Individual participant data meta-analysis

Catrin Tudur Smith
cat1@liv.ac.uk

MRC North West Hub for Trials Methodology Research,
Department of Biostatistics,
University of Liverpool
Acknowledgements

- Thomas Debray, UMC Utrecht
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- Tony Marson, University of Liverpool
- Paula Williamson, University of Liverpool
Outline

- What is IPD?
- Why IPD?
- How to get and process IPD
- How to analyse IPD
  (i) treatment effect
  (ii) treatment-covariate interaction
- Further issues
- Practical session (using R)
Aggregate Data (AD) published

Table 4. Summary of Efficacy Results: Overall Survival and Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>%</th>
<th>GemCis</th>
<th>Gem</th>
<th>HR</th>
<th>Log-Rank P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median OS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>190</td>
<td>7.5</td>
<td>6.0</td>
<td>0.80</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>39</td>
<td>10.3</td>
<td>10.4</td>
<td>0.68</td>
<td>.29</td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>151</td>
<td>7.2</td>
<td>4.7</td>
<td>0.82</td>
<td>.23</td>
<td></td>
</tr>
<tr>
<td>KPS 70%-80%</td>
<td>76</td>
<td>4.9</td>
<td>4.8</td>
<td>1.13</td>
<td>.64</td>
<td></td>
</tr>
<tr>
<td>KPS 90%-100%</td>
<td>84</td>
<td>10.7</td>
<td>6.9</td>
<td>0.62</td>
<td>.051*</td>
<td></td>
</tr>
<tr>
<td><strong>6-month survival</strong></td>
<td></td>
<td>59.0</td>
<td>50.5</td>
<td></td>
<td></td>
<td>.45</td>
</tr>
<tr>
<td><strong>12-month survival</strong></td>
<td></td>
<td>25.3</td>
<td>24.7</td>
<td></td>
<td></td>
<td>.21</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>190</td>
<td>5.3</td>
<td>3.1</td>
<td>0.75</td>
<td>.053</td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>39</td>
<td>8.6</td>
<td>3.2</td>
<td>0.30</td>
<td>.0053</td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>151</td>
<td>4.2</td>
<td>3.1</td>
<td>0.84</td>
<td>.31</td>
<td></td>
</tr>
<tr>
<td>KPS 70%-80%</td>
<td>76</td>
<td>2.8</td>
<td>2.9</td>
<td>0.91</td>
<td>.69</td>
<td></td>
</tr>
<tr>
<td>KPS 90%-100%</td>
<td>84</td>
<td>7.7</td>
<td>2.8</td>
<td>0.54</td>
<td>.013†</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GemCis, gemcitabine plus cisplatin; Gem, gemcitabine alone; HR, hazard ratio; OS, overall survival; KPS, Karnofsky performance status; PFS, progression-free survival.

*Peto-Wilcoxon-Test P = .0079.
†Peto-Wilcoxon-Test P = .0020.
## Individual participant data (IPD)

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Treatment</th>
<th>Survival Time (Days)</th>
<th>Status</th>
<th>Age</th>
<th>Sex</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>E</td>
<td>44</td>
<td>Dead</td>
<td>67</td>
<td>m</td>
<td>IV</td>
</tr>
<tr>
<td>2</td>
<td>E</td>
<td>54</td>
<td>Dead</td>
<td>64</td>
<td>m</td>
<td>III</td>
</tr>
<tr>
<td>3</td>
<td>E</td>
<td>67</td>
<td>Alive</td>
<td>55</td>
<td>f</td>
<td>III</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>43</td>
<td>Dead</td>
<td>79</td>
<td>f</td>
<td>IV</td>
</tr>
<tr>
<td>5</td>
<td>C</td>
<td>70</td>
<td>Alive</td>
<td>62</td>
<td>m</td>
<td>IV</td>
</tr>
<tr>
<td>6</td>
<td>E</td>
<td>88</td>
<td>Dead</td>
<td>60</td>
<td>f</td>
<td>IV</td>
</tr>
<tr>
<td>7</td>
<td>C</td>
<td>99</td>
<td>Alive</td>
<td>57</td>
<td>m</td>
<td>III</td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>45</td>
<td>Dead</td>
<td>66</td>
<td>m</td>
<td>III</td>
</tr>
<tr>
<td>9</td>
<td>E</td>
<td>90</td>
<td>Alive</td>
<td>59</td>
<td>f</td>
<td>III</td>
</tr>
<tr>
<td>10</td>
<td>C</td>
<td>23</td>
<td>Dead</td>
<td>53</td>
<td>m</td>
<td>IV</td>
</tr>
</tbody>
</table>
IPD vs AD

