Use of Simulation to Compare the Performance of Minimisation with Stratified Blocked Randomisation

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Outline of Talk

- What's included
  - Simulation to compare minimisation with stratified randomisation
    - Treatment balance
    - Validity of conventional statistical inference
  - Examples
  - Conclusions and further work
- What's not included
  - Advantages claimed for minimisation
  - Controversies with minimisation
  - Details of how to implement minimisation
  - Details of how to do randomisation tests

Example 1: Simulations for Treatment Balance

- 120 patients, equal allocation to treatment A:B
- Recruitment:

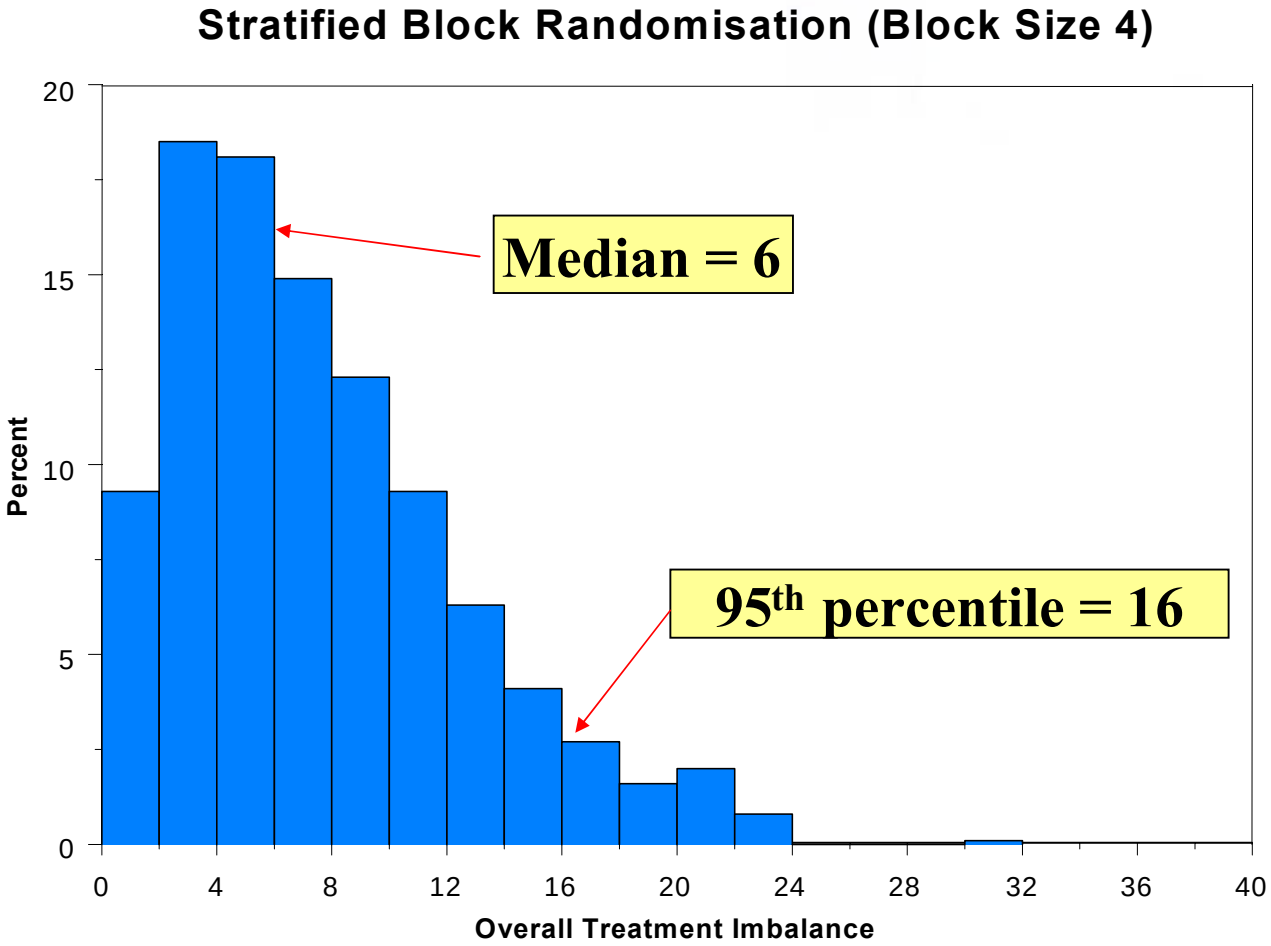
Sites 2 small, 16 medium, 2 large	Probabilities 1/120, 6/120, 11/120
Stratification S1 x S2 x S3 (each with 2 levels)	Probabilities 1/2, 1/10, 1/10, 1/10, 1/20, 1/20, 1/20, 1/20

- 1000 simulations
  - Site and strata assignments regenerated each time
  - Minimisation (various assignment probabilities)
  - Stratified Randomisation (block size 4)

Example 1: Simulations for Treatment Balance

- Measures of treatment imbalance
  - Overall treatment imbalance
  - Proportion of sites with treatment imbalance > 2
  - Other possibilities
- Summarising the simulation results
  - Graphical summary of the imbalance distribution
  - Median and other percentiles
  - Proportion of simulations (95% CI) where the imbalance exceeds some threshold

