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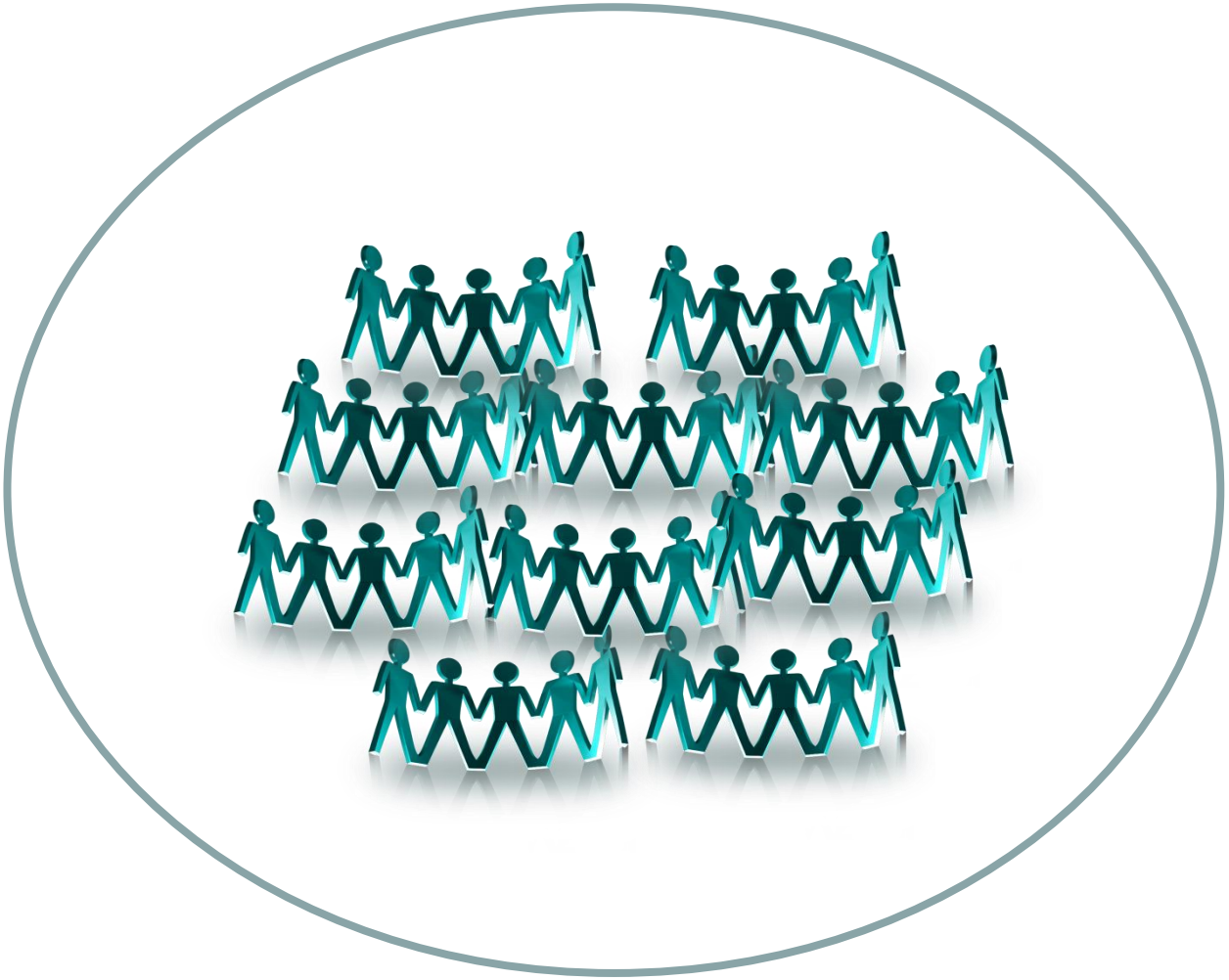
Designing a Series of Hybrid Trials with Continuous Outcomes

Siew Wan Hee

SCT 34th Annual Meeting (2013)

