Designs for dose-escalation trials

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Dose-escalation trials

For First-in-Human trials of any new drug,
healthy volunteers are recruited in cohorts.

Several doses of the drug are proposed: for safety reasons, only the lowest dose may used for the first cohort, and no new dose may be used until the one below has been used in a previous cohort.

Placebo (for example, inject sugar solution) must be included,
partly for comparison,
partly because of the 'placebo effect' amongst humans.

There are usually cohort effects.

How should such trials be designed?

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.

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?

I shall treat cohort effects as fixed
(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 $0 \le i < j \le n$.
(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 $1 \le j \le n$.)

Scaled variance

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

"Variance (dose $i-$ dose j)" means $\mathrm{Var}(\widehat{\tau}_i - \widehat{\tau}_j)$.

If we double the number of subjects getting each dose in each cohort, then all variances are divided by 4. We want to know which pattern of design is good irrespective of the number of subjects.

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

$$\frac{2(n+1)\sigma^2}{\text{number of observations}}$$

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.

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

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

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

Senn's design

Aim:

- only doses 0 and k in cohort k
- minimize pairwise variances if there are cohort effects.

$$s_{ki} = \begin{cases} \frac{m}{2} & \text{if } i = 0 \\ \frac{m}{2} & \text{if } 0 < i = k \\ 0 & \text{otherwise.} \end{cases}$$

Example: $n = 4$, $m = 8$

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

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

Lessons from experience with block designs: I

The design is effectively a block design, with the cohorts as blocks.

If any cohort has more than half of its subjects allocated to dose i, then no contrast between i and other treatments can be orthogonal to that cohort.

Principle

In each cohort,
no treatment should be allocated to more than half of the subjects.

Principle

Each cohort should have as many different treatments as possible.

In 2006–2009 I investigated various patterns of design satisfying these principles.

Proposed "uniform halving" designs

Aim:

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

$$s_{ki} = \begin{cases} \frac{m}{2} & \text{if } i = k \\ \text{nonzero} & \text{if } 0 \le i < k \\ 0 & \text{otherwise.} \end{cases}$$

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.

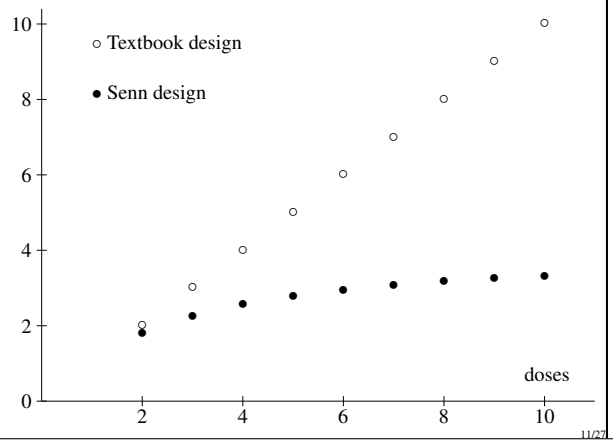
Example of a uniform halving design

Example: $n = 4$, $m = 8$

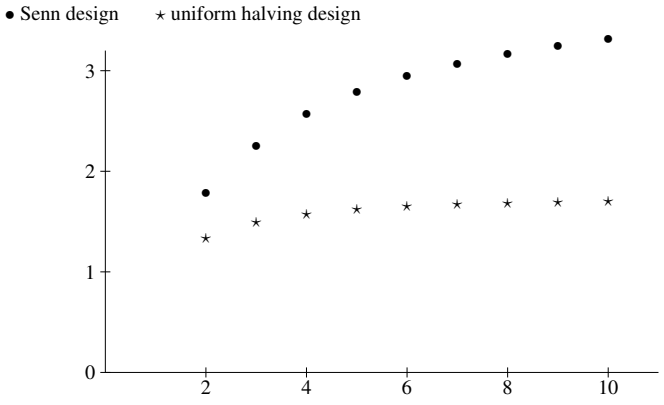
Dose	0	1	2	3	4
Cohort 1	4	4	0	0	0
Cohort 2	2	2	4	0	0
Cohort 3	1	1	2	4	0
Cohort 4	1	1	1	1	4

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

Average scaled pairwise variance



Average scaled pairwise variance: continued



Lessons from experience with block designs: II

In the standard designs,
the highest dose has all of its subjects in the final cohort.

In ordinary block designs, treatment differences are well estimated if and only if block differences are well estimated,
so you would never limit any treatment to just one block.

Principle

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

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.

Cohort 1 subjects may receive only dose 1 or placebo.

In Cohort i, for $2 \le i \le n$, 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.

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

Example: $n = 4$, $m = 8$

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

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

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.

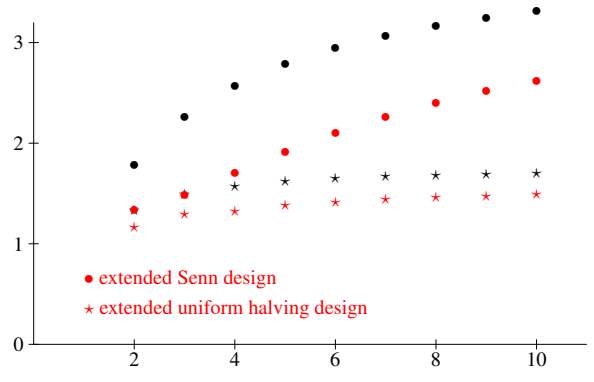
Example: $n = 4$, $m = 8$

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

Average scaled pairwise variance: continued (again)

standard designs extended designs

• Senn design ⋆ uniform halving design



Two designs for 4 doses using 40 subjects

Numbers of subjects

	Dose	0	1	2	3	4
Std TB	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

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

	Dose	0	1	2	3	4
Ext UH	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

average 0.33

Simple rule

Among the standard designs examined, the uniform halving designs are best.

Among the extended designs examined, the best are the uniform halving designs with the particular extension given.

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

- Variance is reduced by a factor of two or more.
- The allocation rule is simple,
  and can be applied to any number of subjects per cohort.
- If the trial has to be stopped early because dose i is harmful, then fewer subjects will have been exposed to dose i than would have been with the textbook design.
- If the trial has to be stopped early because dose i is harmful, then the previous $i-1$ cohorts form the recommended standard design for $i-1$ doses; if desired, they can be followed by an extra cohort for treatments $0, \ldots, i-1$ only.
- If cohort effects are small and random, the variance is very little more than for the textbook design (not shown here).
- Blinding is more effective than in textbook designs.

More recent work: I integer optimization

Dose	0	1	…	n
Cohort 1	s_{10}	s_{11}	…	0
…				
Cohort k	s_{k0}	s_{k1}	…	s_{kn}
…				

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

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}
…				

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

Brendan O'Neill optimized the proportions w_{ki}, but cut down the search by restricting a design for c cohorts to use the best design for $c-1$ cohorts and just optimize the proportions in the final cohort.

Given the number m of volunteers per cohort,

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

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

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

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

(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

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

References

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