Design of dose-escalation trials

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Abstract

In one form of dose-escalation trial, several cohorts of subjects are recruited. Each cohort takes part at a different time period. The doses are ordinally labelled 0, 1, . . . , where 0 denotes placebo. Because higher doses may have more adverse side-effects, no subject can be exposed to dose i until some information is obtained about the effect of dose $i - 1$.

One possiblity is to use dose i for everyone in cohort i. Then there is no blinding; moreover, dose effects are completely confounded with cohort effects and period effects. A modification of this uses a certain number of placebo subjects in each cohort. If there are no cohort effects then the proportion of placebo in each cohort should be such that the design is equireplicate if it proceeds to the planned largest dose. If there are cohort effects, then more precise comparisons between doses can be made if half of each cohort receives placebo.

I shall discuss a new design that does at least as well as both of these, whether or not there are cohort effects, and whether or not within-cohort information is combined with between-cohort information

Design of the TeGenero trial

Cohort	TGN1412		Placebo
	Dose mg/kg bodyweight	Number of Subjects	Number of Subjects
1	0.1	6	2
2	0.5	6	2
3	2.0	6	2
4	5.0	6	2

What happened to Cohort 1 on 13 March 2006

Healthy Volunteer	Randomised to	Time of intravenous administration	Time of transfer to critical care
A	TGN1412 8.4mg	0800	2400
B	Placebo	0810	
C	TGN1412 6.8mg	0820	2350
D	TGN1412 8.8mg	0830	0030
E	TGN1412 8.2mg	0840	2040
F	TGN1412 7.2mg	0850	0050
G	TGN1412 8.2mg	0900	0100
H	Placebo	0910	

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- generic issues

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- proper interval between dosing subjects
  (sudden adverse effects → do not dose further subjects;
  delayed adverse effects → ill subjects can be treated one by one)

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Planned analysis of the TeGenero trial

Cohort	TGN1412		Placebo
	Dose	Number	Number
1	1	6	2
2	2	6	2
3	3	6	2
4	4	6	2

If all responses are uncorrelated with variance σ^2 then
Variance (dose $i -$ placebo) in cohort i is $\left(\frac{1}{6}+\frac{1}{2}\right)\sigma^2 = \frac{2}{3}\sigma^2$

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Variance (dose $i -$ placebo) is $\left(\frac{1}{6} + \frac{1}{8}\right)\sigma^2 = \frac{7}{24}\sigma^2$

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Variance (dose $i -$ dose j) is $\left(\frac{1}{6}+\frac{1}{6}\right)\sigma^2 = \frac{1}{3}\sigma^2$ if there are no cohort effects

Are there cohort effects?

- Different types of people can volunteer at different times.

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- Protocols for using subsidiary equipment may change.

There have been many trials, in many topics, where, with hindsight, cohort effects swamp treatment effects.

Analysis of the TeGenero trial with cohort effects

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	Dose	Number	Number
1	1	6	2
2	2	6	2
3	3	6	2
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$$\text{Variance (dose } i - \text{ placebo) in cohort } i = \left(\frac{1}{6} + \frac{1}{2}\right)\sigma^2 = \frac{2}{3}\sigma^2.$$

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$$\begin{aligned}
&\text{Estimator of (dose } i - \text{ dose } j) = \\
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$$\text{So variance (dose } i - \text{ dose } j) = \left(\frac{2}{3} + \frac{2}{3}\right)\sigma^2 = \frac{4}{3}\sigma^2.$$

Senn's proposed design

Cohort	TGN1412		Placebo
	Dose	Number	Number
1	1	4	4
2	2	4	4
3	3	4	4
4	4	4	4

Senn's proposed design

Cohort	TGN1412		Placebo
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2	2	4	4
3	3	4	4
4	4	4	4

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Cohort	TGN1412		Placebo
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$$\text{Variance (dose } i - \text{ placebo) in cohort } i = \left(\frac{1}{4} + \frac{1}{4}\right)\sigma^2 = \frac{1}{2}\sigma^2 < \frac{2}{3}\sigma^2.$$

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The TeGenero design is inadmissible because everything can be estimated, from the same resources, with smaller variance, by another design.

Dose-escalation trials: standard designs

There are n doses, with dose $1 <$ dose $2 < \cdots <$ dose n.

0 denotes the placebo.

There are n cohorts of m subjects each.

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no subject receives dose j if $j > i$.

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There are n cohorts of m subjects each.

Cohort 1 subjects may receive only dose 1 or placebo.

In Cohort i, some subjects receive dose i;
no subject receives dose j if $j > i$.

Put $s_{ik} =$ number of subjects who get dose i in cohort k. Then

$$
\begin{aligned}
s_{ik} &> 0 \quad \text{if} \quad i = k \\
s_{ik} &= 0 \quad \text{if} \quad i > k
\end{aligned}
$$

Scaled variance

Assume that the expectation of the response of a subject who gets dose i in cohort k is $\tau_i + \beta_k$, and that responses are uncorrelated with common variance σ^2.