- IPD and AD meta-analysis can be equivalent
  - if data are equivalent
  - If treatment effect measure are equivalent

- Discrepancies usually arise because IPD data sets include different data to AD
  - IPD may reinstate patients originally excluded
  - IPD may include additional follow-up data
  - IPD may use more appropriate effect measure
IPD vs AD

AD (11 trials 1911 patients)  
IPD (13 trials 2103 patients)  

OR 0.65 (95% CI) 0.53 to 0.83  
HR 0.83 (95% CI) 0.76 to 0.92

IPD vs AD

- Empirical evidence - precision and size of effect varies compared to AD but no systematic pattern
- Further empirical evidence is needed:
  Individual patient data meta-analyses compared with meta-analyses based on aggregate data. Clarke MJ, Stewart L, Tierney J, Williamson PR
  Protocol for methodology review – Cochrane Library

“..the balance of gains and losses of the approach will vary according to the disease, treatment, and therapeutic questions explored” Stewart and Tierney 2002
Why IPD?

Reinstate patients into the analysis who were originally excluded

- Tierney and Stewart (2005) IPD meta-analysis in soft tissue sarcoma
- 99% of the 344 patients that had been excluded from published individual trial analyses were recovered

Meta-analysis with exclusions: $HR=0.85 \ (p=0.06)$
Meta-analysis reinstating all exclusions: $HR=0.90 \ (p=0.16)$
Why IPD?

Overcome outcome reporting bias (ORB)

- Definition: Selection of a subset of the original recorded outcomes, on the basis of the results, for inclusion in publication

The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews

Jamie J Kirkham,1 Kerry M Dwan,1 Douglas G Altman,2 Carrol Gamble,1 Susanna Dodd,1 Rebecca Smyth,3 Paula R Williamson1

- ORB suspected in at least one trial in 34% of 283 Cochrane reviews
- 42 significant meta-analyses
  - 8 (19%) would not have remained significant
  - 11 (26%) would have overestimated the treatment effect by > 20%

*BMJ* (2010); 340:c356
Why IPD?

Detailed exploration of participant level covariates’ influence on treatment effect

- Meta-analysis of 5 RCTs of anti-lymphocyte antibody induction therapy vs control for renal transplant patients (Berlin et al., 2002)
- Difference in treatment effect between patients with elevated antibodies compared to non-elevated?

  - Aggregate Data to estimate across-trials interaction:
    estimated difference in log odds ratio between elevated and non-elevated patients = -0.01 \( (p = 0.68) \)

  - IPD to estimate the pooled within-study interaction:
    estimated difference in log odds ratio between elevated and non-elevated patients = -1.33 \( (p = 0.01) \)
## Why IPD?

<table>
<thead>
<tr>
<th>Data checking &amp; standardisation of analysis</th>
<th>• Outcome definition can be standardised across trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>More complete analysis</td>
<td>• Include follow-up beyond initial publication</td>
</tr>
<tr>
<td></td>
<td>• Reinstate patients into the analysis who were originally excluded</td>
</tr>
<tr>
<td></td>
<td>• May be able to overcome outcome reporting bias</td>
</tr>
<tr>
<td>Detailed exploration of participant level covariates influence on treatment effect</td>
<td>• Maximum information using patient as unit of analysis - more power to identify clinically moderate interaction</td>
</tr>
<tr>
<td></td>
<td>• Direct interpretation for individual patient</td>
</tr>
<tr>
<td></td>
<td>• No reporting bias of subgroup analyses</td>
</tr>
<tr>
<td></td>
<td>• No ecologic bias</td>
</tr>
<tr>
<td>More thorough analysis of time-to-event data</td>
<td>• Check model assumptions eg proportional hazards</td>
</tr>
<tr>
<td></td>
<td>• More accurate (if published AD restricted)</td>
</tr>
</tbody>
</table>

