Y_2=y_2 \mid Y_1=y_1, U_1(y_1)=u_1, V_1(y_1)=y_1-n_1+t_1-1) \Big\} \\
&\quad + \sum_{y_1=\max(r_1,n_1-t_1+2)}^{n_1} \sum_{v_1=0}^{y_1-n_1+t_1-2} \Big\{ P_{Y_1-1}(U_1(y_1-1)=r_1-1, V_1(y_1-1)=v_1)\, p_r \\
&\qquad \times \sum_{y_2=\max(m_1,n-y_1-m_2+1)}^{n-y_1} P_{\mathrm{II,R}}(Y_2=y_2 \mid Y_1=y_1, U_1(y_1)=r_1-1, V_1(y_1)=v_1) \Big\}
\end{aligned}
$$

$$E_{BC}(N \mid p) = E_{BC\_I}(Y_1) + E_{BC\_II}(Y_1) + E_{BC\_IIR}(Y_2) + E_{BC\_IIA}(Y_2)$$

Bivariate curtailed two-stage design
design parameters

Errors requirement



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

Ψ_{BC}

Minimax design

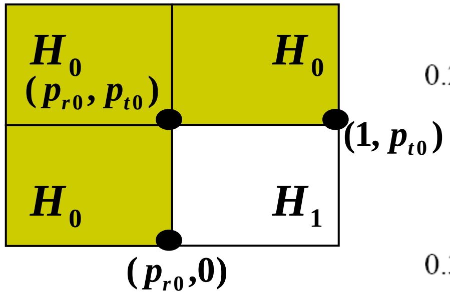
Minimim total sample size $\Phi_{BC} = \{(n_1, r_1, t_1, n_2, r_2, t_2) \mid \min_{\Psi_{BC}} (n_1 + n_2)\}$

Minimim expected total sample size $\min_{\Phi_{BC}} E_C(N \mid p_0)$

Bivariate curtailed two-stage design design parameters

$p_{to} = 0.30$

$p_{t1} = 0.15$



(p_{r0}, p_{t0}) $(p_{r0}, 0)$ $(1, p_{t0})$ (p_{r1}, p_{t1})

Design parameters									size			power	$p = (p_{r0}, p_{t0})$
p_{r0}	p_{r1}	ϕ	n_1	r_1	t_1	n	r_2	t_2	α_1	α_2	α_3	$1-\beta'$	$E_{BC}(N \mid p)$
0.1	0.35	2	21	2	8	49	10	10	0.0005	0.0212	0.0479	0.8000	26.6052
		4	27	3	9	49	10	10	0.0002	0.0213	0.0479	0.8000	27.6104
		6	23	2	9	49	10	10	0.0001	0.0213	0.0479	0.8002	28.2139
		8	23	2	9	49	10	10	0.0001	0.0213	0.0479	0.8001	28.1236
0.2	0.45	2	20	5	7	53	17	11	0.0005	0.0235	0.0476	0.8028	21.9691
		4	20	5	7	53	17	11	0.0002	0.0235	0.0476	0.8015	21.4122
		6	20	5	7	53	17	11	0.0001	0.0235	0.0476	0.8009	21.0958
		8	20	5	7	53	17	11	0.0000	0.0235	0.0476	0.8006	20.8815
0.3	0.55	2	20	7	7	53	22	11	0.0010	0.0439	0.0476	0.8029	21.9129
		4	20	7	7	53	22	11	0.0004	0.0439	0.0476	0.8017	21.2901
		6	20	7	7	53	22	11	0.0002	0.0439	0.0476	0.8012	20.9385
		8	20	7	7	53	22	11	0.0001	0.0439	0.0476	0.8010	20.6986
0.4	0.65	2	18	8	7	53	28	11	0.0008	0.0362	0.0481	0.8000	21.9863
		4	21	9	7	53	28	11	0.0003	0.0378	0.0473	0.8025	22.0996
		6	21	9	7	53	28	11	0.0002	0.0378	0.0473	0.8021	21.7577
		8	21	9	7	53	28	11	0.0001	0.0378	0.0473	0.8019	21.5306

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