IPD Meta-Analysis of Clinical Trials

Part 1

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IBC Victoria, July 2016

Standard Meta-Analysis

• Based on data taken from publications

• Summary effect estimates
  – Relative risk
  – Mean difference
  – Hazard ratio

• Summary data
  – Numbers of events and patients
  – Mean outcome in trial arms
Publication bias and selection bias

- Not all trials are published
- Not all outcomes are reported

Missing trials: biased results?

Poor reporting

- Papers may present:
  - P-values not confidence intervals
  - Figures not tables
  - Correlations
  - Unconventional analyses

- Can’t include in a meta-analysis
Individual participant data: The solution?

- Collaborate with trialists
- Obtain original trial data on all participants
- Include unpublished trials
- Data on all outcomes of interest
- AND
  - Patient characteristics (age, sex…)
  - Treatment data (dose, duration…)

The advantages

- Access to all trial data
  - Reduces bias and uncertainty
- Updated and corrected data
- Consistent analysis of all trials
- Data on modifiers of treatment effect
- Collaboration with trialists and experts
The disadvantages

- May not get all data
  - Refusal of collaboration, loss of data, high cost of data
- Needs more collaboration
  - Time consuming and expensive
- Multiple data formats and codings
  - Complex data management and security
- More difficult to analyse

Obtaining IPD

- The usual way:
  - Identify papers through database searching
  - Contact trial authors to request data
  - Build a collaboration

- The future?
  - Identify trials from trial registries
  - Obtain data from (online) data repositories
Popularity of IPD

- rhBMP2 inserted between vertebrae
- Encourages bone growth
- Alternative to fusion using hip bone graft
- Manufactured by MEDTRONIC™
Controversy

- Growing concerns that benefits have been overstated
- Adverse events understated and unreported
  - Excess bone growth
  - Post-operative pain
  - Cancer risk
- Publication authors funded by Medtronic
  - “Ghost” authorship?

Obtaining the IPD

- Medtronic made all trial data available
  - To Yale Open Data Access (YODA)
- YODA authorised York team to perform an IPD meta-analysis
- 17 trials
  - Only a subset were eligible for primary analyses
- All clinical study reports, protocols, etc.
- Around 1800 files in total
- Over 400 SAS data files
Meta-analysis: fusion after 2 years

Published data

IPD

The real outcome: Pain

Back pain

Leg pain

Crawford

SF36 PCS

Mean difference in outcome (nBMP-2 vs iliac crest)

Time since operation (months)
Methods of IPD Meta-Analysis

“One-stage” and “Two-stage”
Treat IPD like a trial

- **NO!**
  - Ignores differences between trials
  - Ignores within-trial randomisation

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Standard meta-analysis

1. Find summary effect from each trial
2. Combine in a meta-analysis

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Two-stage meta-analysis

1. Use IPD to estimate summary effect from each trial
2. Combine in a meta-analysis
   • Similar to an analysis of published data

Advantages of two-stage approach

• Independent analyses of each trial

• Consistent analyses of trials
  – Same method / model
  – Same effect measure

• Can use standard meta-analysis methods and software
  – Forest plots
  – Heterogeneity assessment (e.g. I^2)
  – Fixed and random effects models
One-stage meta-analysis

- Analyse all data together
- **BUT**
- Retain differentiation between trials

Trial Data  
Combined Data Set  
One analysis model

Two-stage MA: Stage 1

Binary data: successful fusion at 24 months

<table>
<thead>
<tr>
<th>Trial A</th>
<th>Fusion</th>
<th>No fusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>rhBMP2</td>
<td>123</td>
<td>7</td>
</tr>
<tr>
<td>Control</td>
<td>106</td>
<td>13</td>
</tr>
</tbody>
</table>

Log relative risk: 0.060  
Standard error: 0.038

Log odds ratio: 0.768  
Standard error: 0.487

<table>
<thead>
<tr>
<th>Trial B</th>
<th>Fusion</th>
<th>No fusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>rhBMP2</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td>13</td>
<td>6</td>
</tr>
</tbody>
</table>

