Tailor-made Crossover Trials: *the clots in lines study*

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Two themes

- Study is to compare two solutions for preventing clots forming in indwelling lines
  - not many children have haemodialysis (only 6 to 9 in Newcastle)
  - multicentre trial probably not practical
  - use crossover design with many periods?
- Models for multi-period crossover trials have been criticised

Example

- Patients generally dialysed Mon, Wed, Fri
- Some dialysed Mon and Fri only
- Patients have an indwelling line for venous access
- Between sessions clots form in the line and these must be removed before dialysis proceeds
- Aim to prevent this by inoculation of heparin
- If a clot forms, clinicians use a ‘clot-busting’ drug called Alteplase®

Study Question

- Question is whether it would be better to use Alteplase in place of heparin as a routine ‘lock’?
- At start of each session the nurses withdraw the fluid in the line and can recover the clot by passing fluid through a gauze swab. So the weight of clot is the outcome variable.

Study Design

- Not many patients available: only 8 in Newcastle
- Other centres have different protocols
- In any case, we can observe the patients we do have many times – quite a captive group
- Propensity to form clots likely to vary between patients
- Crossover design seems to be appropriate.
- What design?

Multi-period Crossover Trials

- Many designs around - largely stemming from Latin squares
- For two treatments there have been many papers looking at optimal designs
  (Kershner & Federer 1981; Matthews 1987,1990; Kunert 1991; Kushner; 1997.)
- All results based around a model, different papers consider different forms of model

What Model?

- Model is usually for continuous outcome
- Often of the form

$$y_{ij} = x_i + p_j + t_{d(i,j)} + g_{d(i,j-1)} + e_{ij}$$

- Here ξ is a patient effect, π a period effect, τ a *direct* treatment effect and γ a *carryover* treatment effect.
- All sorts of variants possible

- Patient effects – random or fixed?
- Error term – independent within patient or not?
- Period effect – cows in sheds
- Carryover effect – is it plausible?

- Can be criticised on general grounds
- E.g. Senn criticises ‘mathematical carryover’

- Much of Senn’s criticism stems from a pharmacological view of the processes underlying these trials
- Standard methods are too generic
- Could interpret criticism as saying that usual approach makes too much use of ‘off the shelf’ models.

Model for Dialysis example

- One way forward is to try to base design on a model that is more closely based on the specific application.

- However, there is unlikely to be any work on optimal designs, or even decent ones, for the new model.

- Might be able to use existing designs, but these may be unnecessarily restrictive

Model for Example

- Suppose weight of clot for patient *i* in period *j* is y_{ij}.
- Model is:

$$y_{ij} = x_i + p(i,j) + td(i,j) + e_{ij}$$

- x is a patient term – there is likely to inter-patient variation in clot-forming propensity.
  (?allow a trend – no, trial too short and patients fairly stable wrt to clot formation)

- Treatment term, *d(i,j),*=1 (heparin) and -1 for Alteplase.
- No carryover term needed: lines flushed through very thoroughly by dialysis session, so no residual of clot or of ‘lock’ solution by end of session.
- A realistic ‘period’ term is more complicated
- Residuals – might be correlated?

Period effect

- Let set of patients dialysed thrice weekly be D_3 and twice weekly be D_2. These sets have sizes N_3 and N_2 respectively
- $p(i,j)$ = p_1 if $i \in D_3$ and j is a Monday
  = p_2 if $i \in D_3$ and j is a Wednesday
  = p_3 if $i \in D_3$ and j is a Friday
- $p(i,j)$ = p_4 if $i \in D_2$ and j is a Monday
  = p_3 if $i \in D_2$ and j is a Friday
- Weight of clot depends on inter-dialytic period and typical activities

Optimal Designs

- Suppose trial lasts *w* weeks
- We will obtain $m=3wN_3+2wN_2$ observations
- Randomise patent *i* to a sequence of treatments – which sequences?
- Determined by design matrix

$$X = (A \mid B_1 \mid B_2)$$

A is Rx, B_1 'period', B_2 patient, matrices

- Information for t in full model is

$$\sigma^{-2} A^{T} \wp^{\perp}([B_1 \mid B_2]) A$$

where $\wp^{\perp}(M)=I-\wp(M)$ and $\wp(M)=M(M^{T}M)^{-}M^{T}$

- Information in model omitting patient effect is

$$\sigma^{-2} A^{T} \wp^{\perp}(B_1) A$$

- Easier to handle as dimension of B_1 is m x 4 whereas dimension of B_2 is m x (N_1+N_2).