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If doses could be equally replicated within each cohort, then each pairwise variance would be

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so define the scaled variance v_{ij} to be

$$\frac{\text{Variance (dose } i - \text{ dose } j) \times \text{number of observations}}{2(n+1)\sigma^2}.$$

Textbook design

Aim:

- only doses 0 and k in cohort k
- equal replication overall.

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$$s_{ik} = \begin{cases} \dfrac{m}{n+1} & \text{if } i = 0 \\[2ex] \dfrac{nm}{n+1} & \text{if } 0 < i = k \\[2ex] 0 & \text{otherwise.} \end{cases}$$

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Example: $n = 3$, $m = 8$

Dose	0	1	2	3
Cohort 1	2	6	0	0
Cohort 2	2	0	6	0
Cohort 3	2	0	0	6

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$$v_{0i} = \frac{n+1}{2} \qquad v_{ij} = n+1$$

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Example: $n = 3$, $m = 8$

Dose	0	1	2	3
Cohort 1	4	4	0	0
Cohort 2	4	0	4	0
Cohort 3	4	0	0	4

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Example: $n = 3$, $m = 8$

Dose	0	1	2	3
Cohort 1	4	4	0	0
Cohort 2	4	0	4	0
Cohort 3	4	0	0	4

$$v_{0i} = \frac{2n}{n+1} \qquad v_{ij} = \frac{4n}{n+1}$$

My proposed “halving” design

Aim:

- make pairwise variances lower than in other designs, whether or not there are cohort effects.

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$$s_{ik} = \begin{cases} \dfrac{m}{2^k} & \text{if } i = 0 \\[2ex] \dfrac{m}{2^{k-i+1}} & \text{if } 0 < i \leq k \\[2ex] 0 & \text{otherwise.} \end{cases}$$

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Cohort 3	1	1	2	4

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Dose	0	1	2	3
Cohort 1	4	4	0	0
Cohort 2	2	2	4	0
Cohort 3	1	1	2	4

In Cohort 1: $\dfrac{m}{2}$ subjects get dose 1; $\dfrac{m}{2}$ subjects get placebo.

In Cohort i: $\dfrac{m}{2}$ subjects get dose i; remaining subjects are allocated as in Cohort $i-1$ with numbers halved.

Calculating variances in the halving design ($n = 3$, $m = 8$)

	Cohort 1	Cohort 2	Cohort 3
Dose	0 0 0 0 1 1 1 1	0 0 1 1 2 2 2 2	0 1 2 2 3 3 3 3

Calculating variances in the halving design ($n = 3$, $m = 8$)

	Cohort 1	Cohort 2	Cohort 3
Dose	0 0 0 0 1 1 1 1	0 0 1 1 2 2 2 2	0 1 2 2 3 3 3 3

	cohort 1	cohort 2	cohort 3
$\tau_0 + \tau_1 + 2\tau_2 - 4\tau_3$	not estimable	not estimable	estimable

Calculating variances in the halving design ($n = 3$, $m = 8$)

	Cohort 1	Cohort 2	Cohort 3
Dose	0 0 0 0 1 1 1 1	0 0 1 1 2 2 2 2	0 1 2 2 3 3 3 3
Z_3			$+ + + + - - - -$

	cohort 1	cohort 2	cohort 3
$\tau_0 + \tau_1 + 2\tau_2 - 4\tau_3$	not estimable	not estimable	estimable

Z_3 is the best linear unbiased estimator of $\tau_0 + \tau_1 + 2\tau_2 - 4\tau_3$.

Calculating variances in the halving design ($n = 3$, $m = 8$)

	Cohort 1	Cohort 2	Cohort 3
Dose	0 0 0 0 1 1 1 1	0 0 1 1 2 2 2 2	0 1 2 2 3 3 3 3
Z_3			$+ + + + - - - -$

	cohort 1	cohort 2	cohort 3
$\tau_0 + \tau_1 + 2\tau_2 - 4\tau_3$	not estimable	not estimable	estimable
$\tau_0 + \tau_1 - 2\tau_2$	not estimable	orthogonally estimable	

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Dose	0 0 0 0 1 1 1 1	0 0 1 1 2 2 2 2	0 1 2 2 3 3 3 3
Z_3			+ + + + − − − −
Z_2		+ + + + − − − −	+ + − −

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Calculating variances in the halving design ($n = 3$, $m = 8$)

	Cohort 1	Cohort 2	Cohort 3
Dose	0 0 0 0 1 1 1 1	0 0 1 1 2 2 2 2	0 1 2 2 3 3 3 3
Z_3			+ + + + − − − −
Z_2		+ + + + − − − −	+ + − −

	cohort 1	cohort 2	cohort 3
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$\tau_0 - \tau_1$	orthogonally estimable		

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Dose	0 0 0 0 1 1 1 1	0 0 1 1 2 2 2 2	0 1 2 2 3 3 3 3
Z_3			+ + + + − − − −
Z_2		+ + + + − − − −	+ + − −
Z_1	+ + + + − − − −	+ + − −	+ −

	cohort 1	cohort 2	cohort 3
$\tau_0 + \tau_1 + 2\tau_2 - 4\tau_3$	not estimable	not estimable	estimable
$\tau_0 + \tau_1 - 2\tau_2$	not estimable	orthogonally estimable	
$\tau_0 - \tau_1$	orthogonally estimable		

Z_3 is the best linear unbiased estimator of $\tau_0 + \tau_1 + 2\tau_2 - 4\tau_3$.
$Z_2/3$ is the best linear unbiased estimator of $\tau_0 + \tau_1 - 2\tau_2$.
$Z_1/7$ is the best linear unbiased estimator of $\tau_0 - \tau_1$.