But the IPD approach will be more resource intensive!
How to get IPD

• Eligible trials identified by search as in an AD review
• Identify contact author eg email address published in journal
• Response to request can vary

- No reply
- No with reason provided
- Yes, we will send the data
- Yes, here’s the data

• Variation in data format and supporting material
How to get IPD

• Initiatives to encourage data sharing and clinical trial transparency
How to get IPD

freeBIRD
Bank of Injury and Emergency Research Data

Sandercock et al. Trials 2011, 12:101
http://www.trialsjournal.com/content/12/1/101

The International Stroke Trial database

Peter AG Sandercock\textsuperscript{1*}, Maciej Niewada\textsuperscript{2,3}, Anna C\l{}onkowska\textsuperscript{2,3} and for the International Stroke Trial Collaborative Group
How to get IPD

13 sponsors
> 2100 studies

2 sponsors
> 100 studies
What to do when you get the IPD

1. Understand the data (need to check the trial protocol and decipher the variable codes)
2. Replicate published results (to help with 1 and identify queries)
3. Check the data (e.g. check chronological randomisation sequence, are there any missing patients?)
4. Raise queries if possible
5. ‘Clean’ data
6. Recode to a consistent format across trials (depends on analysis approach)
7. Define outcomes consistently across trials
8. Analyse data - good practice to have a pre-specified statistical analysis plan
9. May need to share results with data provider
Reporting IPD meta-analysis

Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data
The PRISMA-IPD Statement

Lesley A. Stewart, PhD; Mike Clarke, DPhil; Maroeska Rovers, PhD; Richard D. Riley, PhD; Mark Simmonds, PhD; Gavin Stewart, PhD; Jayne F. Tierney, PhD; for the PRISMA-IPD Development Group

Meta-analysis of IPD
Meta-Analysis of IPD – two stage

Stage 1: Fit model to IPD in each trial e.g. for time to event data:

\[ \lambda_{k(i)} = \lambda_{0(i)}(t) \exp(\beta_{(i)}x_{k(i)}) \]

where \( x_{k(i)} = 1 \) for treatment and 0 for control for patient \( k \) in trial \( i \)

Stage 2: combine treatment effects (\( \hat{\beta}_{(i)} \)) and variance using standard meta-analysis method

\[ \hat{\beta} = \frac{\sum_i w_i \hat{\beta}_{(i)}}{\sum_i w_i} \]

- either fixed effect or random effects
Meta-Analysis of IPD - one stage

combine all patient data from all studies in one single model taking into account the clustering of patients within study e.g. for time to event data

**Fixed effect**

\[ \lambda_{ik} = \lambda_{0i}(t) \exp(\beta x_{ik}) \]
where \( x_{ik} = 1 \) for treatment and 0 for control for patient \( k \) in trial \( i \)

**Random effects**

\[ \lambda_{ik} = \lambda_{0i}(t) \exp(\beta_i x_{ik}) \]
\[ \beta_i = \beta + b_i \text{ and } b_i \sim N(0, \tau^2) \]

Treatment effect (logHR) – assumed common ‘fixed’

