

Stratified Randomisation: A Hidden Form of Clustering?

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Outline

- Definition of clustering
- Impact of clustering in randomised trials
- Stratified randomisation as a form of clustering
- Impact of stratified randomisation in real world situations
- Recommendations

Clustering in Clinical Trials

- Clustering can be said to occur when observations can be grouped together based upon common attributes
- Common examples:
 - Multicentre trials (where patients are grouped by centres)
 - Crossover trials (where observations are grouped by patients)

Impact of Clustering in Randomised Trials

- Well known in certain situations (crossover trials, cluster randomised trials etc) that clustering needs to be accounted for in analysis
- Clustering does not always need to be taken into account in the analysis for valid results
- Results from Parzen et al [1] show in which specific instances clustering can be safely ignored in the analysis
- When clustering is present, the true variance of the treatment effect is:
 - $\text{Var}(\text{treatment effect}) = V_0 + V_E$
- where V_0 is the variance ignoring clustering, and V_E is an inflation (or deflation) factor based on the clustering
- Whether clustering can be safely ignored depends on V_E

Clustering in Clinical Trials

- V_E depends on:
 - The correlation between outcomes for patients in the same cluster (the intraclass correlation coefficient)
 - The correlation between treatment assignment for patients in the same cluster
- When $V_E=0$, clustering can be ignored in the analysis
- This means clustering can be ignored when the clusters are not involved in the randomisation process (i.e. simple randomisation)
 - Only valid when clusters are formed *before* randomisation
- If V_E is not 0, clustering needs to be accounted for in the analysis, otherwise the SEs for treatment will be biased

Clustering in Clinical Trials

- Using clusters in the randomisation process introduces correlation in treatment assignments between patients in the same cluster
- Crossover trials:
 - Treatments usually balanced within patients
 - Creates negative correlation in treatment assignments within patients
- Cluster randomised trials:
 - Entire clusters are randomised to treatment
 - Creates positive correlation in treatment assignments within clusters

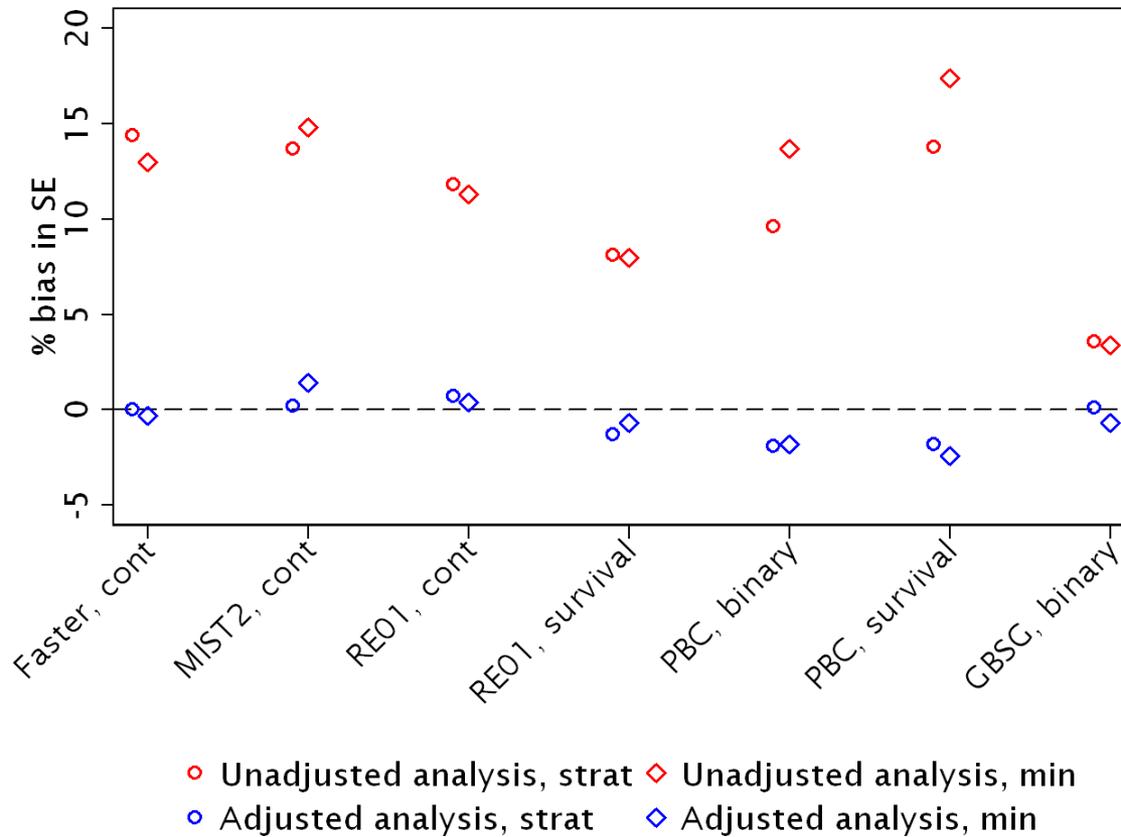
Stratified randomisation – a form of clustering

