Designs for dose-escalation trials

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How should such trials be designed?

Standard designs

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

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There are n cohorts of m subjects each.

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

$$s_{ki} > 0 \quad \text{if} \quad i = k$$
$$s_{ki} = 0 \quad \text{if} \quad i > k.$$

How to assess designs?

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(there is analogous work for random cohort effects).

I shall seek to minimize the average of the pairwise variances,
comparing dose i with dose j for $0 \leq i < j \leq n$.
(Another approach is to concentrate on comparisons with placebo
and seek to minimize the average of the variances for
comparing dose 0 with dose j for $1 \leq j \leq n$.)

Scaled variance

Assume that the expectation of the response of a subject who gets dose i in cohort k is $\tau_i + \beta_k$,
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so define the scaled variance v_{ij} to be

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

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Example: $n = 4$, $m = 10$

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

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Example: $n = 4, m = 8$

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

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In 2006–2009 I investigated various patterns of design satisfying these principles. I am enormously grateful to the INI, who welcomed me to work here while I was recuperating from surgery, while my own institution banned me because their insurance apparently would not allow staff on sick leave to work on the premises.

Proposed "uniform halving" designs

Aim:

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

In Cohort k: $\frac{m}{2}$ subjects get dose k; remaining subjects are allocated as equally as possible to treatments 0 to $k-1$, with larger values given to make the 'replication so far' as equal as possible.