Calculating variances in the halving design (continued)

In general, put $Z_j =$
(sum of responses on doses $0, \ldots, j-1$ in cohorts $j, \ldots, n$)
$-$ (sum of responses on dose j)

The Z_j are uncorrelated, with known means and known variances. Linear combinations of them give estimators of all contrasts in the doses.

Hence . . .

Calculating variances in the halving design (continued)

In general, put $Z_j =$
(sum of responses on doses $0, \ldots, j-1$ in cohorts $j, \ldots, n$)
− (sum of responses on dose j)

The Z_j are uncorrelated, with known means and known variances. Linear combinations of them give estimators of all contrasts in the doses.
Hence …

$$\begin{aligned} v_{ij} &= 2^{n-1}\left(\frac{n}{n+1}\right)\left(\sum_{t=i}^{j-1}\frac{1}{f(t)}+\frac{4}{f(j)}\right) && \text{if } 0 < i < j \\ v_{0j} &= v_{1j} && \text{if } 1 < j \\ v_{01} &= 2^{n-1}\left(\frac{n}{n+1}\right)\frac{4}{f(1)} \end{aligned}$$

where

$$f(j) = 2^{n+1} - 2^j.$$

$n = 3, m = 8$

Numbers of subjects

T

Dose	0	1	2	3
Cohort 1	2	6	0	0
Cohort 2	2	0	6	0
Cohort 3	2	0	0	6

S

Dose	0	1	2	3
Cohort 1	4	4	0	0
Cohort 2	4	0	4	0
Cohort 3	4	0	0	4

H

Dose	0	1	2	3
Cohort 1	4	4	0	0
Cohort 2	2	2	4	0
Cohort 3	1	1	2	4

$n = 3, m = 8$ — Scaled variance of differences

Numbers of subjects — no cohort effect

T

Dose	0	1	2	3
Cohort 1	2	6	0	0
Cohort 2	2	0	6	0
Cohort 3	2	0	0	6

	1	2	3
0	1.00	1.00	1.00
1		1.00	1.00
2			1.00

S

Dose	0	1	2	3
Cohort 1	4	4	0	0
Cohort 2	4	0	4	0
Cohort 3	4	0	0	4

	1	2	3
0	1.00	1.00	1.00
1		1.50	1.50
2			1.50

H

Dose	0	1	2	3
Cohort 1	4	4	0	0
Cohort 2	2	2	4	0
Cohort 3	1	1	2	4

	1	2	3
0	0.86	0.93	1.18
1		0.93	1.18
2			1.25

$n = 3, m = 8$

Numbers of subjects — Scaled variance of differences, no cohort effect

T

Dose	0	1	2	3
Cohort 1	2	6	0	0
Cohort 2	2	0	6	0
Cohort 3	2	0	0	6

	1	2	3
0	1.00	1.00	1.00
1		1.00	1.00
2			1.00

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Dose	0	1	2	3
Cohort 1	4	4	0	0
Cohort 2	4	0	4	0
Cohort 3	4	0	0	4

	1	2	3
0	1.00	1.00	1.00
1		1.50	1.50
2			1.50

H

Dose	0	1	2	3
Cohort 1	4	4	0	0
Cohort 2	2	2	4	0
Cohort 3	1	1	2	4

	1	2	3
0	0.86	0.93	1.18
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$n = 3, m = 8$ — Scaled variance of differences

Design	Numbers of subjects: Dose	0	1	2	3	Fitting cohort effect	1	2	3	No cohort effect	1	2	3
T	Cohort 1	2	6	0	0	0	2.00	2.00	2.00	0	1.00	1.00	1.00
	Cohort 2	2	0	6	0	1		4.00	4.00	1		1.00	1.00
	Cohort 3	2	0	0	6	2			4.00	2			1.00

Design	Dose	0	1	2	3		1	2	3		1	2	3
S	Cohort 1	4	4	0	0	0	1.50	1.50	1.50	0	1.00	1.00	1.00
	Cohort 2	4	0	4	0	1		3.00	3.00	1		1.50	1.50
	Cohort 3	4	0	0	4	2			3.00	2			1.50

Design	Dose	0	1	2	3		1	2	3		1	2	3
H	Cohort 1	4	4	0	0	0	0.86	1.21	1.96	0	0.86	0.93	1.18
	Cohort 2	2	2	4	0	1		1.21	1.96	1		0.93	1.18
	Cohort 3	1	1	2	4	2			1.75	2			1.25

