Methods research programme

Catherine Hewitt
Professor of Trials and Statistics and Deputy Director York Trials Unit
Main streams of research

Trial design

Trial delivery

Trial analysis
Trial design

- Randomisation
- Preference designs
- Zelen’s design
- Factorials trials
- Regression discontinuity with tie breaker randomisation
- Stepped wedge trials
- Registry trials
- Trials within a cohort
- Sample size
Adequacy and reporting of allocation concealment: review of recent trials published in four general medical journals
Catherine Hewitt, Seokyung Hahn, David J Torgerson, Judith Watson, J Martin Bland

Potential for technical errors and subverted allocation can be reduced if certain guidelines are followed: Examples from a web-based survey
Catherine E. Hewitt1,*, David J. Torgerson2, Vance W. Berger3
1York Trials Unit, Department of Health Sciences, University of York, YO10 5DD, United Kingdom
2National Cancer Institute and University of Maryland at Baltimore County, Biomatry Research Group, National Cancer Institute, Bethesda, MD 20892-7354, USA
Accepted 3 June 2008

Allocation concealment in randomised controlled trials: are we getting better?
Laura Clark and colleagues assess the allocation concealment methods in a sample of randomised controlled trial publications
Laura Clark research fellow, Caroline Fairhurst research fellow, David J Torgerson director
York Trials Unit, University of York, York YO10 5DD, UK

Understanding controlled trials
Randomisation methods: concealment
David J Torgerson, Chris Roberts
Subverted allocation

• Survey of those involved in some aspect of RCTs
• Thirty cases of manipulation reported
• Focused on how, why and impact of manipulation
• How manipulated: ranged from open lists to prediction and manipulation of remote randomisation
• The immediate impact of the manipulation on the trial depended upon when the manipulation was identified
  • If during the trial then randomisation stopped or changed method or reinforced protocol
  • If during the analysis stage then sensitivity analysis reported
• Longer term impact involved individual learning and/or warnings to others
Interest of participant(s): “He fancied her! She was pretty! They thought they were doing the best for her. Doctor fancied patient, doctor just changed the treatment.”

Show treatment worked: “The individual was putting younger fitter individuals into the intervention surgical technique so it appeared that they were trying to improve the results.”

Treatment preference: “Some obstetricians registered a lack of approval of the intervention by refusing to comply with the random allocation ... they felt that the conventional intervention was more conveniently performed.”

Practical technical concern: “They knew that my father was really unsuitable for general anaesthetic.”
Trial delivery
Trial delivery

- York Trials Unit has undertaken the largest number of studies within a trial (SWATs)
- In a SWAT, an intervention to improve the conduct of a trial is tested in the context of an ongoing trial
- Most of the trials we undertake have embedded studies within them
- Most have focused on interventions to improve recruitment, retention and data collection methods
Recent SWATs
Systematic techniques for assisting recruitment to trials (START): study protocol for embedded, randomized controlled trials

Jo Rick¹, Jonathan Graffy², Peter Knapp³, Nicola Small⁴, David J Collier⁵, Sandra Eldridge⁴, Anne Kennedy⁵, Chris Salisbury⁶, Shaun Treweek⁶, David Torgerson⁷, Paul Wallace⁸, Vichithranie Madurasighe⁹, Adwoa Hughes-Morley¹¹ and Peter Bower¹²

Producing better evidence on how to improve randomised controlled trials

Effective recruitment and retention are essential to successful clinical research but we have little good evidence about how to achieve this. Joy Adamson and colleagues call for more use of methodological trials embedded within clinical trials to improve our knowledge.

Joy Adamson senior lecturer, Catherine E Hewitt deputy director, David J Torgerson director

York Trials Unit, Department of Health Sciences, University of York, York YO10 5DD, UK
Trial analysis
Trial analysis

- Non-compliance
- Attrition bias
- Multiple imputation
- Clustering within individually randomised trials
- Baseline imbalance
- Methods of cluster analysis
- Predictors, mediators and moderators
- Blinded outcome assessment
- Repeated measure analysis
Attrition bias
Attrition bias

Research methods

Reporting attrition in randomised controlled trials

Jo C Dumville, David J Torgerson, Catherine E Hewitt

Loss to follow-up can greatly affect the strength of a trial’s findings. But most reports do not give readers enough information for them to be able to understand the potential effects.

