Simplicity, Complexity and Modelling in Clinical Trials

Stephen Senn
Acknowledgements

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However, some of the ideas grew out of work on the EPSRC Simplicity Complexity and Modelling project EP/E018173
An apology

Although I have worked for many years on clinical trials, my only involvement with cancer has been occasional membership of data safety monitoring boards.

Thus, my examples are not taken from trials in cancer.

The relevance (or not) to cancer of anything I have to say I leave for others to judge.
Outline

• Examples where we have a considerable gain by increasing complexity
• Examples where we do better to be simple
• Examples where more complex designs and modelling can teach us to be simpler
• Recommendations and conclusions
General thesis: as complex as necessary but no more

For complexity
• Complex allocation needs complex analysis
• Baseline covariates carry useful information
• Some apparently simple transformations mislead and destroy information and should be avoided

For simplicity
• Some complex models have unfortunate side-effects
• Overfitting can reduce capacity to predict
• Complex models can hide dangerous implicit assumptions

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For complexity

Where we lose information by being too simple
Failure to allow for design in analysis
Survey by Kahan and Morris 2012

Survey of trials published in *BMJ, JAMA, NEJM* & *Lancet* in 2010

© Kahan and Morris, BMJ, 2012

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Findings as regard analysis

### Balancing by centre

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Number</th>
<th>Percent</th>
</tr>
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<tr>
<td>Adjusted in primary analysis</td>
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</tr>
<tr>
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<td>68</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>120</strong></td>
<td><strong>100%</strong></td>
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Did not adjust + unclear = 71%

### Balancing by prognostic factors

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<td>11%</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>111</strong></td>
<td><strong>100%</strong></td>
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</table>

Did not adjust + unclear = 52%

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In summary

• K & M Found fewer than 50% of clinical trials (in leading journals) that balanced by centre or prognostic factor declared that the main analysis took account of this

• An opportunity for increasing efficiency is being missed

• For linear models, the standard errors will be larger than they should be

• For non-linear models, effective treatments will have estimates biased towards the null

• This is something of a scandal
Change from baseline
Waste in the name of simplicity

• A common habit for ‘true’ baselines is to use them to construct a change-score by simple subtraction

• Assuming equal variances at baseline and outcome this increases the variance unless the correlation is greater than 0.5

• Analysis of covariance (invented 1931) is (asymptotically) better than either raw scores or change scores

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Responder dichotomies
Criminal waste in the name of simplicity

• Responder dichotomies compound the change score crime by replacing them by a binary score

• If the cut-point is at the median, the sample size must be increased by
  \[100 \times (\pi/2 - 1) \approx 57\%
  \]

• For other cut-points it is worse

• Encourages false belief in causal differences between ‘responders’ and non-responders
  • To be picked up later
For simplicity

Where we lose information by being too complex
Repeated measures analysis

- Much repeated measures analysis using mixed models could be simply replaced by a summary measures approach
- This will often be nearly as efficient
  - In fact for simple correlation structures and complete data will be fully efficient
- Helps understanding
- Furthermore some repeated measures approach implicitly violate intention to treat. See
  - Senn, Stevens and Chaturvedi, 2000
  - Bamia, White, Kenward, 2013
How analysis of repeated measures can violate ITT

What everybody agrees is unacceptable

• It is common advice that you should not correct for post randomisation covariates
• For example, measures of the form $Y_3-Y_1$ instead of $Y_3-Y_0$

What everybody assumes is fine

• Ordinary least squares estimates of slopes
• But suppose that you have three post randomisation measurements at equal intervals
• The ordinary least squares measure of the slope is $\frac{(Y_3-Y_1)}{2}$

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An example of the wrong sort of complexity: Thall and Vail, 1990

- Repeated seizures for 59 patients over 4 two week periods
  - Compares two treatments Placebo and progabide
- Has been cited 461 times by 2017 according to Google Scholar
- Cites Leppik et al (1985) for the data
- Seven different covariance models proposed by Thall & Vail
- Very many different models proposed since

..., the predicted mean seizure rate for the progabide group is either higher or lower than that for the placebo group, accordingly as the baseline count does or does not exceed a critical threshold.... This suggests that progabide may be contraindicated for patients with high seizure rates.