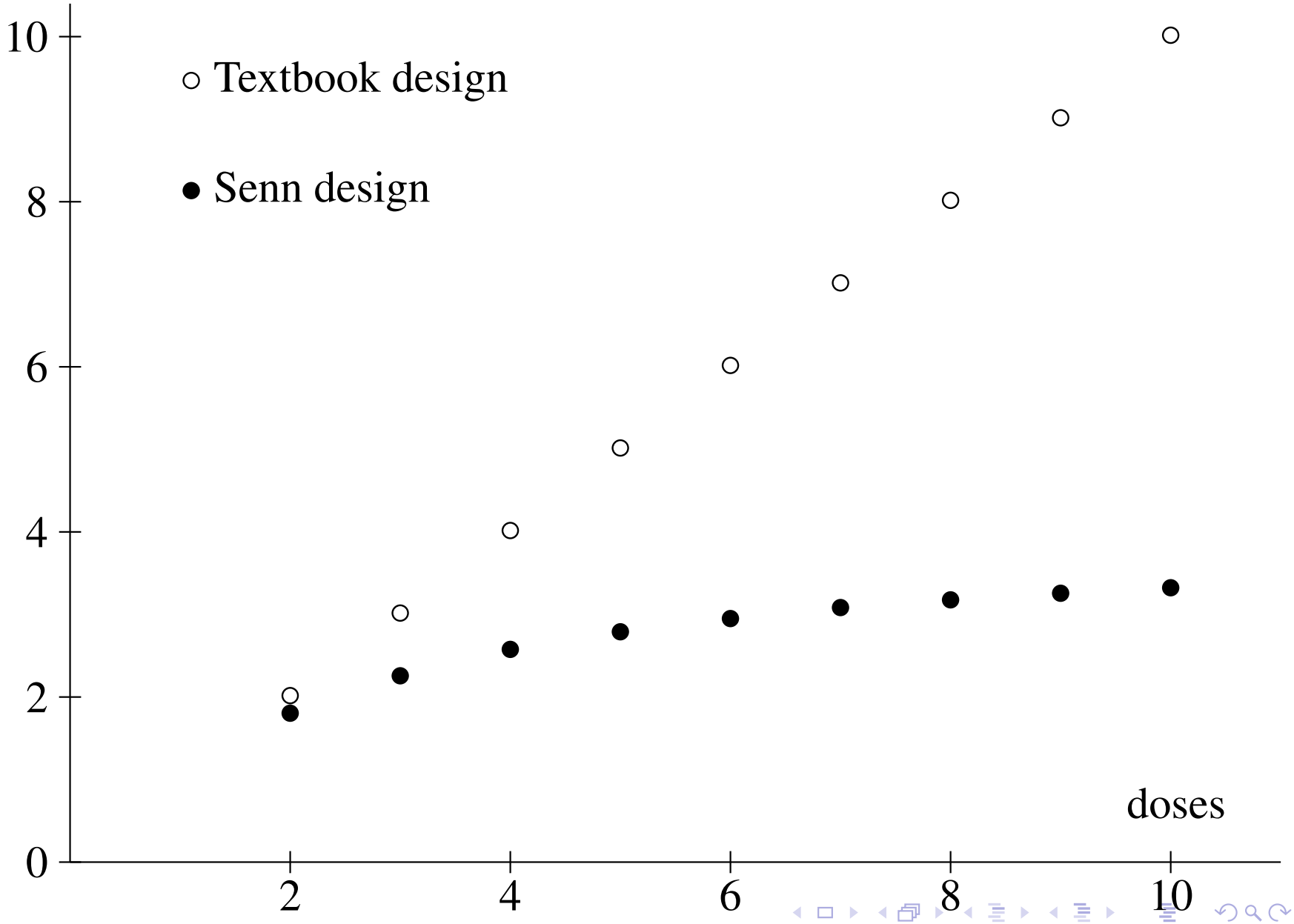
Example of a uniform halving design

Example: $n = 4, m = 8$

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

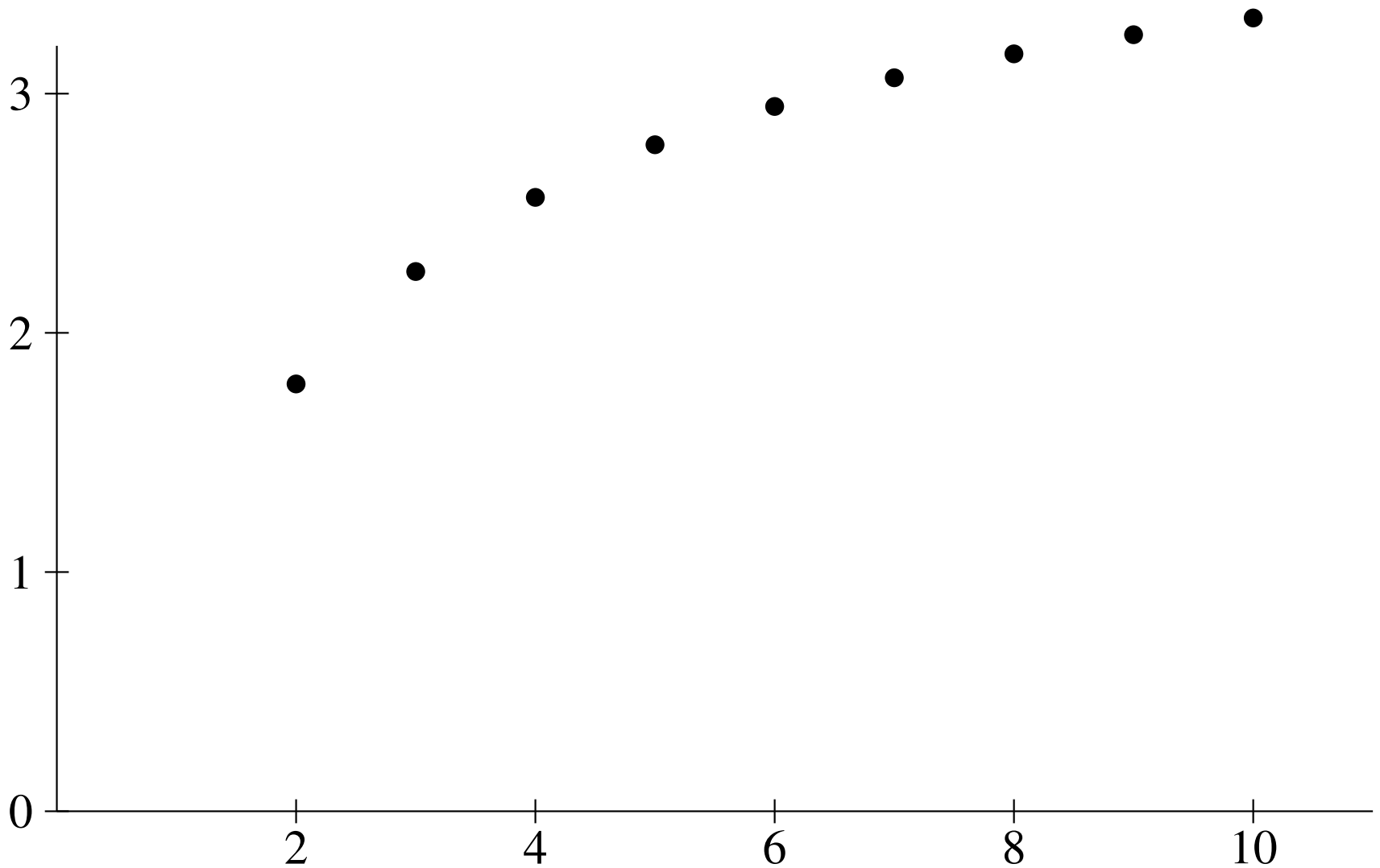
The scaled variances v_{ij} have to be calculated numerically.

