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
  \[ y_{ij} = \xi_i + \pi_j + \tau_{d(i,j)} + \gamma_{d(i,j-1)} + \epsilon_{ij} \]

- Here \( \xi \) is a patient effect, \( \pi \) a period effect, \( \tau \) a direct treatment effect and \( \gamma \) 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:
  $$y_{ij} = \xi_i + \pi(i,j) + \tau d(i,j) + \varepsilon_{ij}$$

• $\xi$ 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.

- $\pi(i,j)$
  - $= \pi_1$ if $i \in D_3$ and $j$ is a Monday
  - $= \pi_2$ if $i \in D_3$ and $j$ is a Wednesday
  - $= \pi_3$ if $i \in D_3$ and $j$ is a Friday

- $\pi(i,j)$
  - $= \pi_4$ if $i \in D_2$ and $j$ is a Monday
  - $= \pi_3$ 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 patient $i$ 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 \( \tau \) in full model is

\[
s^{-2}A^T \mathcal{\rho}^\perp([B_1 \mid B_2])A
\]

where \( \mathcal{\rho}^\perp(M) = I - \mathcal{\rho}(M) \) and \( \mathcal{\rho}(M) = M(M^TM)M^T \)

• Information in model omitting patient effect is

\[
s^{-2}A^T \mathcal{\rho}^\perp(B_1)A
\]

• Easier to handle as dimension of \( B_1 \) is \( m \times 4 \) whereas dimension of \( B_2 \) is \( m \times (N_1 + N_2) \).
Deriving optimal designs

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

\[ \mathcal{S}^\perp([B_1 \mid B_2]) = \mathcal{S}^\perp(B_1) - \mathcal{S}(\mathcal{S}^\perp(B_1)B_2) \]

- So \( A^T \mathcal{S}^\perp([B_1 \mid B_2])A \leq A^T \mathcal{S}^\perp(B_1)A \)

  with equality if \( A^T \mathcal{S}(\mathcal{S}^\perp(B_1)B_2)A = 0 \)

  \[ \Leftrightarrow A^TB_2 = A^T \mathcal{S}(B_1)B_2 \]
• So, we need to find a design which maximises

\[ A^T \varphi^\perp(B_1)A \] (information under reduced model)

and which also obeys

\[ A^TB_2 = A^T \varphi(B_1)B_2 \] (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 administrations 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
- \( \sigma^{-2} A^\top \delta \ominus (B_1 ) A = \sigma^{-2} [m - q^\top R q] \)
  where \( q \) is the 4 x 1 vector of the \( q_s \) and
  \( R = w^1 \text{diag}(N_3, N_3+N_2, N_3, N_2)^{-1} \)

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

- \( A^\top \delta(B_1)B_2 \) 1 x (\( N_2+N_3 \)) vector comprises two quantities: \( q^\top R P_2 \) and \( q^\top R P_3 \) 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 \( \text{var}(\tau) = \sigma^2 / (3wN_3 + 2wN_2) \)

  provided errors are independent
- Some pilot data available, giving estimate of within-patient SD of 22 mg
- Clinically important difference, \( 2\tau_0 = 10\text{mg} \)
- For 80% power at 5% level \( (\tau_0 / \sigma) \sqrt{m} = 1.96 + 0.84 = 2.8 \)
- At planning stage, \( N_3=4, \ N_2=2 \), so \( m=16w \), so \( w \approx 10 \text{ weeks} \).
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

<table>
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<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<th>a</th>
<th>b</th>
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Apply random permutation, e.g.

| C | B | d | A | b | E | c | D | a | e |

- Allocate $X \in \{\text{AAA, AAH, AHH, AHA}\}$ 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