Thall and Vail p666

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But data and what they mean are important

• The data are not from Leppik et al 1985 but 1987

• It should be obvious from the patient numbers that it is a two centre trial, but nobody appears to notice this

• The division into four two-week periods has no clinical meaning whatsoever

• Modelling this as a correlated series is pointless and possible misleading

Table 2

<table>
<thead>
<tr>
<th>ID</th>
<th>Y1</th>
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<th>Y3</th>
<th>Y4</th>
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<th>Age</th>
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<td>26</td>
</tr>
</tbody>
</table>

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In my view the analysis of data as four visits is pointless and we might as well analyse the totals. Leppik et al. (1987), using all the data of the original crossover trial, found no convincing evidence of a treatment effect and I am suspicious of any analyses of the first-period data only, including those of Lee and Nelder and Thall and Vail (1990), that do. Fitting total seizures as a function of centre, age and base-line seizure in addition to treatment using either Poisson regression and allowing for overdispersion or a negative binomial model, or using the square root of the number of seizures in a linear model, I find no convincing evidence of a treatment effect.
Increasing the number of covariates in a linear model

- Adding predictive covariates to a model makes the residual error smaller
- But it makes the design matrix somewhat less well-conditioned
- Second order efficiency is also affected
  - Fewer degrees of freedom for estimating the error variance
  - Less favourable t-distribution for confidence intervals
- Eventually as we add covariates we lose
- Problem in small trials
Complexity that may yield simplicity

How being complex can sometimes yield insights that lead to simplicity

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A complex design in asthma

<table>
<thead>
<tr>
<th>Dose</th>
<th>Formulation of Formoterol</th>
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<tbody>
<tr>
<td>0 µg</td>
<td>Placebo</td>
</tr>
<tr>
<td>6 µg</td>
<td>ISF6  MTA6</td>
</tr>
<tr>
<td>12 µg</td>
<td>1SF12  MTA12</td>
</tr>
<tr>
<td>24 µg</td>
<td>ISF24  MTA24</td>
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- Parallel assay
- Cross-over
- Incomplete blocks
- Seven treatments
- Five periods
- Twenty-one sequences
- Forced expiratory volume in one second (FEV₁)
- 18 time-points over 12 hours
- Log AUC of FEV₁ as main outcome

Results

• Perfect dose response 6μg, 12μg, 24μg within each formulation
• Big surprise is complete separation of formulations
• Formulations not at all equivalent
• MTA 24μg appears to be less potent than ISF 6μg
## Analysis of Contrasts

<table>
<thead>
<tr>
<th>Contrast</th>
<th>ISF (Reference)</th>
<th>MTA (Test)</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>6</td>
<td>12</td>
<td>24</td>
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<tr>
<td>Active</td>
<td>1/6</td>
<td>1/6</td>
<td>1/6</td>
</tr>
<tr>
<td>Formulation</td>
<td>-1/3</td>
<td>-1/3</td>
<td>-1/3</td>
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<td>Dose</td>
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<td>Curvature</td>
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<td>-1</td>
</tr>
<tr>
<td>Opposing curvature</td>
<td>-1</td>
<td>2</td>
<td>-1</td>
</tr>
</tbody>
</table>

![Graph showing log AUC of FEV₁](image)

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Implications

As regards comparing formulations
• The formulations are clearly not equipotent
• The difference between formulations is a great as the difference between doses
• But the model adequacy contrasts are all non-significant
• Linear (in the log dose) appears to work
• A careful complicated design killed the new formulation

But there is more
• The fact that patients have been measured many times enables us to say something about individual response
• Consider a common (very stupid) definition of response
  • 15% increase in FEV$_1$ above baseline
• Now look at ‘responders’ 12 hours after treatment for two of the formulations...

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The case for personalised medicine

- There seem to be a number of patients who respond to B and not to A and vice versa.
- Clearly if we can find predictive characteristics of them we can improve treatment.
- Next stop, precision medicine.
The case against personalised medicine

- A is ISF 12µg, the second most potent of the six formulations and doses tested
- B is ISF 24µg the most potent of the six formulations and doses tested
- It is biologically extremely implausible that patients could respond to 12µg and not to 24µg
- Yet apparently 8 out of 71 patients did
- Conclusion: naïve simple views of causality and response aren’t good enough and more complex design and analysis is needed

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Responder analysis is the work of the devil

Any statistician who collaborates in this crime deserves to languish in data-analysis hell
Example of Atrial Fibrillation

• Such patients are at higher risk of stroke
• Meta-analysis (reproduced in Hart et al 2007) concluded that warfarin has a beneficial protective effect
• But there is a risk of intracranial bleeding
• Who should get warfarin?
6 trials of warfarin in atrial fibrillation

Placebo-controlled trials

Q statistic = 11.92
P = 0.03587

Data from Hart, 2007
6 trials of warfarin in atrial fibrillation

Q statistic = 2.955
P = 0.707

Data from Hart, 2007

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The line gives the prediction if the common log-odds ratio estimate is applied to the control group rate.
Recommendations and conclusions

Reminding ourselves why we do this
Conclusions

• The appropriate degree of complexity is a matter of judgement
• The key to getting the right degree is maintaining a sense of purpose
  • Does the complexity reflect pharmacology etc to the degree needed?
  • Have we followed through: analysis that reflects design and design that serves the analysis needed?
  • Are we doing it to increase our understanding of the effects of treatment?
• Are we being complex in the right places
  • Elaborate models of responder dichotomies are pointless
• Measurement matters

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Recommendation

Always ask yourself this:

Am I really interested in finding out about the effects of treatment?