Log relative risk: 0.368  
Standard error: 0.151

Log odds ratio: 3.161  
Standard error: 1.506

* With continuity correction (add 0.5)
Alternative: logistic regression

Fit a logistic regression in each trial:

\[
\log \left( \frac{p_i}{1 - p_i} \right) = \alpha + \theta x_i
\]

Probability of fusion in person \( i \)  | Log odds ratio  | Standard error
--- | --- | ---
A | 0.768 | 0.487
B * | 3.161 | 1.538

* Penalised logistic regression

Stage 2: Meta-analysis

- Effect estimate and standard error for each trial
- Apply any standard meta-analysis technique
  - Forest plots
  - Fixed and random-effects analyses
  - Heterogeneity estimation and testing
  - Cochran’s Q test, \( I^2 \)
  - Subgroup analyses
Inverse-variance meta-analysis

- Effect estimate $\hat{\theta}_s$ and variance $\sigma^2_s$
  \[ \hat{\theta} = \frac{\sum_s w_s \hat{\theta}_s}{\sum_s w_s} \]
  \[ \text{var}(\hat{\theta}) = \frac{1}{\sum_s w_s} \]
  \[ w_s = \frac{1}{\sigma^2_s + \tau^2} \]

- For a fixed effect analysis $\tau^2 = 0$
- For random effects need an estimate of $\tau^2$
  - E.g. DerSimonian-Laird

Assessing heterogeneity

- Cochran’s Q test
  \[ Q = \sum_s w_s (\hat{\theta}_s - \hat{\theta}_{FE})^2 \] compared to $\chi^2_{S-1}$

- $I^2$
  - Proportion of variation attributable to heterogeneity
  \[ I^2 = \frac{Q - (S - 1)}{Q} = \frac{\tau^2}{\tau^2 + \sigma^2} \]
Random-effects analysis of relative risk

Using contingency table approach
With continuity corrections

Random-effects analysis of odds ratios

Using penalised logistic regression approach
Continuous outcomes

- Change in Oswestry score after 24 months

<table>
<thead>
<tr>
<th>Trial A</th>
<th>Number</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>rhBMP2</td>
<td>132</td>
<td>-27.80</td>
<td>20.01</td>
</tr>
<tr>
<td>Control</td>
<td>121</td>
<td>-29.19</td>
<td>21.40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial B</th>
<th>Number</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>rhBMP2</td>
<td>24</td>
<td>-33.33</td>
<td>17.91</td>
</tr>
<tr>
<td>Control</td>
<td>20</td>
<td>-17.30</td>
<td>17.20</td>
</tr>
</tbody>
</table>

Mean difference: 1.39
Standard error: 2.61
Standardised MD: 0.07

Mean difference: -16.03
Standard error: 5.31
Standardised MD: -0.89

Alternative: linear regression

- Fit a linear regression in each trial:

\[ y_i = \alpha + \theta x_i + \epsilon_i \]

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<tr>
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<th>Mean difference</th>
<th>Standard error</th>
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<tr>
<td>A</td>
<td>1.39</td>
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Random-effects analysis of Oswestry score

Using linear regression approach

Software

- IPD needs lots of data management
  - Merging files, subsetting, restructuring…
  - SAS most flexible, R an option
  - Or specialist database software

- "First stage" needs standard statistical methods
  - Tabulation, calculate means, regression
  - SAS, R, Stata, SPSS, Excel
Software

• “Second stage” can use standard meta-analysis software
  – R: meta and metafor libraries
  – Stata: meta and metan
  – RevMan
  – Commercial software:
    • Comprehensive meta-analysis

Further possibilities

• New general methods in meta-analysis
  – Different estimators of heterogeneity:
    – Paul-Mandel, REML…
    – Different confidence intervals
    – Hartung-Knapp confidence intervals, prediction intervals

• Methods specific to IPD

• More complex models in “first stage”
  – Adjusting for confounders
  – Correlation of baseline and treatment effects
  – Multivariate analysis
In session 3…

- “One-stage” meta-analysis
- Modifiers of treatment effect
- Survival analysis
- Missing data

References