Deriving optimal designs

- (see Stufken, 1996 for a good review)
- Kunert (1983) used the identity

$$\wp^{\perp}([B_1 \mid B_2]) = \wp^{\perp}(B_1) - \wp(\wp^{\perp}(B_1)B_2)$$

- So $A^{\mathsf{T}}\wp^{\perp}([B_1 \mid B_2])A \leq A^{\mathsf{T}}\wp^{\perp}(B_1)A$

  with equality if $A^{\mathsf{T}}\wp(\wp^{\perp}(B_1)B_2)A = 0$

$$\Leftrightarrow A^{\mathsf{T}}B_2 = A^{\mathsf{T}}\wp(B_1)B_2$$

- So, we need to find a design which maximises

$$A^{\mathsf{T}} \wp^{\perp}(B_1) A$$ (information under reduced model)

and which also obeys

$$A^{\mathsf{T}} B_2 = A^{\mathsf{T}} \wp(B_1) B_2$$ (essentially an orthogonality constraint)

- Need to consider each of the red quantities in turn, but first some notation

- $q_W = q_{Wh} - q_{Wa}$ q_{Wh} (q_{Wa}) is number of adminstrations of heparin (Alteplase) on a Wednesday
- $q_F = q_{Fh} - q_{Fa}$ As above but counting Fridays not Wednesdays
- $q_{M3} = q_{M3h} - q_{M3a}$ As above but counting Mondays and only for the thrice-weekly patients
- $q_{M2} = q_{M2h} - q_{M2a}$ As above but counting Mondays and only for the twice-weekly patients

- $s^{-2}A^{T}\wp^{\perp}(B_1)A = \sigma^{-2}[m - q^{T}Rq]$
  where q is the 4 x 1 vector of the qs and $R=w^{-1}\text{diag}(N_3, N_3+N_2, N_3, N_2)^{-1}$

- $A^{T}B_2$ is 1 x (N_2+N_3) vector: i^{th} element is difference between number of times patient i receives heparin and Alteplase

- $A^{T}\wp(B_1)B_2$ 1 x (N_2+N_3) vector comprises two quantities: $q^{T}RP_2$ and $q^{T}RP_3$ for the twice and thrice weekly patients respectively.

- So, if we arrange for $q_F=q_W=q_{M3}=q_{M2}=0$, and each patient to receive heparin and Alteplase the same number of times, we have an optimal design.

Sample Size Calculation

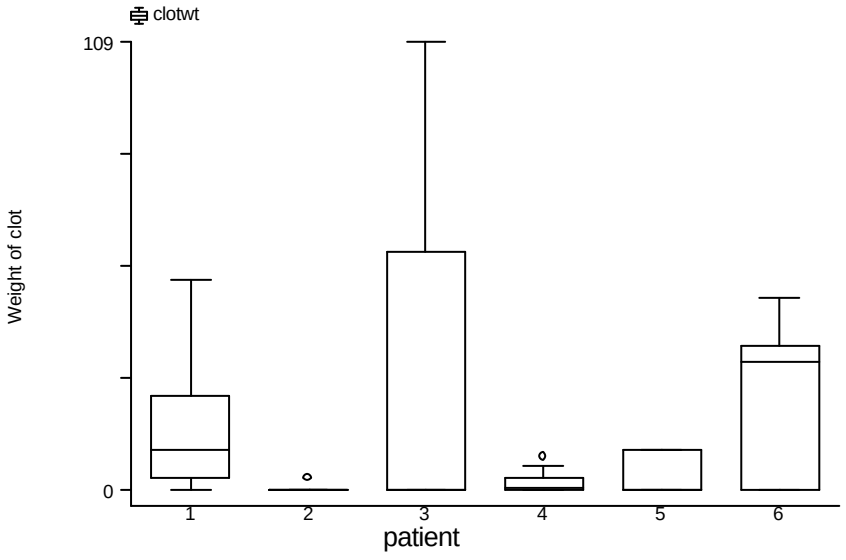
- For an optimal design $\text{var}(\hat{t}) = s^2/(3wN_3 + 2wN_2)$

  provided errors are independent
- Some pilot data available, giving estimate of within-patient SD of 22 mg
- Clinically important difference, $2t_0$ = 10mg
- For 80% power at 5% level $(t_0/\hat{s})\sqrt{m} = 1.96 + 0.84 = 2.8$

- At planning stage, N_3=4, N_2=2, so m=16w,
  so w≈10 weeks.

Construct design

- Choose a 3-sequence of As and Hs for each week
- Dual pair is sequence with As and Hs interchanged
- Randomize appropriately – pilot data suggests you might be grateful to be able to use a randomization test when the day comes



Details for thrice weekly patient

A	B	C	D	E	a	b	c	d	e
Apply random permutation, e.g.									
C	B	d	A	b	E	c	D	a	e

- Allocate $X \in \{AAA, AAH, AHH, AHA\}$ to a with probabilities 0.1, 0.2, 0.2, 0.5 respectively, with dual pair being allocated to A.
- Repeat for b, c , d and e.
- Automatically ensures optimal design as over pairs of weeks A and a, B and b etc. number of allocations to A and H are balanced in total and over days of week

Why the unequal probabilities?

- What if the error term is correlated?
- No detailed analysis but if there is no carryover in model, Matthews (1987) showed that a design with rapidly altering allocations was optimal for +ve autocorrelation
- Assuming +ve autocorrelation most likely form of dependence, want a tendency to have alternating treatments
- But do want trial to be sufficiently flexible to allow a randomization analysis, so allow sequences other than AHA

General remarks

- Attempting a 30 period crossover
- Reasonably captive population
- Some go for transplant
- Some switch from twice to thrice weekly (& also vice versa)
- Also, nine patients have been entered
- With more conventional period effect, adding extra patients, or patients switching cycles could be awkward
- Within-patient elimination of ‘period’ effects allows easy, randomization-based method of construction
- Refs at www.mas.ncl.ac.uk/~njnsm/talks/titles.htm