Example 1: Overall Treatment Imbalance



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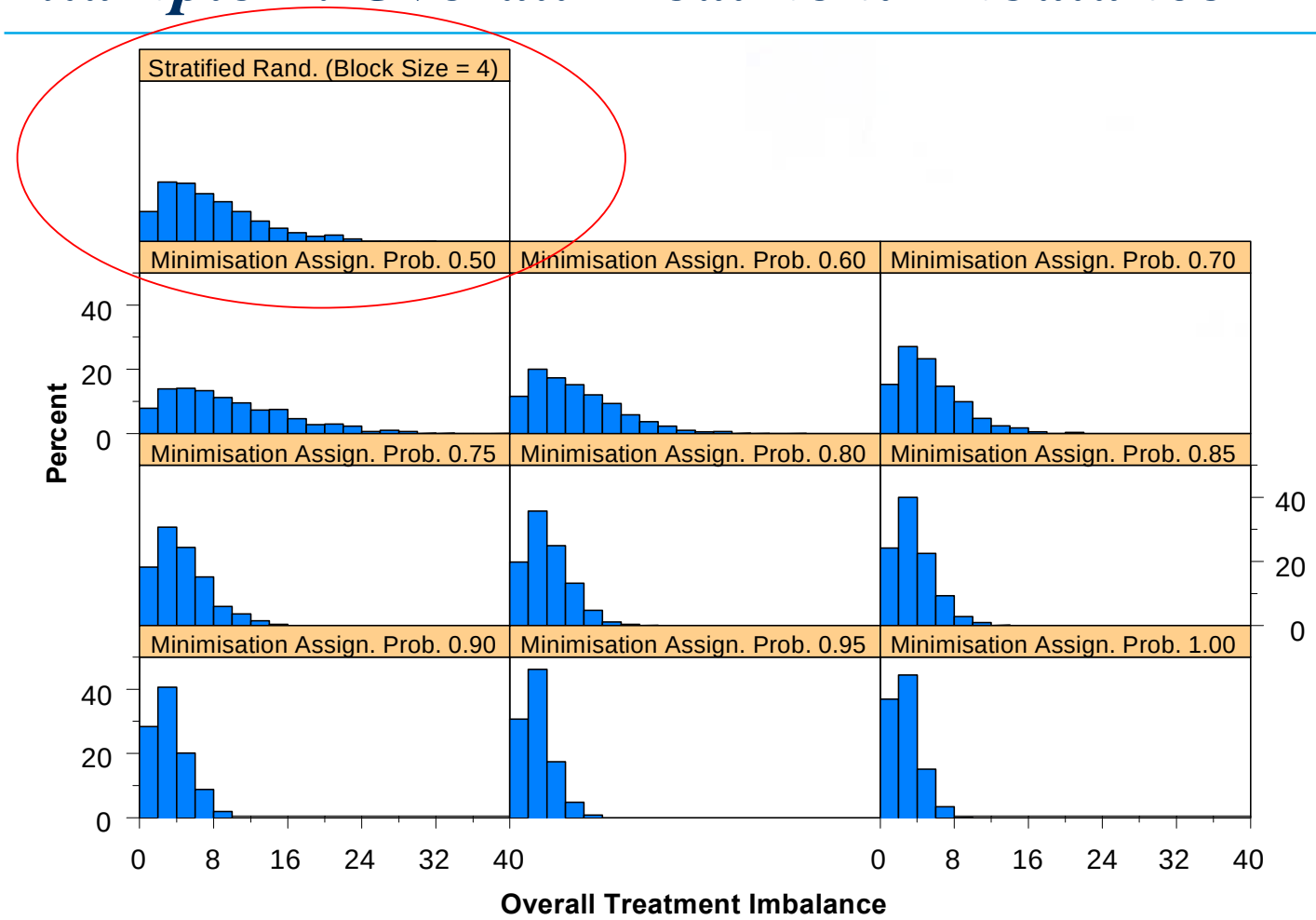

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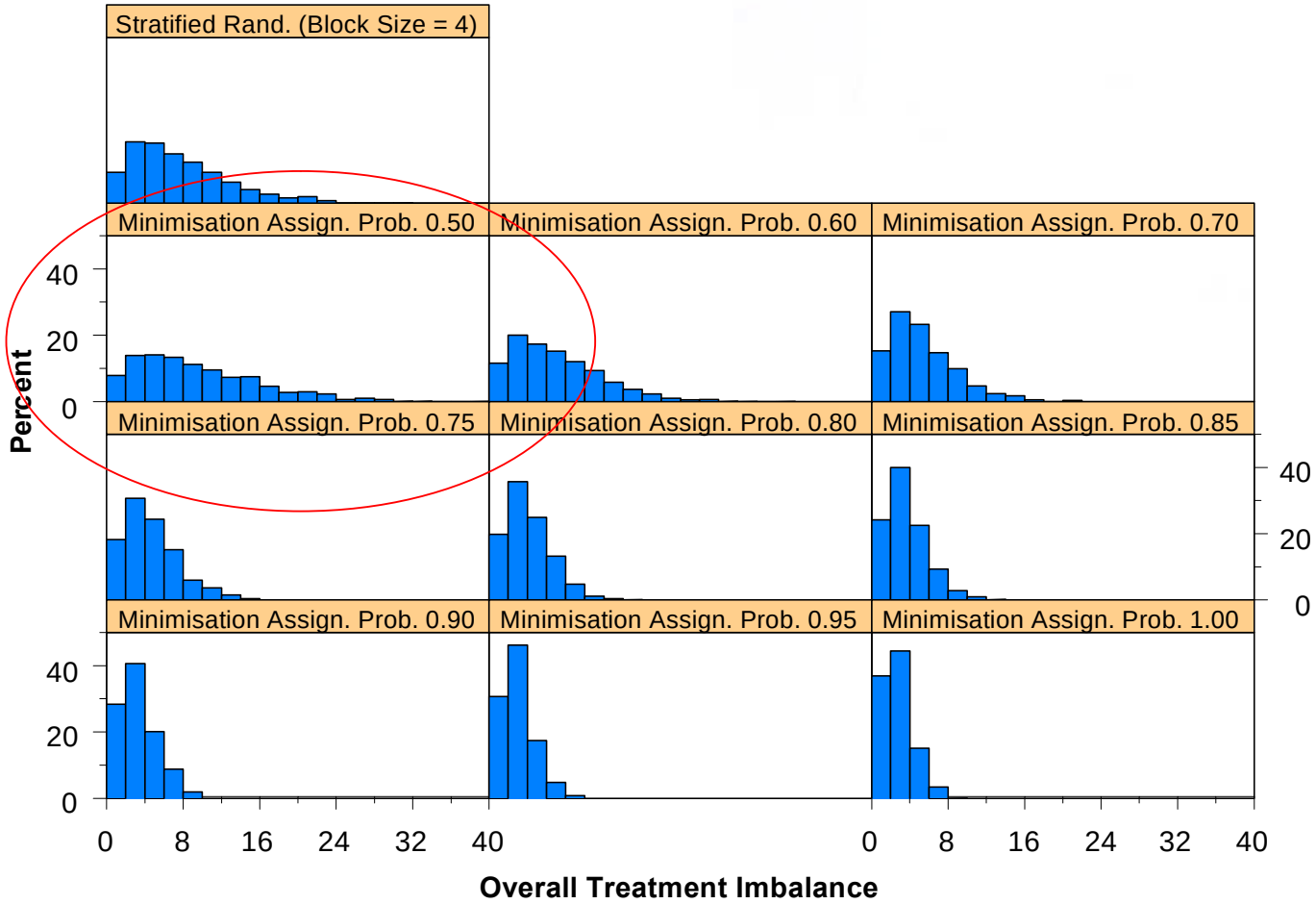