$n = 3, m = 8$	Numbers of subjects					Scaled variance of differences: fitting cohort effect				no cohort effect		
	Dose	0	1	2	3		1	2	3		1	2	3

Design	Dose	0	1	2	3		1	2	3		1	2	3
T	Cohort 1	2	6	0	0	0	2.00	2.00	2.00	0	1.00	1.00	1.00
	Cohort 2	2	0	6	0	1		4.00	4.00	1		1.00	1.00
	Cohort 3	2	0	0	6	2			4.00	2			1.00
S	Cohort 1	4	4	0	0	0	1.50	1.50	1.50	0	1.00	1.00	1.00
	Cohort 2	4	0	4	0	1		3.00	3.00	1		1.50	1.50
	Cohort 3	4	0	0	4	2			3.00	2			1.50
H	Cohort 1	4	4	0	0	0	0.86	1.21	1.96	0	0.86	0.93	1.18
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$n = 3, m = 8$							Scaled variance of differences							
	Numbers of subjects					fitting cohort effect				no cohort effect				
	Dose	0	1	2	3		1	2	3		1	2	3
T	Cohort 1	2	6	0	0	0	2.00	2.00	2.00	0	1.00	1.00	1.00
	Cohort 2	2	0	6	0	1		4.00	4.00	1		1.00	1.00
	Cohort 3	2	0	0	6	2			4.00	2			1.00
	Dose	0	1	2	3		1	2	3		1	2	3
S	Cohort 1	4	4	0	0	0	1.50	1.50	1.50	0	1.00	1.00	1.00
	Cohort 2	4	0	4	0	1		3.00	3.00	1		1.50	1.50
	Cohort 3	4	0	0	4	2			3.00	2			1.50
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H	Cohort 1	4	4	0	0	0	0.86	1.21	1.96	0	0.86	0.93	1.18
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Numbers of subjects | fitting cohort effect | no cohort effect

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Dose	0	1	2	3
Cohort 1	2	6	0	0
Cohort 2	2	0	6	0
Cohort 3	2	0	0	6

Fitting cohort effect:

	1	2	3
0	2.00	2.00	2.00
1		4.00	4.00
2			4.00

No cohort effect:

	1	2	3
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1		1.00	1.00
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Fitting cohort effect:

	1	2	3
0	1.50	1.50	1.50
1		3.00	3.00
2			3.00

No cohort effect:

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0	1.00	1.00	1.00
1		1.50	1.50
2			1.50

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How do we calculate variance?

$$r_i = \text{replication of dose } i = \sum_k s_{ik}$$

$$\lambda_{ij} = \text{concurrence of } i \text{ and } j \text{ in cohorts} = \sum_k s_{ik} s_{jk}$$

$$\mathbf{R} = \text{diag}(r_i) \qquad \Lambda = [\lambda_{ij}] \qquad \mathbf{L} = \text{information matrix} = \mathbf{R} - m^{-1}\Lambda$$

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  Feasible if the eigenvectors are "nice" and there are few distinct eigenvalues.
- *Ad hoc* methods for special patterns.

Dose-escalation trials: extended designs

There are n doses, with dose $1 <$ dose $2 < \cdots <$ dose n.

0 denotes the placebo.

There are $n+1$ cohorts of m subjects each.

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0 denotes the placebo.

There are $n+1$ cohorts of m subjects each.

Cohort 1 subjects may receive only dose 1 or placebo.

In Cohort i, for $2 \leq i \leq n$, some subjects receive dose i;
no subject receives dose j if $j > i$.

In Cohort $n+1$, any dose, or placebo, may be used.

Extended textbook design

Maintain overall equal replication in the final cohort.

$$s_{i,n+1} = \frac{m}{n+1} \qquad \text{for } i = 0, \ldots, n$$

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Example: $n = 4$, $m = 15$

Dose	0	1	2	3	4
Cohort 1	3	12	0	0	0
Cohort 2	3	0	12	0	0
Cohort 3	3	0	0	12	0
Cohort 4	3	0	0	0	12
Cohort 5	3	3	3	3	3

Extended Senn design

In the final cohort,
compensate for the previous over-replication of placebo.

$$s_{i,n+1} = \begin{cases} 0 & \text{if } i = 0 \\ \dfrac{m}{n} & \text{otherwise} \end{cases}$$

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Example: $n = 4$, $m = 16$

Dose	0	1	2	3	4
Cohort 1	8	8	0	0	0
Cohort 2	8	0	8	0	0
Cohort 3	8	0	0	8	0
Cohort 4	8	0	0	0	8
Cohort 5	0	4	4	4	4

Extended halving design

Repeat the final cohort of the standard halving design,
to improve comparisons with the highest dose
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Cohort 2	4	4	8	0	0
Cohort 3	2	2	4	8	0
Cohort 4	1	1	2	4	8
Cohort 5	1	1	2	4	8

Calculating variance in the extended Senn design ($n = 4$)

Example: $n = 4$, $m = 16$

Dose	0	1	2	3	4
Cohort 1	8	8	0	0	0
Cohort 2	8	0	8	0	0
Cohort 3	8	0	0	8	0
Cohort 4	8	0	0	0	8
Cohort 5	0	4	4	4	4