Average scaled pairwise variance



Average scaled pairwise variance: continued

- Senn design



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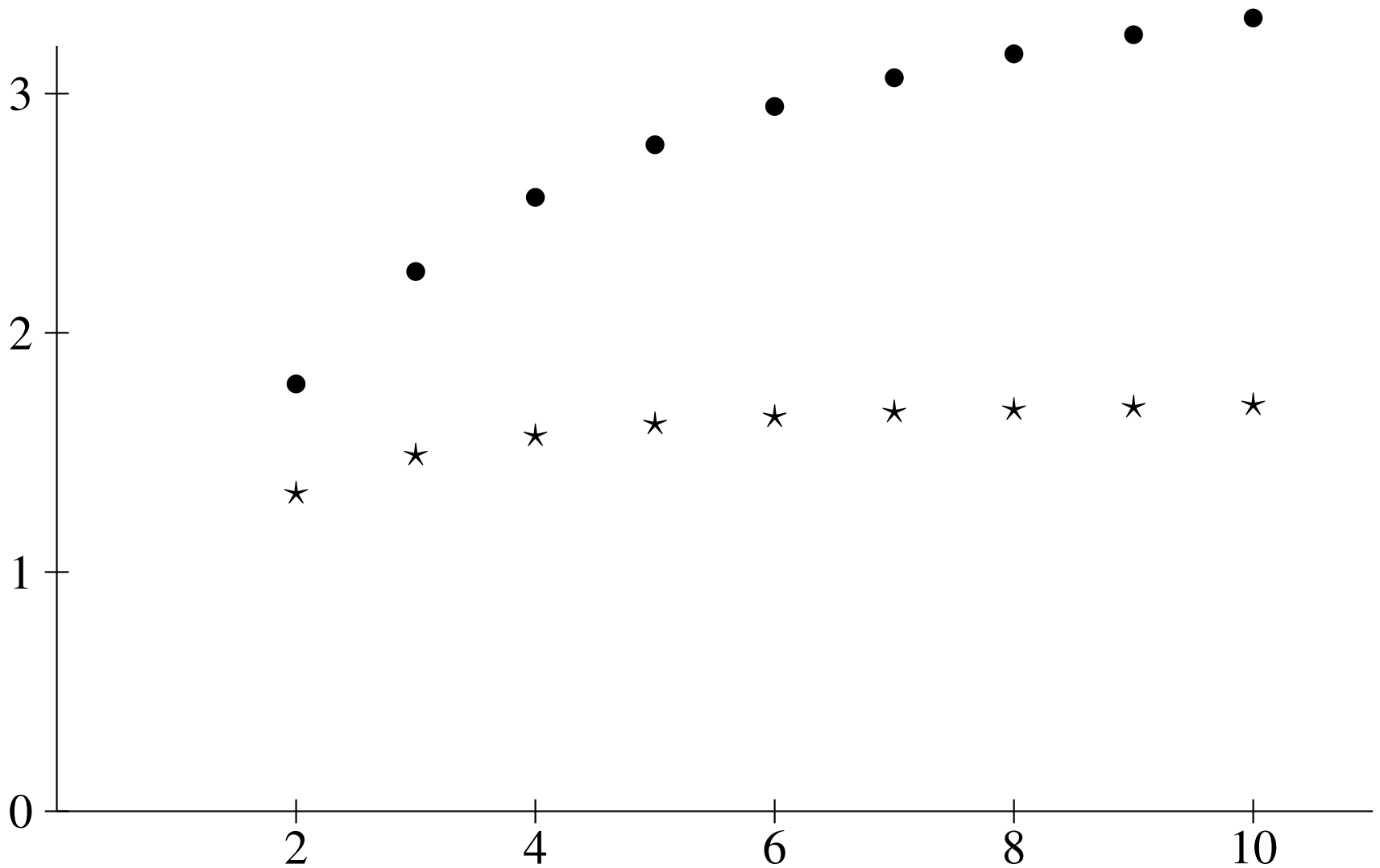
• Senn design ⋆ uniform halving design



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Principle

There should be one more cohort than there are doses,
so that every dose can occur in at least two cohorts.