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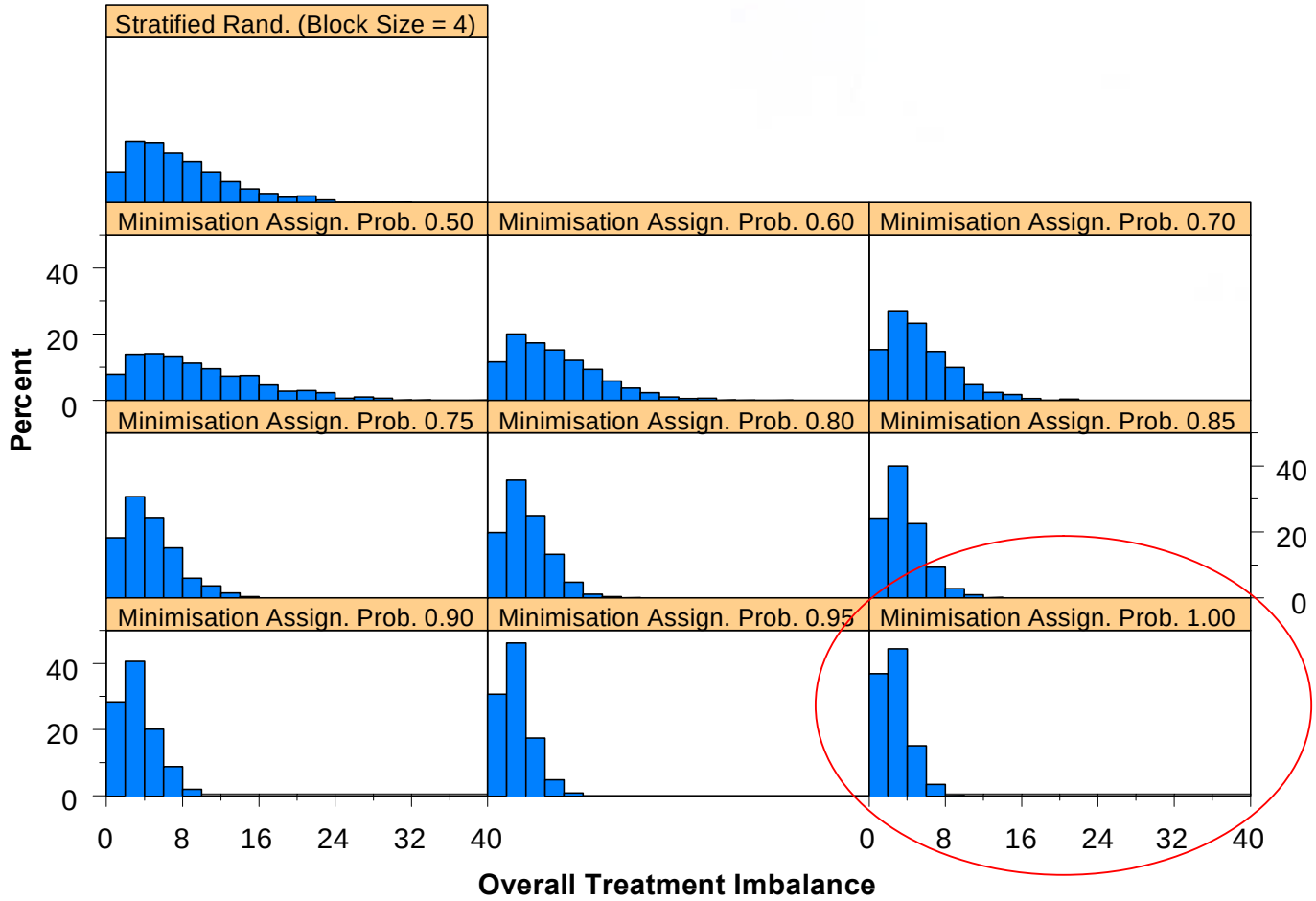

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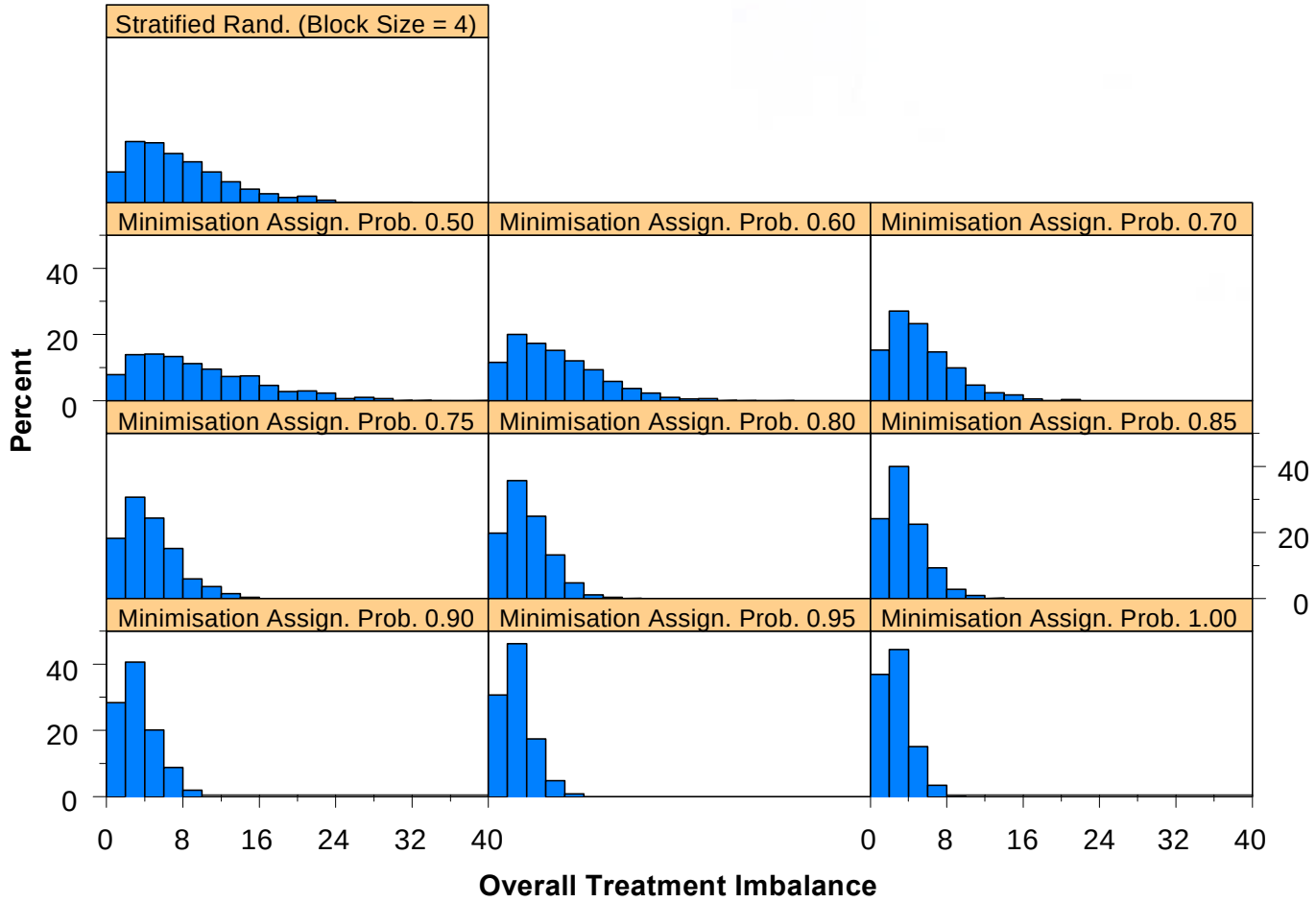