THE UNIVERSITY OF WARWICK

Motivation: Phase II



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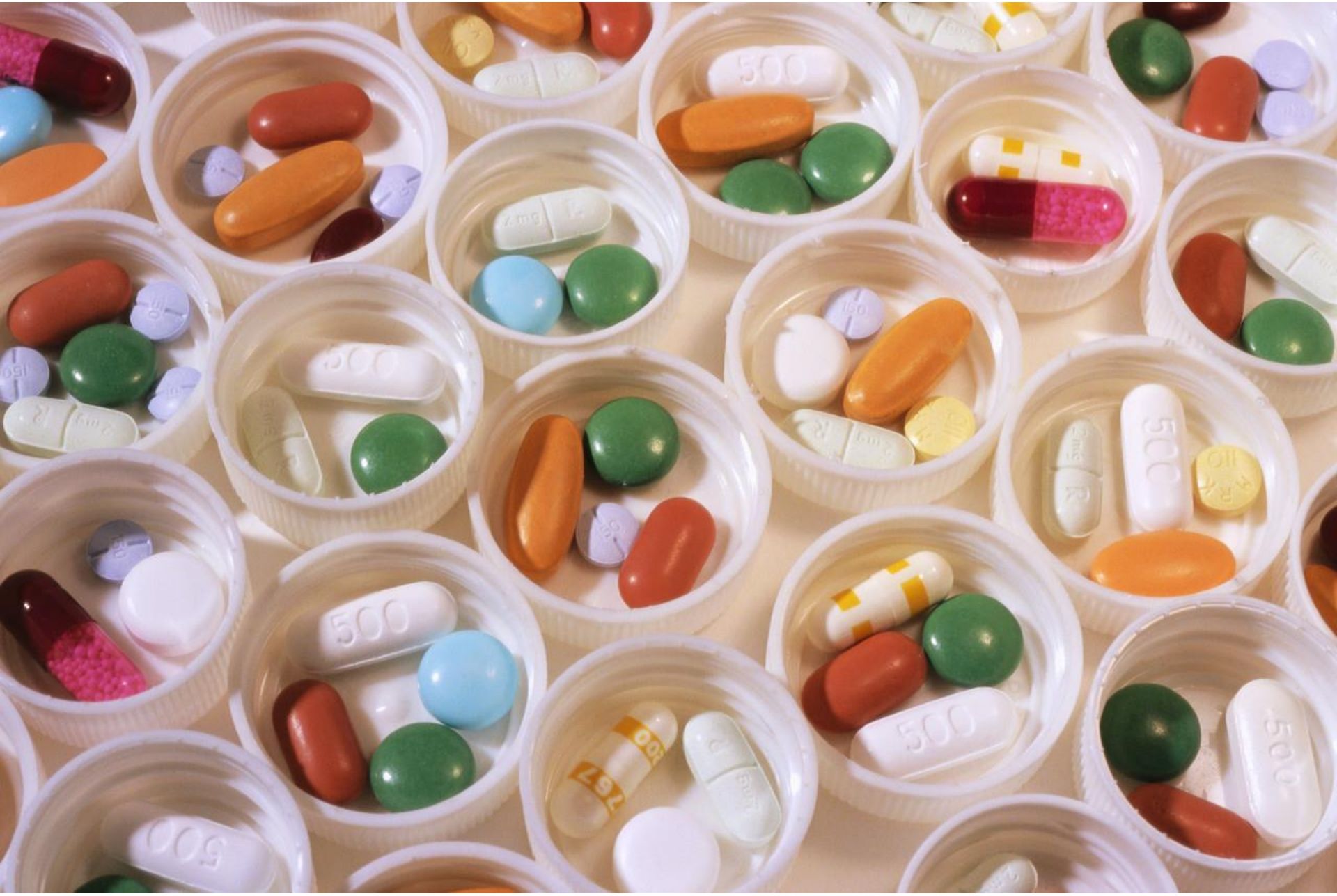