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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 Senn design

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

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

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

Extension of the uniform halving design

About half the subjects in the final cohort are equally split between all treatments,
the remainder being allocated to make the overall replications as equal as possible, with any inequalities favouring the higher doses.

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Cohort 4	1	1	1	1	4
	1	1	1	1	1
					1
				1	1
Cohort 5	1	1	1	2	3

Average scaled pairwise variance: continued (again)

standard designs

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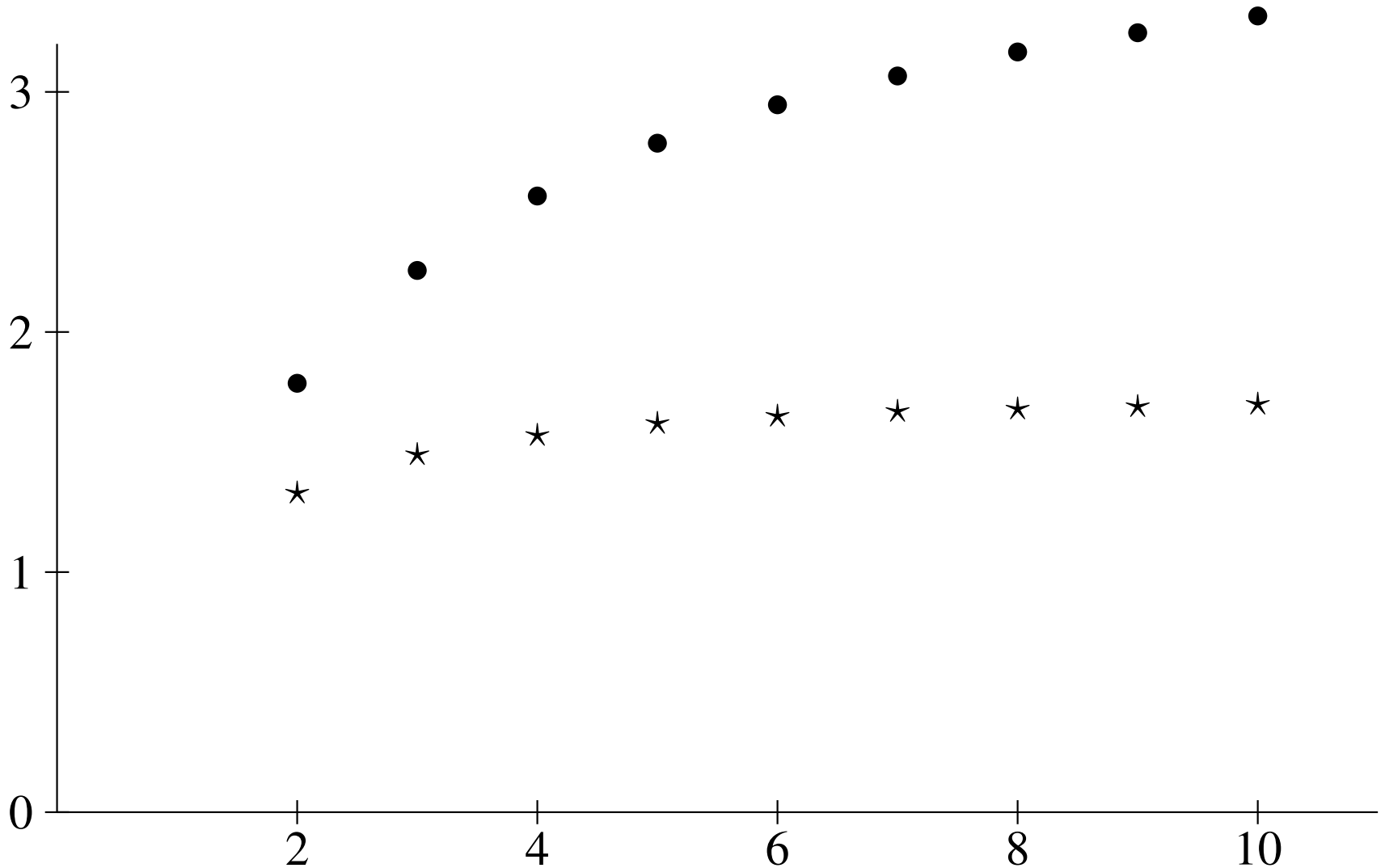