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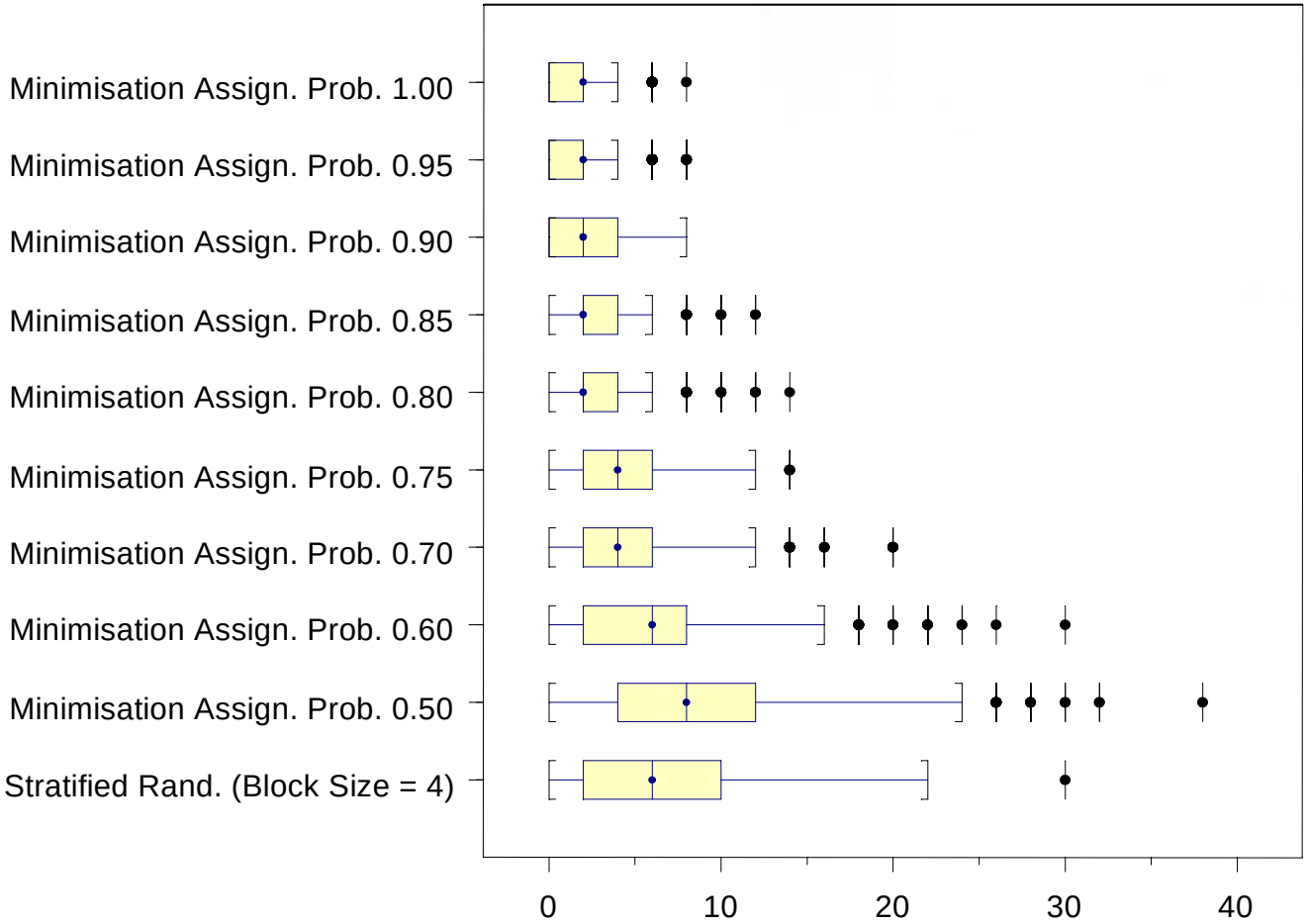
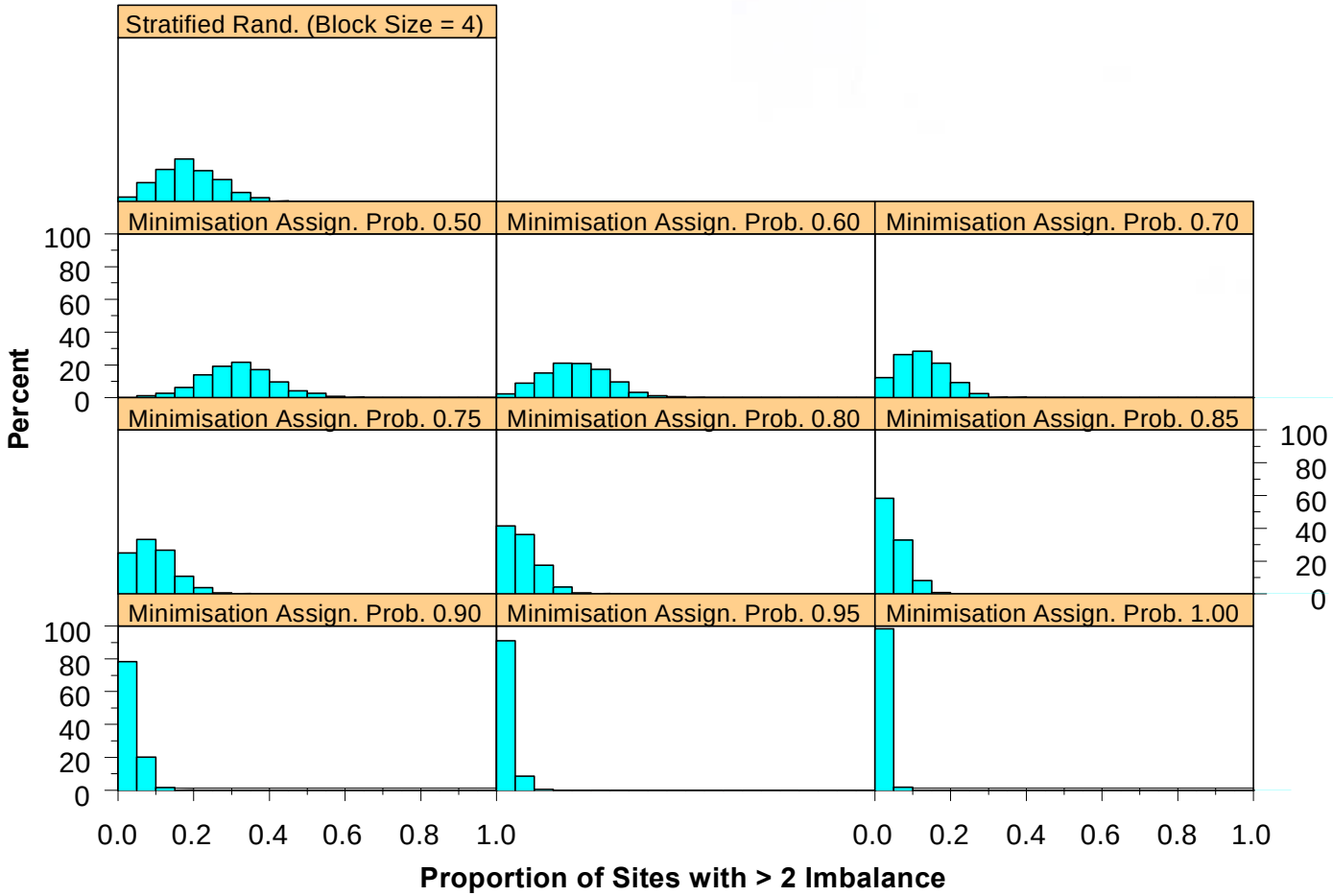