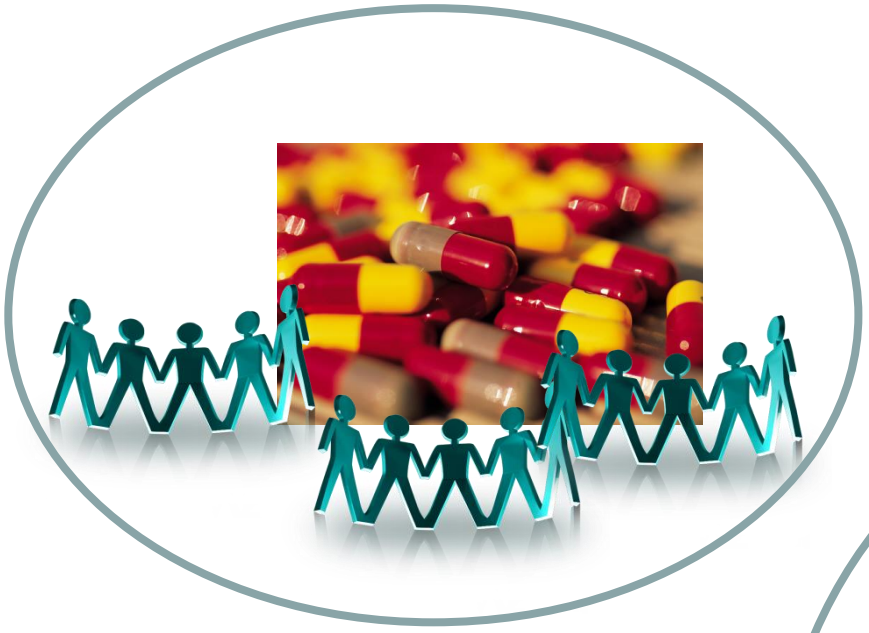

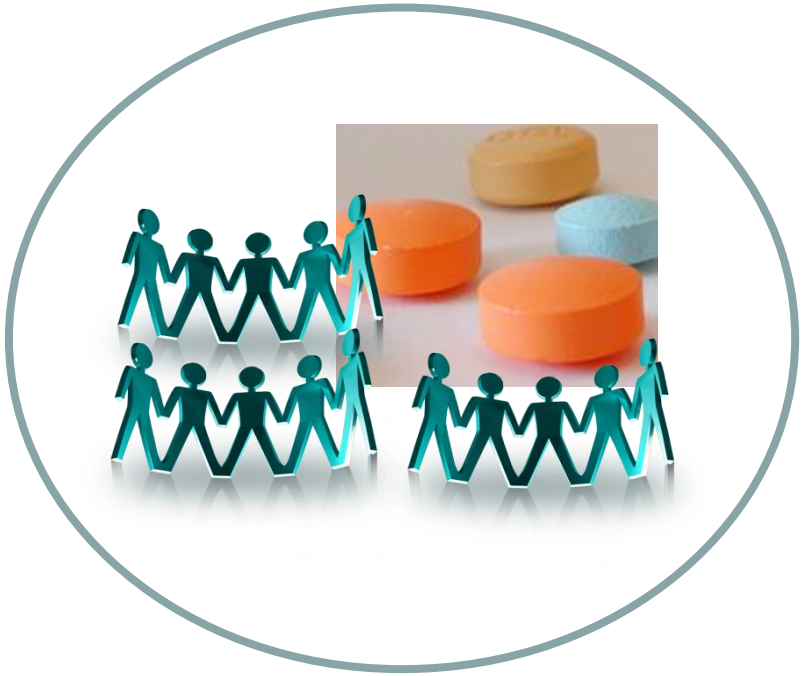

Proposal

$X_1 \sim N(\theta_1, \sigma^2 In)$

$X_2 \sim N(\theta_2, \sigma^2 In)$

… … … …

$X_k \sim N(\theta_k, \sigma^2 In)$

Random parameter

$$\theta_i \sim N(\mu, \tau^2), \qquad i = 1, 2, \ldots, k$$

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Sample Size Determination

$$H_0: \theta_i = \theta_0 \qquad \text{vs.} \qquad H_1: \theta_i \neq \theta_0$$