Example: $n = 4$, $m = 4$

Dose	0	1	2	3	4
Cohort 1	2	2	0	0	0
Cohort 2	2	0	2	0	0
Cohort 3	2	0	0	2	0
Cohort 4	2	0	0	0	2
Cohort 5	0	1	1	1	1

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Cohort 3	8	0	0	8	0
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Cohort 5	0	4	4	4	4

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Dose	0	1	2	3	4
Cohort 1	2	2	0	0	0
Cohort 2	2	0	2	0	0
Cohort 3	2	0	0	2	0
Cohort 4	2	0	0	0	2
Cohort 5	0	1	1	1	1

$$4\mathbf{L} = \begin{bmatrix} 16 & -4 & -4 & -4 & -4 \\ -4 & 7 & -1 & -1 & -1 \\ -4 & -1 & 7 & -1 & -1 \\ -4 & -1 & -1 & 7 & -1 \\ -4 & -1 & -1 & -1 & 7 \end{bmatrix}$$

Calculating variance in the extended Senn design (contd)

$$4\mathbf{L} = \begin{bmatrix} 16 & -4 & -4 & -4 & -4 \\ -4 & 7 & -1 & -1 & -1 \\ -4 & -1 & 7 & -1 & -1 \\ -4 & -1 & -1 & 7 & -1 \\ -4 & -1 & -1 & -1 & 7 \end{bmatrix}$$

Calculating variance in the extended Senn design (contd)

$$4\mathbf{L} = \begin{bmatrix} 16 & -4 & -4 & -4 & -4 \\ -4 & 7 & -1 & -1 & -1 \\ -4 & -1 & 7 & -1 & -1 \\ -4 & -1 & -1 & 7 & -1 \\ -4 & -1 & -1 & -1 & 7 \end{bmatrix}$$

Put $\mathbf{u} = (4, -1, -1, -1, -1)^\top =$ contrast between dose 0 and the rest.
Put $\mathbf{x} = (0, 1, -1, 0, 0)^\top$ or any other contrast between non-zero doses.

Calculating variance in the extended Senn design (contd)

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Then $\mathbf{Lu} = 5\mathbf{u}$ and $\mathbf{Lx} = 2\mathbf{x}$,

Calculating variance in the extended Senn design (contd)

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Put $\mathbf{x} = (0, 1, -1, 0, 0)^\top$ or any other contrast between non-zero doses.
Then $\mathbf{L}\mathbf{u} = 5\mathbf{u}$ and $\mathbf{L}\mathbf{x} = 2\mathbf{x}$, so

$$\mathbf{L} = 5\mathbf{P}_1 + 2\mathbf{P}_2,$$

where $\mathbf{P}_1 =$ the idempotent for contrast $\mathbf{u}$
and $\mathbf{P}_2 =$ the idempotent for contrasts among the non-zero doses.

Calculating variance in the extended Senn design (contd)

$$4\mathbf{L} = \begin{bmatrix} 16 & -4 & -4 & -4 & -4 \\ -4 & 7 & -1 & -1 & -1 \\ -4 & -1 & 7 & -1 & -1 \\ -4 & -1 & -1 & 7 & -1 \\ -4 & -1 & -1 & -1 & 7 \end{bmatrix}$$

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Then $\mathbf{Lu} = 5\mathbf{u}$ and $\mathbf{Lx} = 2\mathbf{x}$, so

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where $\mathbf{P}_1 =$ the idempotent for contrast $\mathbf{u}$
and $\mathbf{P}_2 =$ the idempotent for contrasts among the non-zero doses.

$$\mathbf{L}^- = \frac{1}{5}\mathbf{P}_1 + \frac{1}{2}\mathbf{P}_2,$$

Hence pairwise variances can be calculated.

Variances in three extended designs

Textbook design

$$v_{0i} = \frac{(n+1)(n+2)}{2(2n+1)}$$

$$v_{ij} = \frac{(n+1)^2}{2n+1}$$

Senn design

$$v_{0j} = \frac{2(4+n^2)}{n(4+n)}$$

$$v_{ij} = \frac{4n}{4+n}$$

Variances in three extended designs

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$$v_{0j} = \frac{2(4+n^2)}{n(4+n)}$$
$$v_{ij} = \frac{4n}{4+n}$$

Halving design

$$v_{ij} = \frac{4+j-i}{4} \quad \text{if } 0 < i < j$$
$$v_{0j} = v_{1j} \quad \text{if } 1 < j$$
$$v_{01} = 1$$

$n = 4$ design — Scaled variance of differences

Textbook

Fitting cohort effect:

	1	2	3	4
0	1.67	1.67	1.67	1.67
1		2.78	2.78	2.78
2			2.78	2.78
3				2.78

No cohort effect:

	1	2	3	4
0	1.00	1.00	1.00	1.00
1		1.00	1.00	1.00
2			1.00	1.00
3				1.00

Senn

Fitting cohort effect:

	1	2	3	4
0	1.25	1.25	1.25	1.25
1		2.00	2.00	2.00
2			2.00	2.00
3				2.00

No cohort effect:

	1	2	3	4
0	0.92	0.92	0.92	0.92
1		1.33	1.33	1.33
2			1.33	1.33
3				1.33

Halving

Fitting cohort effect:

	1	2	3	4
0	1.00	1.25	1.50	1.75
1		1.25	1.50	1.75
2			1.25	1.50
3				1.25

No cohort effect:

	1	2	3	4
0	1.00	1.00	1.00	1.00
1		1.00	1.00	1.00
2			1.00	1.00
3				1.00

$n = 4$ design	Scaled variance of differences: fitting cohort effect					av'e	no cohort effect					av'e
		1	2	3	4			1	2	3	4	
Textbook	0	1.67	1.67	1.67	1.67		0	1.00	1.00	1.00	1.00	
	1		2.78	2.78	2.78	2.33	1		1.00	1.00	1.00	1.00
	2			2.78	2.78		2			1.00	1.00	
	3				2.78		3				1.00	
		1	2	3	4			1	2	3	4	
Senn	0	1.25	1.25	1.25	1.25		0	0.92	0.92	0.92	0.92	
	1		2.00	2.00	2.00	1.70	1		1.33	1.33	1.33	1.17
	2			2.00	2.00		2			1.33	1.33	
	3				2.00		3				1.33	
		1	2	3	4			1	2	3	4	
Halving	0	1.00	1.25	1.50	1.75		0	1.00	1.00	1.00	1.00	
	1		1.25	1.50	1.75	1.40	1		1.00	1.00	1.00	1.00
	2			1.25	1.50		2			1.00	1.00	
	3				1.25		3				1.00	

Average pairwise variance

Theorem (Standard)

For a connected design with information matrix $\mathbf{L}$,
the average of the pairwise variances is $2S\sigma^2$, *where*
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> *For designs with all factors qualitative, such as block designs, the problem of scale does not arise and A- and E-optimum designs are frequently employed.*

Atkinson and Donev,
Optimum Experimental Designs,
OUP, 1992, page 107.

Random cohort effects

Now assume that the expectation of the response of a subject who gets dose i in cohort k is τ_i, and that cohort effects are uncorrelated random variables with common variance σ_C^2.

$$\text{Put } \mathbf{C}_{\alpha\beta} = \begin{cases} 1 & \text{if subjects } \alpha \text{ and } \beta \text{ are in the same cohort} \\ 0 & \text{otherwise.} \end{cases}$$

Then the variance-covariance matrix of the responses is

$$\sigma^2\mathbf{I} + \sigma_C^2\mathbf{C} \quad = \quad \sigma^2\left(\mathbf{I} - \frac{1}{m}\mathbf{C}\right) + \sigma^2\theta^{-1}\frac{1}{m}\mathbf{C}$$

where $\sigma^2 + m\sigma_C^2 = \theta^{-1}\sigma^2$,
so $\theta \in [0,1]$ with $\theta = 0$ if cohort effects are fixed
$\theta = 1$ if cohort effects are zero.

Average variance when information is combined

If we know the value of θ and combine within-cohort and between-cohort information, then the variance of the contrast $\mathbf{x}^\top \boldsymbol{\tau}$ is $\mathbf{x}^\top \left(\mathbf{L} + \theta\widetilde{\mathbf{L}}\right)^- \mathbf{x}\sigma^2$, where

$$\begin{aligned}\mathbf{L} &= \operatorname{diag}(r_i) - m^{-1}\Lambda \\ \widetilde{\mathbf{L}} &= m^{-1}\Lambda - \left(\sum r_i\right)^{-1}[r_i r_j].\end{aligned}$$

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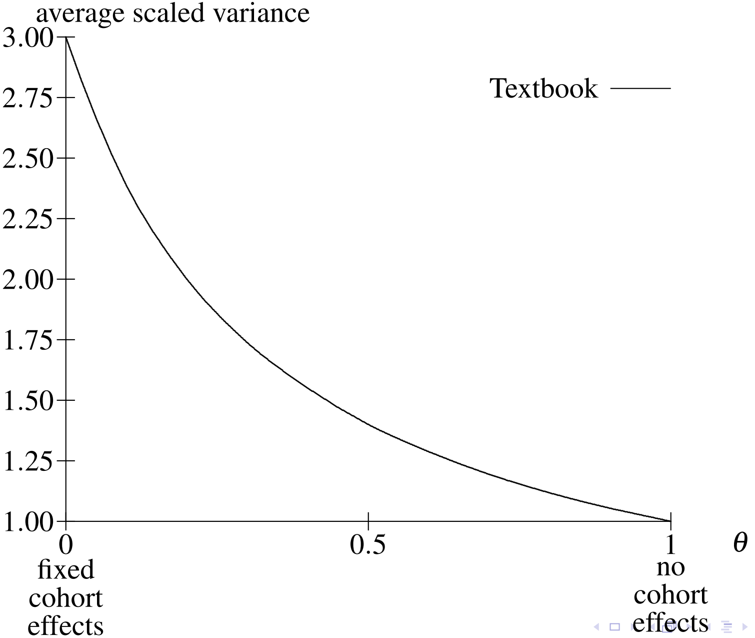
then the sum of the reciprocals of the eigenvalues of $\mathbf{L} + \theta\widetilde{\mathbf{L}}$ is

$$\sum \frac{1}{\gamma_i + \theta\delta_i}.$$

Otherwise, the average variance must be computed numerically for each value of θ.