Example 1: Proportion of Sites with > 2 Imbalance



Example 1: Proportion of Sites with > 2 Imbalance

Proportion (95% CI) of Simulations which had > 10% Sites with Imbalance			
Strat. Rand. (Block Size 4)	**0.78 (0.75, 0.81)**	Min. Pr. 0.80	**0.17 (0.14, 0.19)**
Min. Pr. 0.50	**0.98 (0.96, 0.98)**	Min. Pr. 0.85	0.05 (0.04, 0.07)
Min. Pr. 0.60	0.84 (0.81, 0.86)	Min. Pr. 0.90	0.01 (0.01, 0.02)
Min. Pr. 0.70	0.50 (0.47, 0.53)	Min. Pr. 0.95	0.00 (0.00, 0.01)
Min. Pr. 0.75	0.30 (0.28, 0.33)	Min. Pr. 1.00	0.00 (0.00, 0.00)

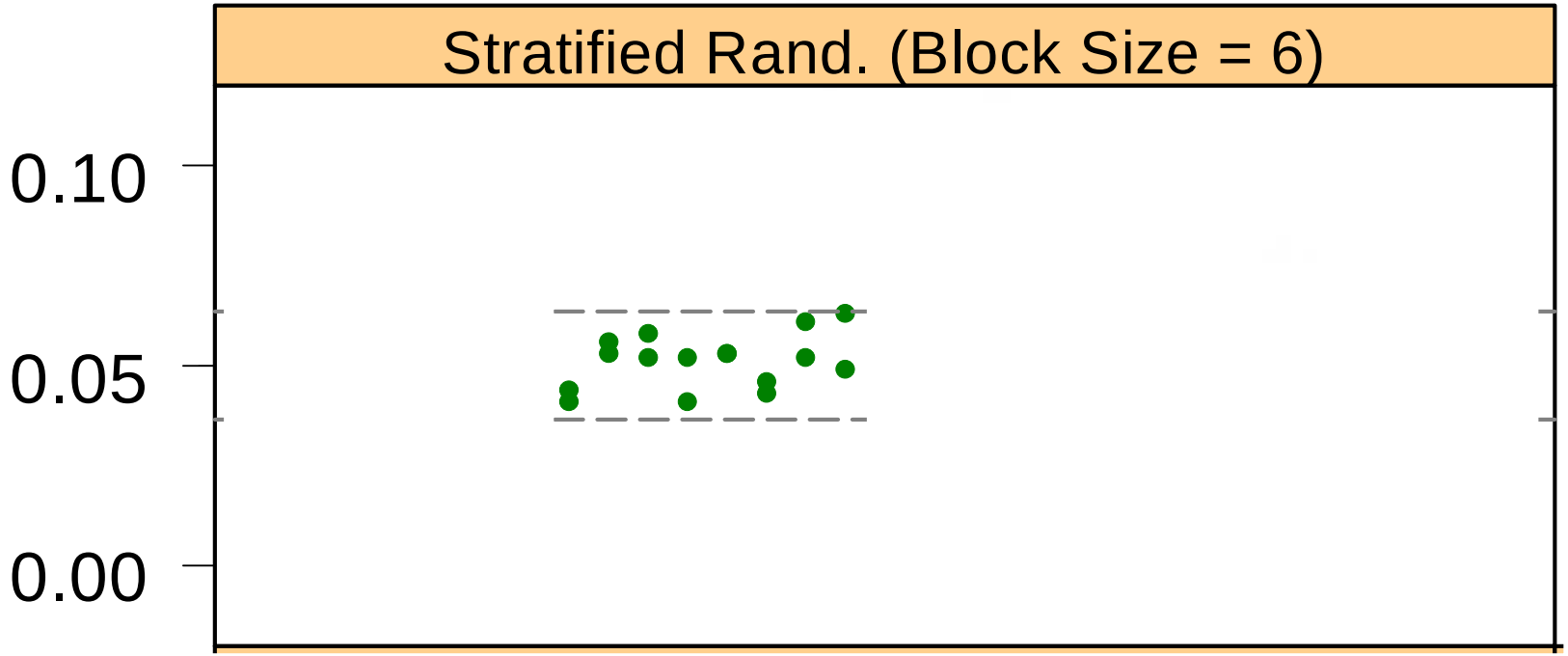
Simulations for Statistical Inference

- Size of conventional hypothesis test under restricted treatment allocation
  - For test of nominal size 5%, we would expect to find significant treatment difference in 5% of trials under H_0
- Can check this by simulation
  - Patient recruitment and generation of outcomes
  - Keep the same patient responses and run patients through the treatment allocation algorithm many times