- θ_0 mean of historical control

- Controlling type I and II errors

$$\Pr(|X_i| > c \mid \theta_i = \theta_0) = \alpha / 2$$

$$\Pr(|X_i| > c \mid \theta_i = \theta_A) = 1 - \beta$$

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Sample Size Determination

$$n = \frac{\sigma^2 \left(z_{1-\alpha/2} - z_{\beta} \right)^2}{\left(\theta_A - \theta_0 \right)^2}$$

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Assurance (Average Power)

$$A(n) = \int (Power)\, f(\theta_i)\, d\theta_i$$

$$= 1 - \Phi\left(\frac{z_{1-\alpha/2} - \sqrt{n/\sigma^2}(\mu - \theta_0)}{\sqrt{1 + n\tau^2/\sigma^2}} \right)$$

Average probability of rejecting H_0 over all possible values of the parameter of interest based on prior density

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Limits of Assurance

$$\lim_{n \to 0} A(n) = 1 - \Phi\left(z_{1-\alpha/2}\right) = \alpha/2$$

$$\lim_{n \to \infty} A(n) \approx \lim_{n \to \infty} 1 - \Phi\left(\frac{z_{1-\alpha/2} - \sqrt{n/\sigma^2}(\mu - \theta_0)}{\sqrt{n\tau^2/\sigma^2}} \right)$$

$$= \Phi\left(\frac{\mu - \theta_0}{\tau} \right)$$

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Maximization of No. of Successful Trials

Population of N

Sample size of n

$$K = N/n$$

$$\tilde{K}(n) = \text{no. of trials reject } H_0$$

$$E\left(\tilde{K}(n)\right) = KA(n)$$

$$\max_{n*} E\left(\tilde{K}(n*)\right) = KA(n^*)$$

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Limits of $E(\tilde{K}(n))$

$$E\left(\tilde{K}(n)\right) = KA(n) = \frac{N}{n} A(n)$$

$$n \to 0$$

$$\lim_{n \to 0} E\left(\tilde{K}(n)\right) \to \infty$$

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Limits of $E(\tilde{K}(n))$

$$E\left(\tilde{K}(n)\right) = KA(n) = \frac{N}{n} A(n)$$

$$n \to \infty$$

$$\lim_{n\to\infty} E\left(\tilde{K}(n)\right) \approx \lim_{n\to\infty} A(n) = \Phi\left(\frac{\mu - \theta_0}{\tau}\right)$$