Average scaled variance for 3 doses in 3 cohorts



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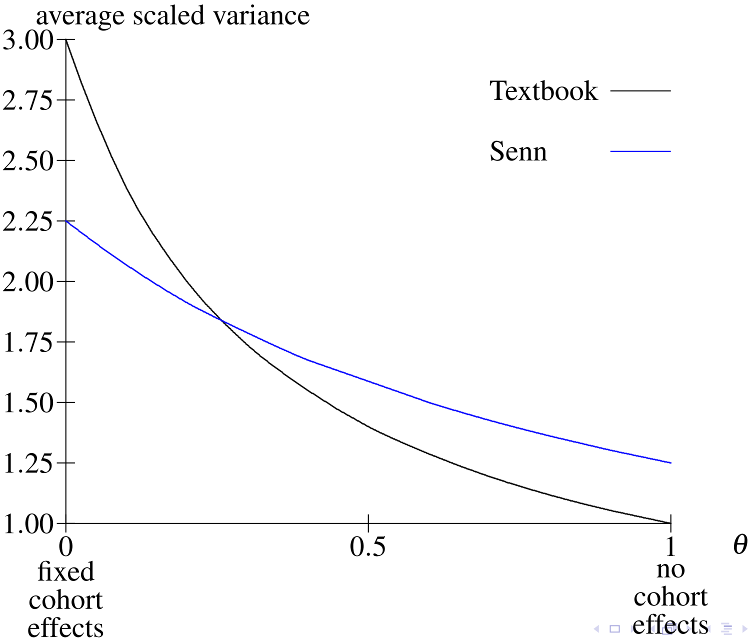

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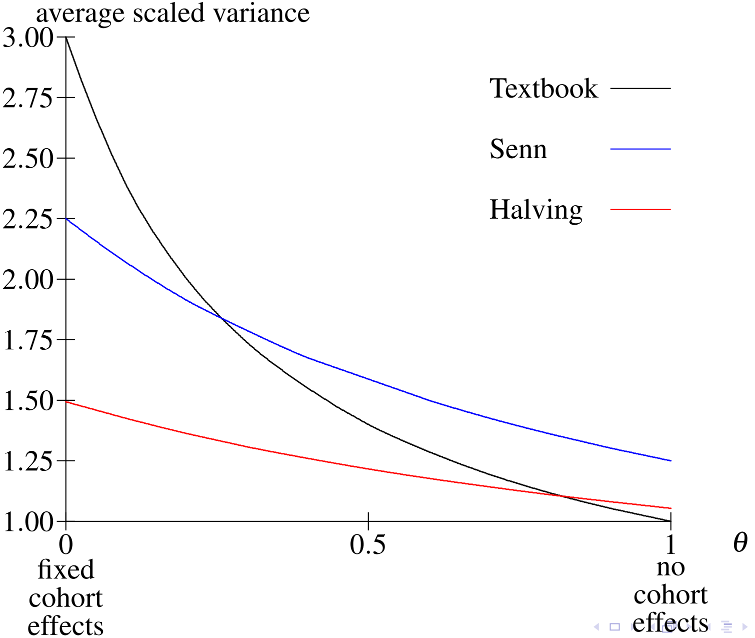
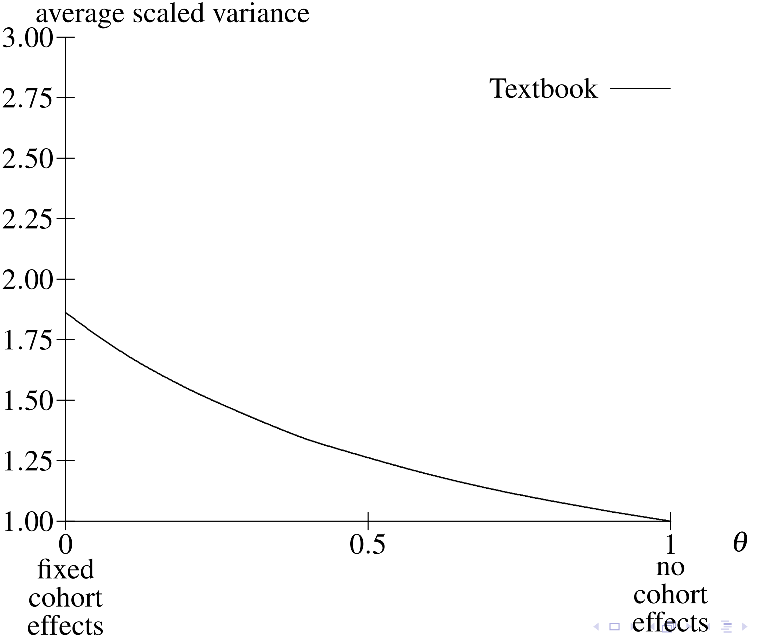