  - What proportion of simulations have p-value < 0.05 calculated using the standard statistical test ?
  - How does this proportion perform over different simulation runs ?

Example 2: Simulations for Statistical Inference

- 120 patients, equal allocation to treatment A:B
- Fixed recruitment: 8 sites (unequal), 2 strata (equal)
- Continuous outcome
  - Patient ~ N(50, 10), Site ~ N(0, 5), Stratum ~ N(0, 10)
  - No treatment effect
  - ANOVA analysis
- 320 runs x 1000 simulations
  - 4 Minimisations plus Stratified Randomisation
  - 4 different sets of 120 patients
  - 8 different permutations of order of entry for each patient set
  - 2 replications of the same order of entry for each permutation

Example 2: Observed Test Size



8 pairs of runs of 1000 simulations for the same set of patients, with the time-order of patients permuted between each pair

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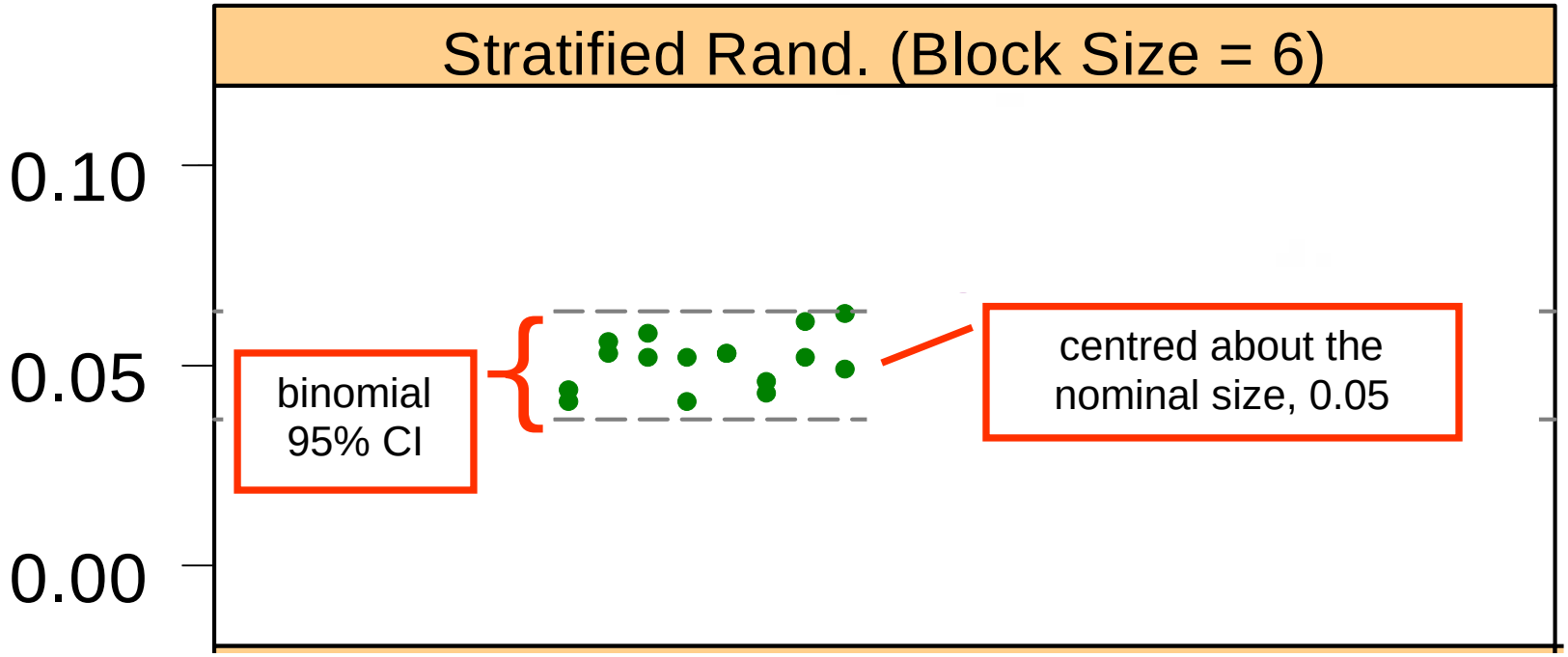