- Stratified randomisation involves grouping patients together into strata based on prognostic factors or centre
- Randomisation is then balanced within these strata
- This leads to correlation between treatment assignments for patients in the same stratum
- If we've picked our stratification factors well, we expect to see correlation in outcomes between patients in the same stratum
- Therefore, stratification factors need to be adjusted for in the analysis in order to obtain valid results

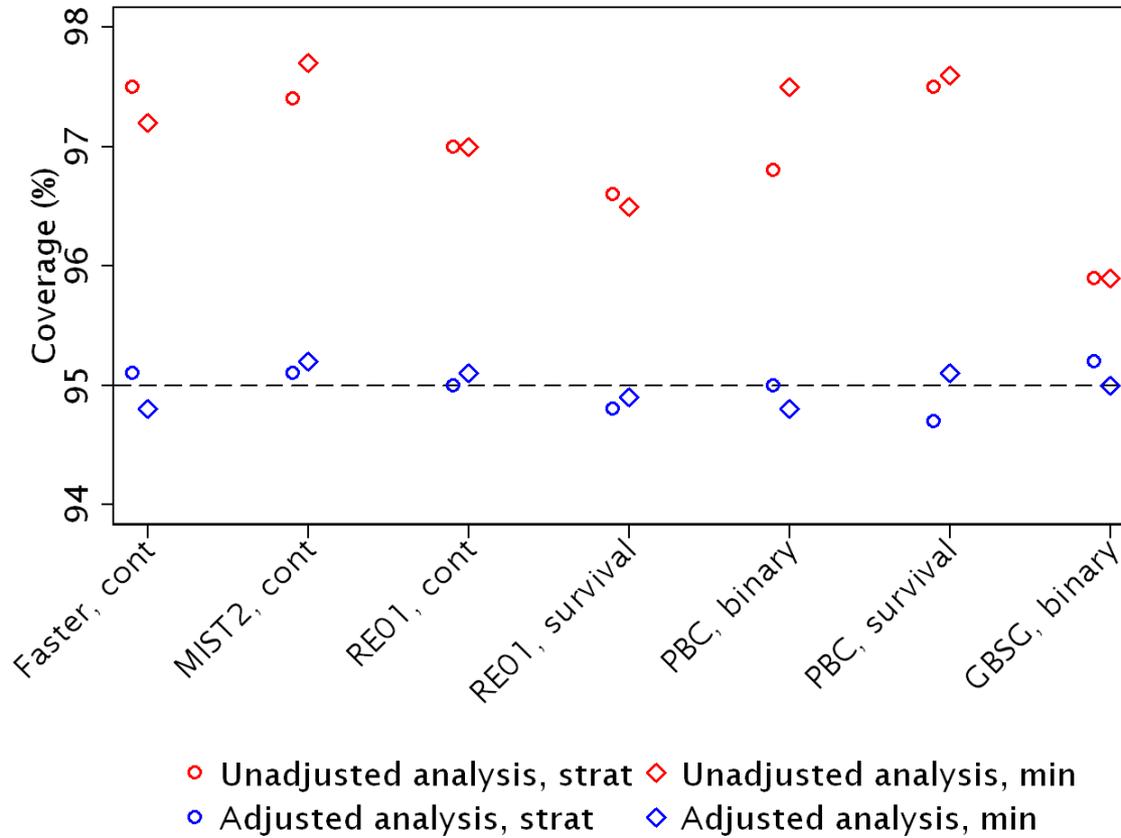
Simulation study based on real data

- Simulation study based on data from 5 trials – MIST2, FASTER, RE01, PBC, and GBSG
- Used between 2 and 5 stratification variables for each trial
- Assessed continuous, binary, and time-to-event outcomes
- Randomisation was done using stratified blocks and minimisation
- Compared adjusted vs unadjusted analyses in terms of % bias in the SEs, coverage, and power

Results - % bias in SEs



Results - Coverage



Results

- Unadjusted analyses lead to:
 - SEs that are biased upwards
 - Confidence intervals that are too wide
 - P-values that are too large
 - A reduction in power
- Can have a large effect in real trials

Recommendations

- It should be pre-specified in the protocol or statistical analysis plan that all stratification factors are adjusted for in the primary analysis
- Stratification factors need to be chosen carefully to avoid over-stratification in the analysis
- New articles, textbooks, and courses describing stratified randomisation should point out the implications for analysis

References

- Parzen M, Lipsitz SR, Dear KBG. Does clustering affect the usual test statistics of no treatment effect in a randomized clinical trial? Biometrical Journal 1998; 40; 385-402