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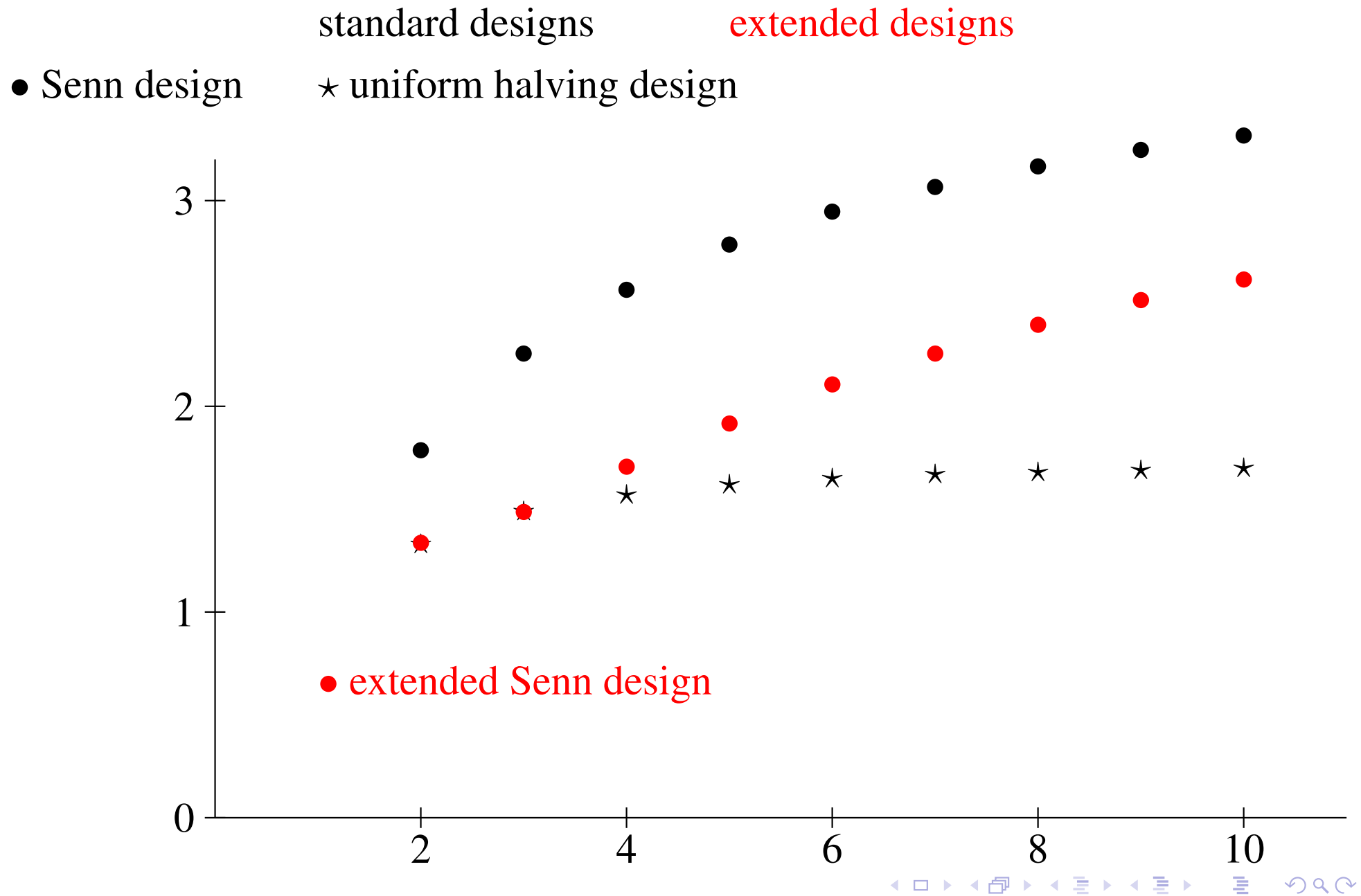