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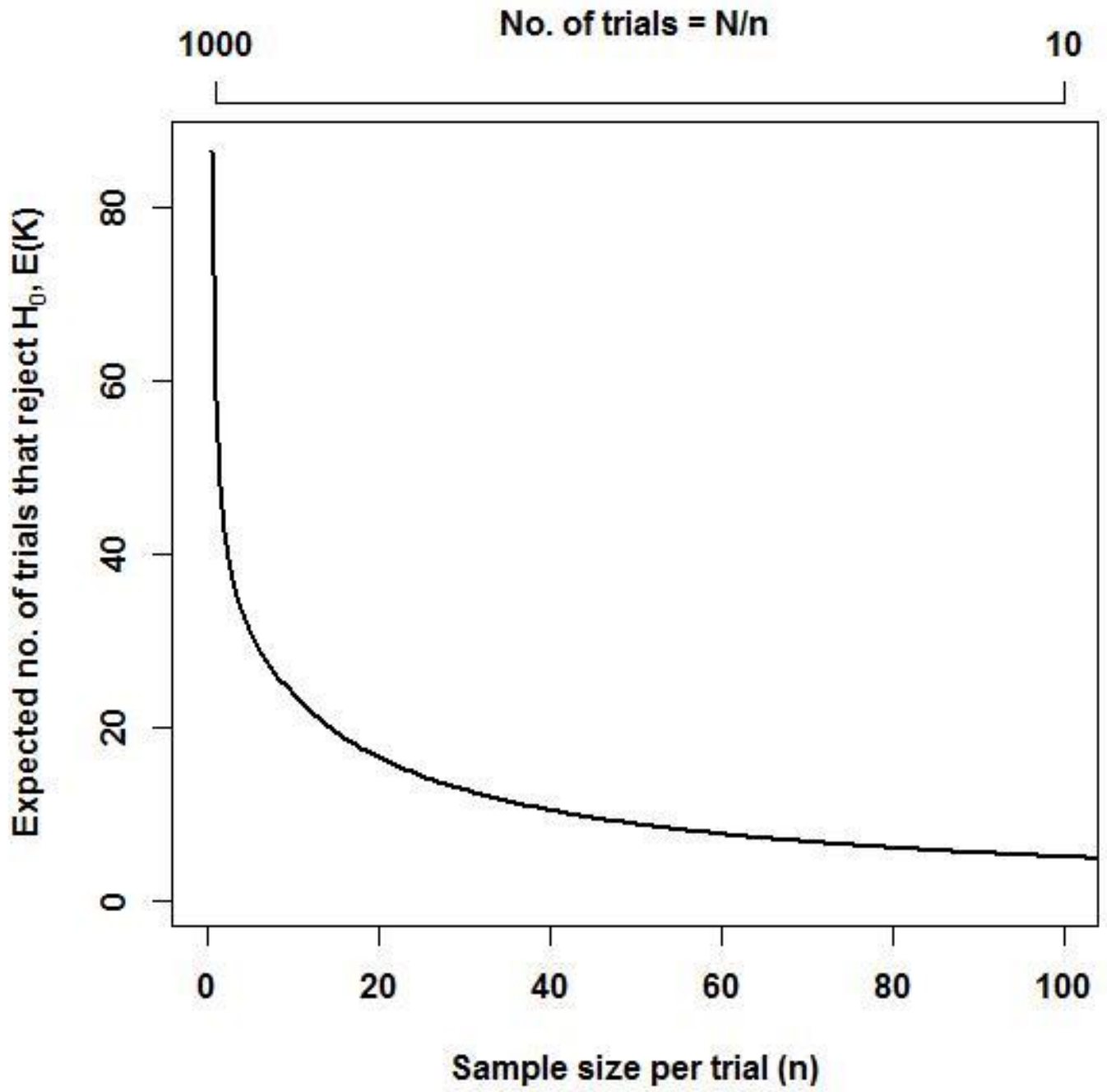
No. of trials = N/n
1000
10
Expected no. of trials that reject H_0, E(K)
0
20
40
60
80
0
20
40
60
80
100
Sample size per trial (n)

Summary

Optimal sample size, $n^* = 0$

Maximum of expected number of successful trials is attainable by not recruiting any patient to the trial

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Include Start-up Cost

1 successful trial = 1 unit of gain

$E\left(\widetilde{K}(n)\right)$ successful trials = $E\left(\widetilde{K}(n)\right)$ units of gain

l_2 = fixed start-up cost of a trial; relative to 1 unit of gain

l_2K = total cost for all trials

$$G(n) = E\left(\widetilde{K}(n)\right) - l_2K$$

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Maximization of Expected Utility