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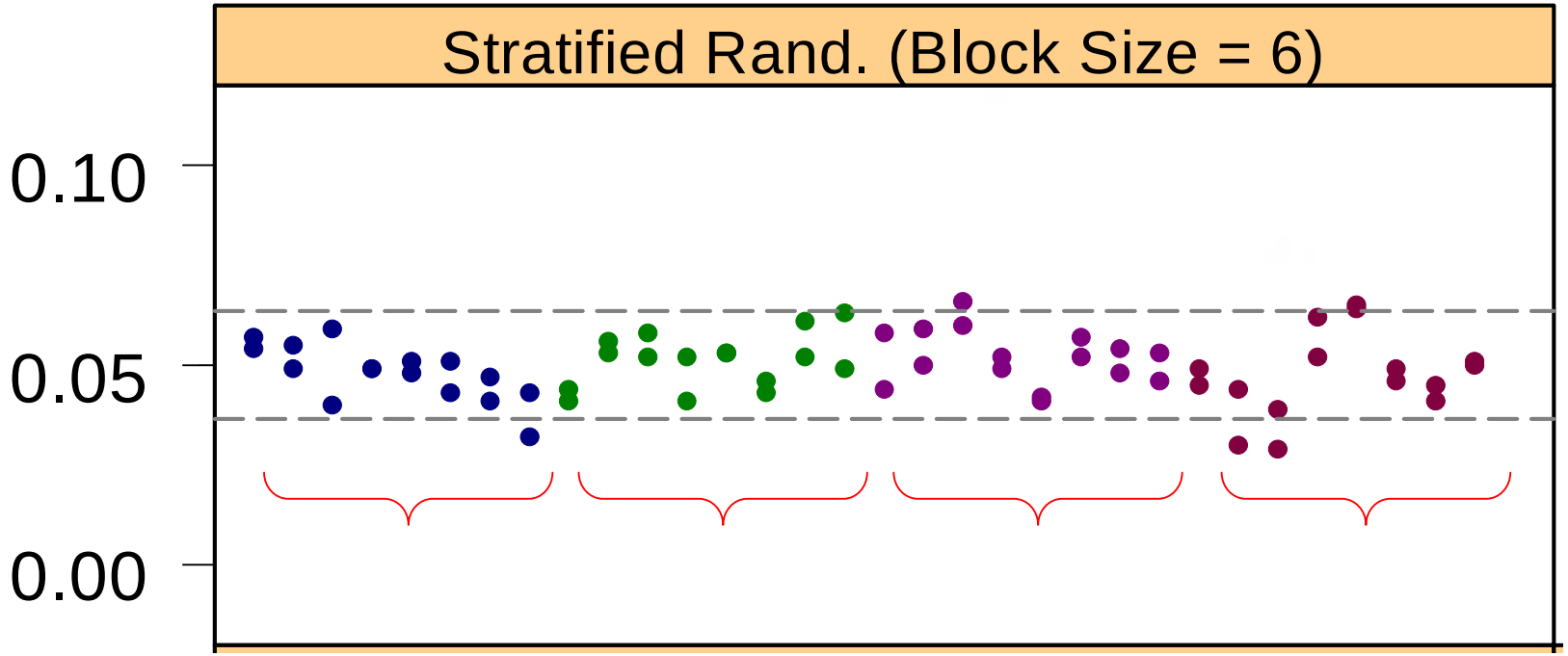

4 sets of patients

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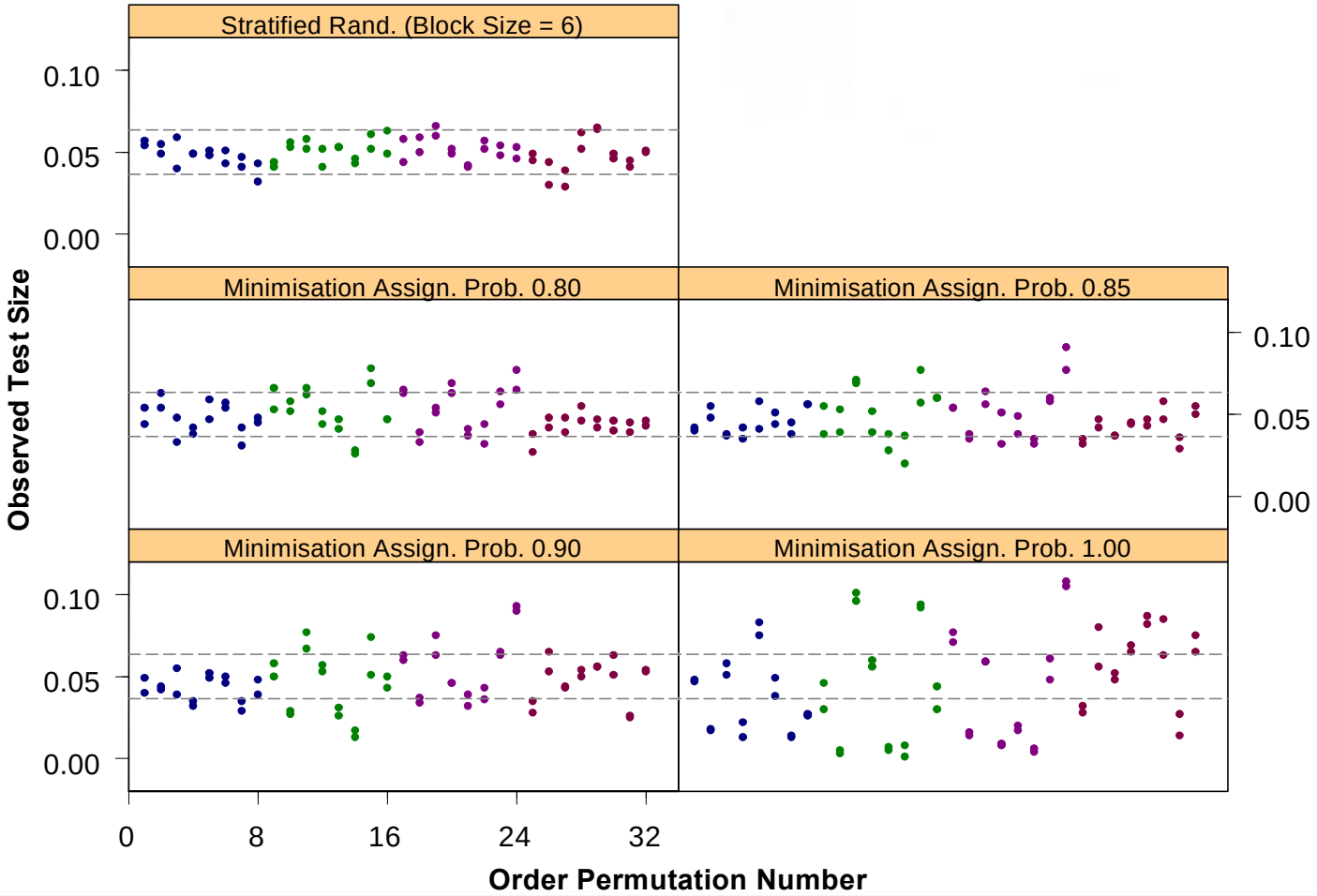

Conclusions and Further Work

- Simulation at the design stage may be helpful:
  - When minimisation may improve treatment balance
    - How low the assignment probability needs to be
  - When conventional statistical tests remain valid
    - Large variability in test size dependent on the order of patient entry unlikely to be acceptable
- Further work:
  - Other measures of balance
  - Power
  - Interval estimation