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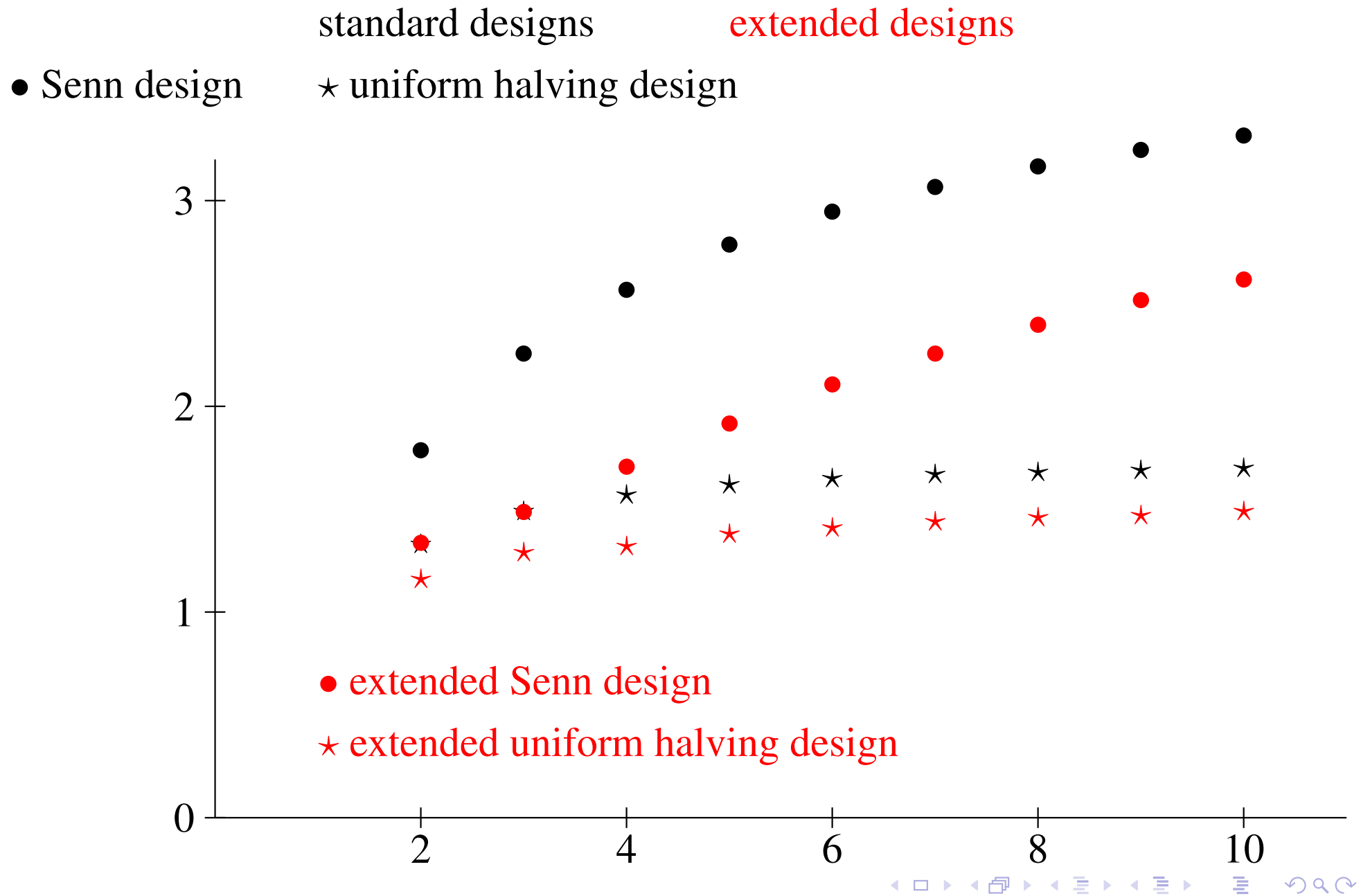

Two designs for 4 doses using 40 subjects

Numbers of subjects

Std TB

Dose	0	1	2	3	4
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Cohort 2	2	0	8	0	0
Cohort 3	2	0	0	8	0
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Actual pairwise variances/σ^2

	1	2	3	4
0	0.625	0.625	0.625	0.625
1		1.250	1.250	1.250
2			1.250	1.250
3				1.250

Ext UH

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

	1	2	3	4
0	0.222	0.285	0.348	0.370
1		0.285	0.348	0.370
2			0.330	0.378
3				0.375

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Actual pairwise variances/σ^2

	1	2	3	4
0	0.625	0.625	0.625	0.625
1		1.250	1.250	1.250
2			1.250	1.250
3				1.250

average 1.00

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Both types can be described by the following simple rule:

Principle

In each cohort,
half of the subjects should be distributed (approximately) equally among all the treatments that have been used in any previous cohort; the remaining subjects should be used to make the replication so far as equal as possible by compensating for previous under-replication.