Average scaled variance for 3 doses in 4 cohorts



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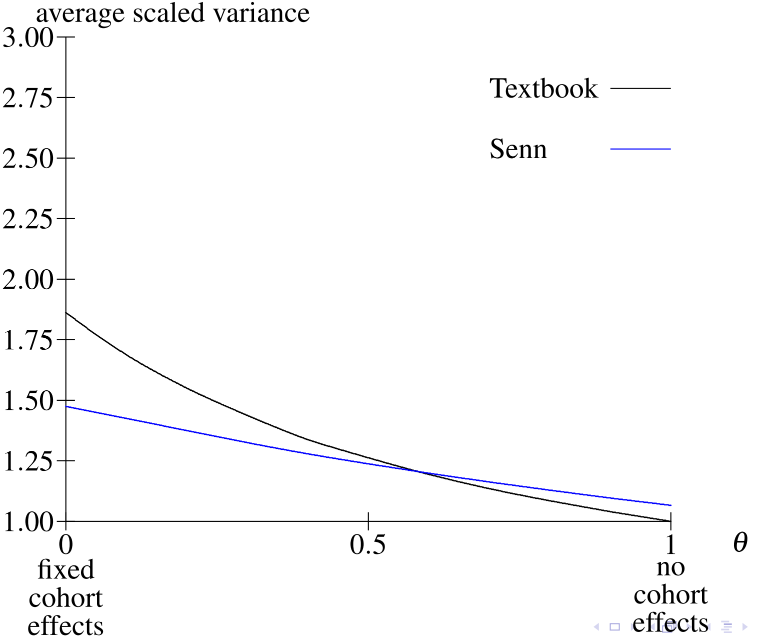

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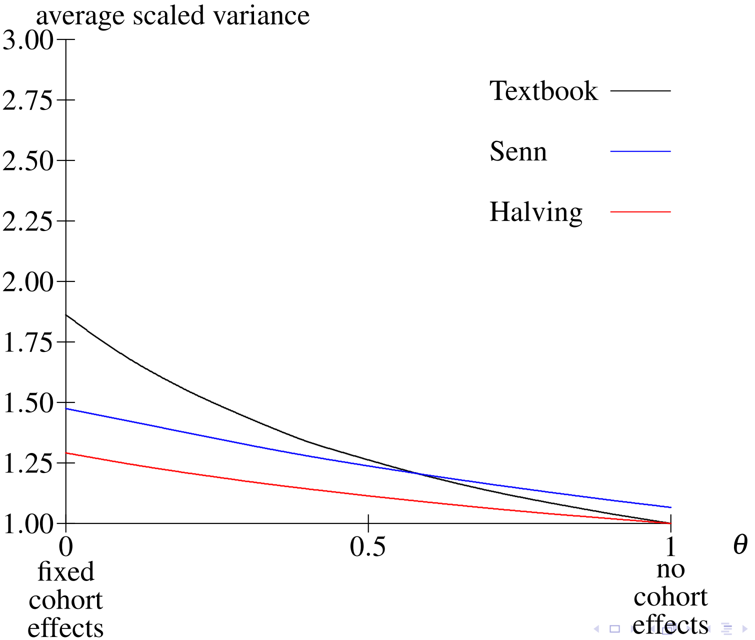

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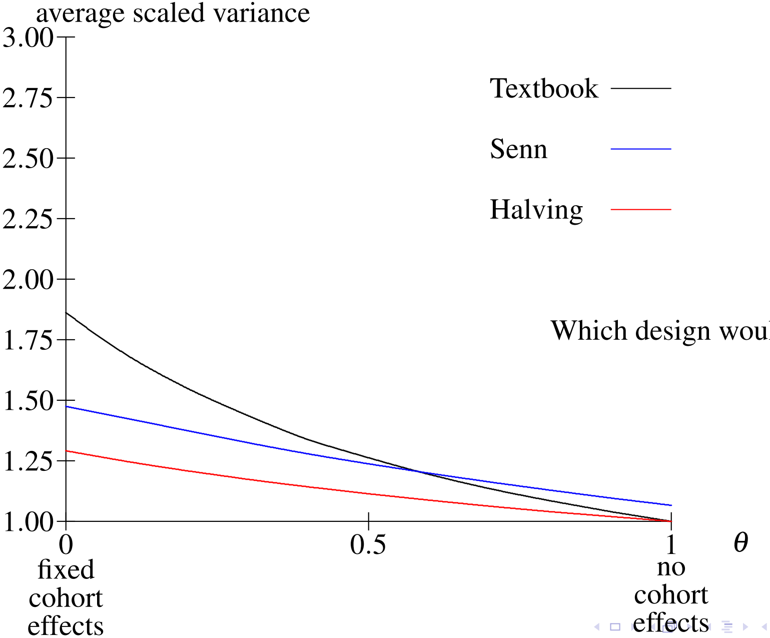

Which design would you use?