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>All participants</th>
<th>Participants lost to follow-up</th>
<th>Remaining participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hip protector</td>
<td>Control</td>
<td>Hip protector</td>
</tr>
<tr>
<td></td>
<td>(n=1388)</td>
<td>(n=2781)</td>
<td>(n=372)</td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
<td>77.9 (5.73)</td>
<td>77.8 (5.48)</td>
<td>78.8 (6.29)</td>
</tr>
<tr>
<td>Mean (SD) weight (kg)</td>
<td>60.8 (11.5)</td>
<td>61.2 (11.4)</td>
<td>60.5 (12.1)</td>
</tr>
<tr>
<td>Weight &lt;58 kg</td>
<td>46.5 (645)</td>
<td>44.2 (1230)</td>
<td>47.6 (177)</td>
</tr>
<tr>
<td>Previous fracture</td>
<td>67.7 (940)</td>
<td>67.7 (1882)</td>
<td>64.2 (239)</td>
</tr>
<tr>
<td>Smoker</td>
<td>12.0 (167)</td>
<td>12.6 (350)</td>
<td>15.9 (59)</td>
</tr>
<tr>
<td>Poor or fair health</td>
<td>38.0 (528)</td>
<td>38.7 (1075)</td>
<td>43.5 (162)</td>
</tr>
<tr>
<td>Fall in past 12 months</td>
<td>43.2 (599)</td>
<td>43.0 (1196)</td>
<td>47.0 (175)</td>
</tr>
<tr>
<td>Volunteers*</td>
<td>14.3 (199)</td>
<td>14.1 (393)</td>
<td>10.5 (39)</td>
</tr>
</tbody>
</table>

*Volunteers are participants who contacted the study coordinators independently in response to media advertising.
The Effects of Attrition on Baseline Comparability in Randomized Experiments in Education: A Meta-Analysis

Jeffrey C. Valentine
University of Louisville

Cathleen M. McHugh
Duke University

Using meta-analysis, randomized experiments in education that either clearly did or clearly did not experience student attrition were examined for the baseline comparability of groups. Results from 35 studies suggested that after attrition, the observed measures of baseline comparability of groups did not differ more than would be expected given sampling error. The degree of either overall or differential attrition did not relate to baseline comparability,
IPD meta-analysis

As randomised

<table>
<thead>
<tr>
<th>Study</th>
<th>Standardised mean difference (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carr et al, 2005</td>
<td>-0.21 (-0.47, 0.04)</td>
<td>7.4</td>
</tr>
<tr>
<td>DAMASK trial team, 2008</td>
<td>-0.04 (-0.21, 0.13)</td>
<td>17.3</td>
</tr>
<tr>
<td>Hay et al, 2003</td>
<td>0.02 (-0.25, 0.30)</td>
<td>6.5</td>
</tr>
<tr>
<td>Klaber Moffett et al, 1999</td>
<td>0.27 (-0.01, 0.56)</td>
<td>5.8</td>
</tr>
<tr>
<td>Klaber Moffett et al, 2005</td>
<td>-0.03 (-0.27, 0.21)</td>
<td>8.4</td>
</tr>
<tr>
<td>Klaber Moffett et al, 2006</td>
<td>0.17 (-0.05, 0.40)</td>
<td>9.6</td>
</tr>
<tr>
<td>Salter et al, 2006</td>
<td>-0.25 (-1.09, 0.59)</td>
<td>0.7</td>
</tr>
<tr>
<td>Thomas et al, 2006</td>
<td>-0.02 (-0.29, 0.24)</td>
<td>6.7</td>
</tr>
<tr>
<td>UK BEAM trial group, 2004</td>
<td>0.03 (-0.10, 0.15)</td>
<td>31.3</td>
</tr>
<tr>
<td>Watson et al, 2008</td>
<td>-0.01 (-0.28, 0.27)</td>
<td>6.2</td>
</tr>
<tr>
<td>Overall</td>
<td>0.01 (-0.06, 0.08)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

As analysed

<table>
<thead>
<tr>
<th>Study</th>
<th>Standardised mean difference (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carr et al, 2005</td>
<td>-0.14 (-0.41, 0.14)</td>
<td>7.8</td>
</tr>
<tr>
<td>DAMASK trial team, 2008</td>
<td>-0.03 (-0.21, 0.15)</td>
<td>17.9</td>
</tr>
<tr>
<td>Hay et al, 2003</td>
<td>0.02 (-0.26, 0.30)</td>
<td>7.6</td>
</tr>
<tr>
<td>Klaber Moffett et al, 1999</td>
<td>0.37 ( 0.06, 0.68)</td>
<td>6.2</td>
</tr>
<tr>
<td>Klaber Moffett et al, 2005</td>
<td>-0.09 (-0.35, 0.17)</td>
<td>8.7</td>
</tr>
<tr>
<td>Klaber Moffett et al, 2006</td>
<td>0.23 (-0.03, 0.50)</td>
<td>8.4</td>
</tr>
<tr>
<td>Salter et al, 2006</td>
<td>-0.25 (-1.12, 0.62)</td>
<td>0.8</td>
</tr>
<tr>
<td>Thomas et al, 2006</td>
<td>-0.02 (-0.30, 0.27)</td>
<td>7.2</td>
</tr>
<tr>
<td>UK BEAM trial group, 2004</td>
<td>0.06 (-0.09, 0.20)</td>
<td>29.0</td>
</tr>
<tr>
<td>Watson et al, 2008</td>
<td>-0.11 (-0.41, 0.20)</td>
<td>6.5</td>
</tr>
<tr>
<td>Overall</td>
<td>0.03 (-0.05, 0.10)</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Meta-regression

![Graph showing a scatter plot with standardised mean difference (absolute value) on the y-axis and level of attrition on the x-axis. The graph includes a trend line and circles representing different studies.](image-url)
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