Minimisation – Reducing Predictability Whilst Retaining Balance Within Centre

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Overview

- Scope of research
- Aims & Objectives
- Methods
- Results
- Conclusions

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Scope of Research

Due to recent controversy, we investigated predictability of treatment allocation when randomisation is via minimisation (deterministic dynamic allocation)

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Guidelines

- Committee for Proprietary Medicinal Products (CPMP) 'Points to Consider' –

  'dynamic allocation is strongly discouraged'

- ICH E9 Guidelines –

  'deterministic dynamic allocation procedures should be avoided and an appropriate element of randomisation should be incorporated for each treatment allocation'

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Results of Hills (2003)

- Predictability by clinician is high when clinician included as a stratification factor
- Predictability significantly reduced when clinician not included
- Recommend clinician is not included as a stratification factor

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Aims & Objectives

- Consider methods of reducing predictability by centre/clinician
- Consider within-centre imbalance
- Identify optimal minimisation method for reducing predictability whilst retaining sufficient balance within centre

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Methods of Reducing Predictability

- Exclude centre as a minimisation factor
- Incorporate a random element, p, into minimisation algorithm

  p=0.95, 0.90, 0.80, 0.75, 0.70

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Methods of Assessing Predictability

- Consider real data from 6 multi-centre clinical trials
- Simulate treatment allocation over 1000 times
- Consider predictability methods according to Hills (2003)

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Prediction Methods

- **M1** Predict alternative to that previously allocated
- **M2** Based on ALL previous allocations to that centre, predict treatment group with least number of patients
- **M3** As in M2 but based on previous 5 allocations only

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Methods of Assessing Predictability

- Compare average predictability rates per trial with those of deterministic minimisation, i.e. no random element, where centre is included as a minimisation factor

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Datasets

Dataset	N	No. factors	No. centres
1	1435	4	11
2	1380	4	43
3	794	4	32
4	357	3	8
5	270	3	26
6	128	2	27

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Results Under Deterministic Minimisation

- Average predictability over all predictability methods as high as 65%
- Maximum within-centre imbalance of 4 patients

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Not Including Centre as a Minimisation Factor

- Maximum reduction in predictability – 9.1%

HOWEVER…

- Maximum within-centre imbalance of 36 patients
- Large imbalances may have logistical implications for centres

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Incorporating a Random Element

- Consider average predictability per trial
- Consider maximum predictability per trial
- Compare maximum with that under simple randomisation

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Incorporating a Random Element

	Random Element					
	None	**0.95**	**0.90**	**0.80**	**0.75**	**0.70**
Max. average predictability (%)	65.2	62.5	60.1	55.5	54.3	51.8
Max. reduction (%)	-	1.5	3.9	9.7	10.9	13.4
Min. reduction (%)	-	1.0	2.5	4.6	5.2	6.4
Max. within-centre imbalance	4	4	5	7	10	10

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Incorporating a Random Element

Max. predictability rates		Minimisation		
Dataset	**Simple rand**	**0.80**	**0.75**	**0.70**
1	64.0	69.1	67.5	64.6
2	73.3	75.6	74.6	74.6
3	74.5	76.4	75.8	74.6
4	65.6	68.0	67.7	64.4
5	71.0	76.5	72.9	72.4
6	72.7	76.3	76.3	73.8

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Incorporating a Random Element

- p=0.70 gives best reduction in predictability however imbalance is high
- Max. imbalance when p=0.80 is only 3 more than max. imbalance under deterministic allocation, and reduction in predictability of at least 4.6%
- p=0.80 - optimum random element

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Summary of Results

- Not including centre as a minimisation factor incurs large within-centre imbalance
- Introducing a random element reduces predictability
- Random element p=0.80 reduces predictability whilst retaining acceptable imbalance

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Do Clinicians Predict Treatment Allocation?

- We asked 25 clinicians / research nurses, identified via the Trials Unit's database, the following questions:
  - **Do you predict treatment allocation?**
  - **Is there a method that you use to predict?**
  - **What are the reasons behind your decisions?**

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Responses

- 21/25 stated that they did not predict
- Reasons for not predicting included:
  - Incurs bias
  - Unaware it was possible
  - Unethical
- For those who did predict, method was to keep a log of previous allocations, which is keeping with the prediction methods we considered

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Conclusions for Multi-centre Trials

- Include centre as a minimisation factor if imbalance is of concern logistically
- Incorporate a random element into the minimisation algorithm – p=0.80 is our recommendation
- Specify that centres should recruit more than 15 patients to minimise possibility of high predictability rates

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S Brown, H Thorpe, K Hawkins & J Brown. Statistics in Medicine 2005; **24**:3715-3727

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