Advantages of the halving designs

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- Blinding is more effective than in textbook designs.

More recent work: I integer optimization

Dose	0	1	...	n
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...				
Cohort k	s_{k0}	s_{k1}	...	s_{kn}
...				

s_{ki} is an integer and $\sum_{i=0}^{n} s_{ki} = m$

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...				

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Linda Haines and Allan Clark have used complete enumeration (for small values of n and m) and exchange algorithms (for larger values) to find the optimal allocation for various combinations of values of n and m.
They consider various optimality criteria, including A-optimality, which is the criterion that I am using.

An example of an optimized design

For 4 doses, 4 cohorts and 8 volunteers per cohort,
Haines and Clark found that this design is A-optimal.

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

More recent work: II continuous designs, using best so far

Dose	0	1	...	n
Cohort 1	w_{10}	w_{11}	...	0
...				
Cohort k	w_{k0}	w_{k1}	...	w_{kn}
...				

$$0 \leq w_{ki} \text{ and } \sum_{i=0}^{n} w_{ki} = 1$$

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Given the number m of volunteers per cohort,

set s_{ki} to be an integer close to mw_{ki} such that $\sum_{i=0}^{n} s_{ki} = m$.

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Different ways of doing this give almost identical variances.

An example of an optimized best-so-far continuous design

Dose	0	1	2	3	4
Cohort 1	0.500	0.500	0	0	0
Cohort 2	0.270	0.270	0.460	0	0
Cohort 3	0.170	0.170	0.219	0.441	0
Cohort 4	0.118	0.118	0.138	0.196	0.430
Cohort 5	0.135	0.135	0.163	0.219	0.348

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If there are 8 volunteers per cohort, this gives the following design for 2 doses in 2 cohorts, 3 doses in 3 cohorts, and 4 doses in 4 or 5 cohorts.

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

More recent work: III continuous designs, using constant ratios

Heiko Großmann and I are optimizing the proportions w_{ki}, but cut down the search by imposing the condition

$$\frac{w_{ki}}{w_{kj}} \quad \text{does not depend on } k \text{ if } j \geq k \text{ and } i \geq k$$

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$$\frac{w_{ki}}{w_{kj}} \quad \text{does not depend on } k \text{ if } j \geq k \text{ and } i \geq k$$

(in some cases, we can prove that the optimal designs must satisfy this).

Examples of optimized designs

Dose	0	1	2
Cohort 1	0.50	0.50	0
Cohort 2	0.27	0.27	0.46

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Dose	0	1	2
Cohort 1	0.50	0.50	0
Cohort 2	0.29	0.29	0.42
Cohort 3	0.29	0.29	0.42

More recent work: IV other criteria

Vlad Dragalin said that the aim of Phase I trials is to find the maximum tolerable dose, so suggested that we we should minimize $\mathrm{Var}(\hat{\tau}_i - \hat{\tau}_{i-1})$ if the trial stops with i as the maximal tolerable dose.

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Val Fedorov suggested minimizing $\mathrm{Var}(\hat{\tau}_i - \hat{\tau}_0)$ for this situation.

Since we do not know i in advance, these both need a best-so-far approach, and the results are slightly different if we intend to have an 'extra' cohort.

Examples of optimized designs

For dose 2, these two criteria are the same.

Dose	0	1	2
Cohort 1	0.500	0.500	0
Cohort 2	0.257	0.257	0.486

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Dose	0	1	2
Cohort 1	0.500	0.500	0
Cohort 2	0.257	0.257	0.486

Dose	0	1	2
Cohort 1	0.500	0.500	0
Cohort 2	0.265	0.265	0.470
Cohort 3	0.265	0.265	0.470

Examples of optimized designs

For dose 2, these two criteria are the same.

Dose	0	1	2
Cohort 1	0.500	0.500	0
Cohort 2	0.257	0.257	0.486

Dose	0	1	2
Cohort 1	0.500	0.500	0
Cohort 2	0.265	0.265	0.470
Cohort 3	0.265	0.265	0.470

Subsequent cohorts become more and more different for the two criteria.

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