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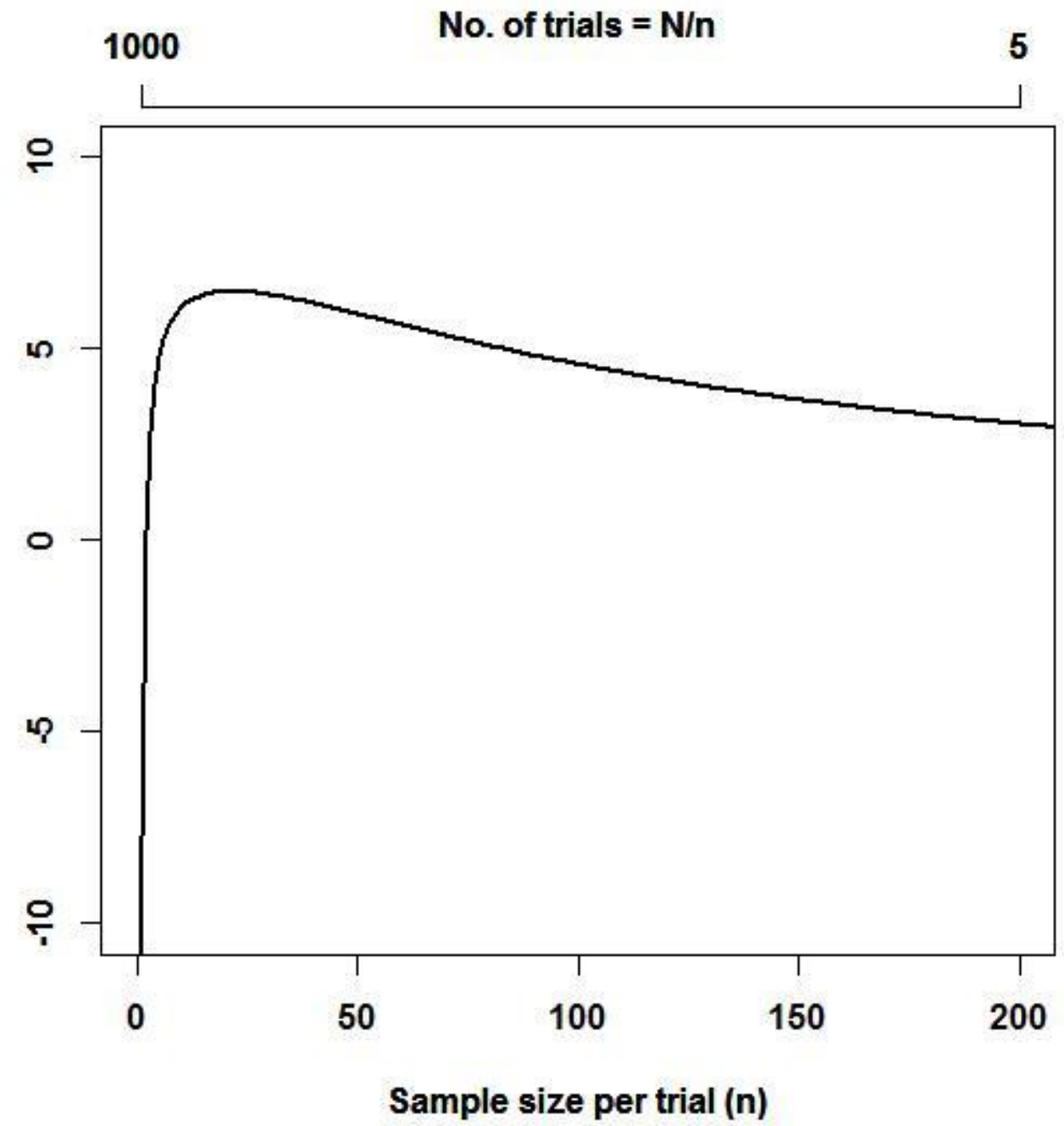
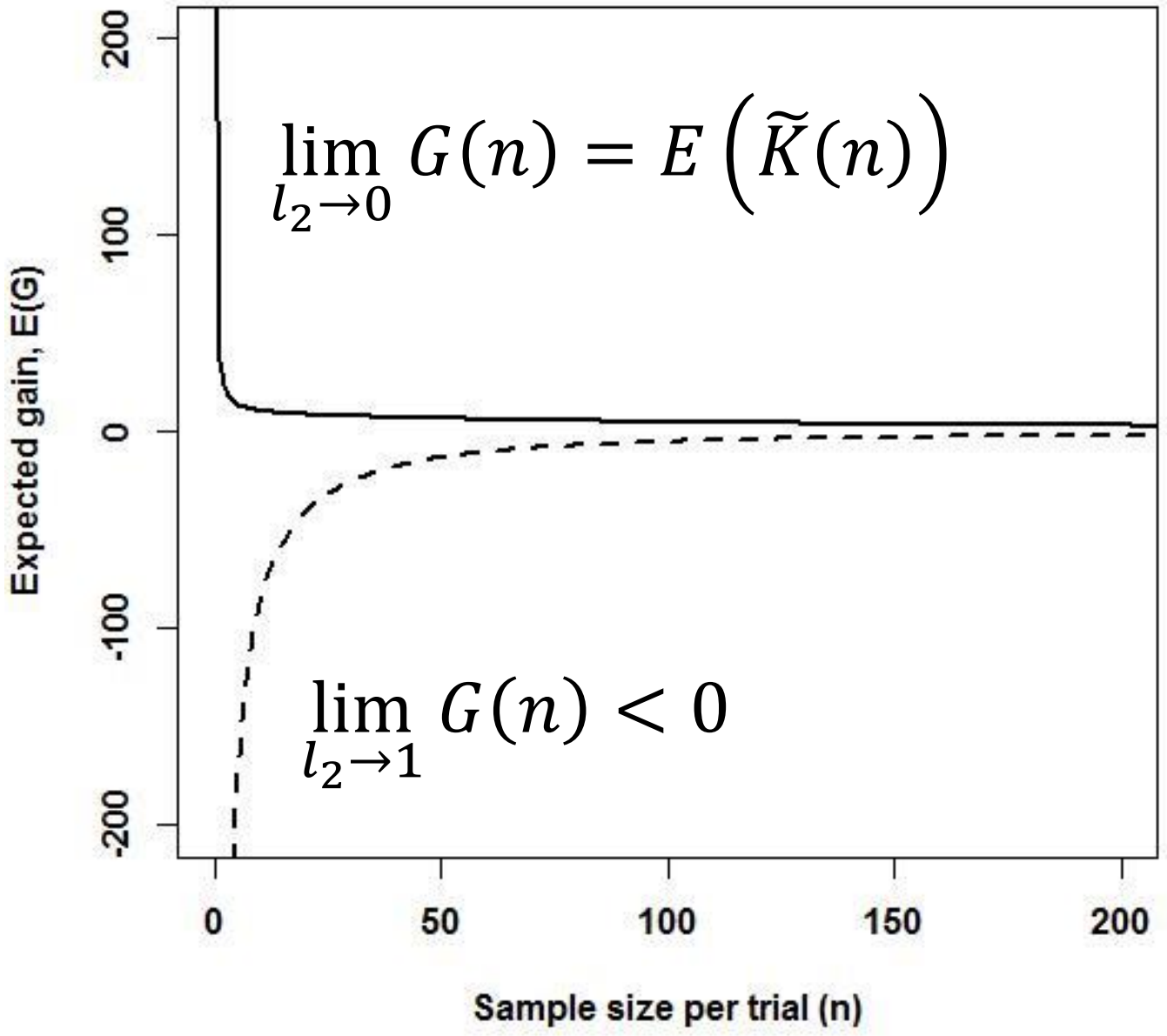

No. of trials = N/n
1000
5
10
5
0
-5
-10
0
50
100
150
200
Sample size per trial (n)


$\lim_{l_2 \to 0} G(n) = E\left(\widetilde{K}(n)\right)$
$\lim_{l_2 \to 1} G(n) < 0$
Expected gain, E(G)
200
100
0
-100
-200
0
50
100
150
200
Sample size per trial (n)

Example: N = 1000

σ	μ	τ	n^*	$G(n)$
1.25	1	1	0.93	132.642
1.25	1	2	0.40	258.465
1.25	1	5	0.09	949.198
2	1	1	2.37	51.813
2	1	2	1.02	100.963
2	1	5	0.24	370.974
5	1	1	14.83	8.290
5	1	2	6.38	16.154
5	1	5	1.51	59.356

Summary

Negligible cost; optimal sample size, $n^* = 0$.

High cost; not worth starting any trial at all.

Variance of prior increases; expected utility increases, sample size decreases.

Variance of likelihood increases; expected utility decreases, sample size increases.

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Conclusion

Combination of classical frequentist and Bayesian.

Design each trial as part of a series of trials so that the long-term gain will be the greatest.

Flexibility to run either sequentially or concurrently.

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References

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