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- Steve Jones, Covance (UK)

References

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Back-Up Slides

Example 1: Overall Treatment Imbalance

Median and 95th Percentile					
Strat. Rand. (Block Size 4)	6.0	16.0	Min. Pr. 0.80	2.0	8.0
Min. Pr. 0.50	8.0	21.0	Min. Pr. 0.85	2.0	6.0
Min. Pr. 0.60	6.0	14.0	Min. Pr. 0.90	2.0	6.0
Min. Pr. 0.70	4.0	11.0	Min. Pr. 0.95	2.0	6.0
Min. Pr. 0.75	4.0	10.0	Min. Pr. 1.00	2.0	4.0

Example 1: Overall Treatment Imbalance

Proportion (95% CI) of Simulations which had Overall Treatment Imbalance > 8			
Strat. Rand. (Block Size 4)	0.27 (0.24, 0.30)	Min. Pr. 0.80	0.02 (0.01, 0.03)
Min. Pr. 0.50	0.40 (0.37, 0.43)	Min. Pr. 0.85	0.01 (0.01, 0.02)
Min. Pr. 0.60	0.24 (0.21, 0.26)	Min. Pr. 0.90	0.00 (0.00, 0.00)
Min. Pr. 0.70	0.10 (0.08, 0.12)	Min. Pr. 0.95	0.00 (0.00, 0.00)
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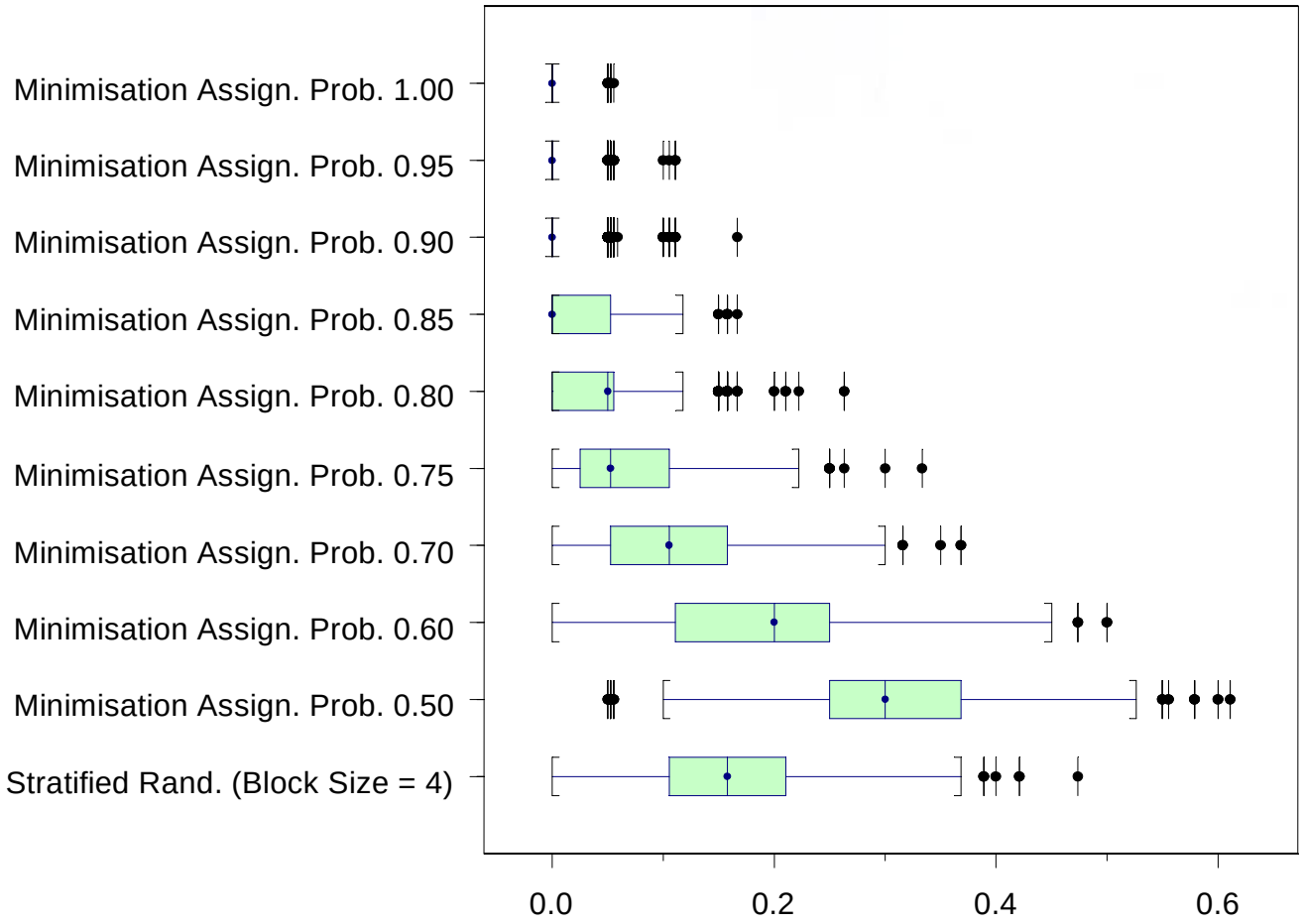

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Median and 95th Percentile					
Strat. Rand. (Block Size 4)	0.16	0.32	Min. Pr. 0.80	0.05	0.13
Min. Pr. 0.50	0.30	0.47	Min. Pr. 0.85	0.00	0.11
Min. Pr. 0.60	0.20	0.35	Min. Pr. 0.90	0.00	0.05
Min. Pr. 0.70	0.11	0.21	Min. Pr. 0.95	0.00	0.05
Min. Pr. 0.75	0.05	0.17	Min. Pr. 1.00	0.00	0.00

Example 2: Observed Test Size

Logistic Regression Analysis				
Model	Change in Deviance		Residual Deviance	
0.05 (Null)	N/A		2419.6	320 df.
+Block Rand	0.2	1 df	2419.4	319 df
+Allocation	52.2	4 df	2367.2	315 df
+Patient Set	40.4	3 df	2326.7	312 df
+ Order Perm. (Pat. Set)	1084.9	28 df	1241.8	284 df
+ Order Perm. (Pat. Set (Allocation))	1108.2	124 df	133.6	160 df