Average treatment effect for a population of possible effects

Degree of heterogeneity
Meta-Analysis of IPD - one stage

<table>
<thead>
<tr>
<th>Outcome data type</th>
<th>Basic Model (assuming random effects)</th>
</tr>
</thead>
</table>
| Continuous        | \[ y_{ik} = \alpha_i + \beta_i x_{ik} + e_{ik} \]  
                      | \[ e_{ik} \sim N(0, \sigma_i^2) \]  
                      | \[ \beta_i \sim N(\beta, \tau^2) \] |
| Binary            | \[ y_{ik} \sim \text{Bernoulli}(p_{ik}) \]  
                      | \[ \text{logit}(p_{ik}) = \alpha_i + \beta_i x_{ik} \]  
                      | \[ \beta_i \sim N(\beta, \tau^2) \] |
| Ordinal           | \[ y_{ijk} \sim \text{Bernoulli}(q_{ijk}) \]  
                      | \[ \text{logit}(p_{ijk}) = \alpha_{ij} + \beta_i x_{ik} \]  
                      | \[ \beta_i \sim N(\beta, \tau^2) \] |
| Count             | \[ y_{ik} \sim \text{Poisson}(\mu_{ik}) \]  
                      | \[ \ln(\mu_{ik}) = \alpha_i + \beta_i x_{ik} \]  
                      | \[ \beta_i \sim N(\beta, \tau^2) \] |
One-stage models

   - Fixed effect – Stratified Cox PH model
   - Random effects – SAS macro

2. **Continuous Outcomes** (see Higgins JPT. et al. Stat Med 2001)
   - Fixed effect - standard ANOVA model
   - Random effects - SAS PROC MIXED, MLwiN, Stata xtmixed, winBUGS

   - Generally based on logistic regression models
   - Fixed effect models - standard stats software eg SAS, R, STATA
   - Random effect models – MLwiN, Stata gllamm, winBUGS

   - Based on proportional odds models
Common practice

- **Simmonds et al (2005)**, n=44, 1999-2001
  - 65% with <=10 trials
  - two-stage methods most common
  - poor reporting

- **Pignon et al (2007)**, lung cancer, n=9, 2006
  - two-stage methods most common

- **Kolamunnage-Dona (2008)**, n=79 (62 with data on number of trials), IPDMWG
  - median 10 trials, range 2-63
  - two-stage methods most common
Two-stage vs One-stage

- Two-stage:
  - More accessible to non-statisticians
  - More in the spirit of traditional meta-analysis (can use RevMan): Forest Plot and Heterogeneity statistics output
  - Random effects easy (not the case for one-stage time to event data)
  - Can easily incorporate both IPD and AD estimates

- But,
  - Less flexibility and more long winded
  - Lower power for detecting nonlinear associations between continuous exposures and the outcome(s) of interest
  - May lead to bias in pooled effects, standard errors, between-study heterogeneity, and correlation between random effects when few studies or few participants (or events) per study are available, when statistical models cannot fully account for follow-up times or for the time between recurrent events (see Debray et al 2015).

- Both approaches give similar (if not identical) results most of the time!
  Discrepancies can largely be explained by different assumptions rather than the number of stages (Morris and Fisher)
Software for Two Stage Approach

- Using Revman (free)

**Stage 1:**

Use standard statistical analysis software to obtain $\hat{\beta}_i$ - estimates of treatment effect and variance within each trial

**Stage 2:**

Input data using Generic Inverse Variance Method in Revman
Software for Two Stage Approach

The Stata Journal (2015)
15, Number 2, pp. 369–396

Two-stage individual participant data
meta-analysis and generalized forest plots

David J. Fisher
MRC Clinical Trials Unit at University College London
London, UK
d.fisher@ucl.ac.uk

Stata command ipdmetan for two-stage IPD meta-analysis of
any measure of effect
- estimates random effects and heterogeneity statistics
- can include additional covariates and interactions
- can combine IPD and AD
- produces detailed and flexible forest plots
Software examples for one-stage meta-analysis

Any software that estimates multilevel mixed-effects linear models (also known as mixed-effects, multilevel, or hierarchical models)

<table>
<thead>
<tr>
<th>Software</th>
<th>command</th>
<th>model</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>lme4</td>
<td>GLMM using ML and REML (mixed linear models) Mixed effects Cox PH model</td>
</tr>
<tr>
<td></td>
<td>coxme</td>
<td></td>
</tr>
<tr>
<td>SAS</td>
<td>PROC MIXED</td>
<td>Mixed linear models using ML, REML or MOM</td>
</tr>
<tr>
<td>Stata</td>
<td>Gllamm mixed</td>
<td>GLMM using ML GLMM using ML, REML and EM</td>
</tr>
<tr>
<td>MLWin</td>
<td>-</td>
<td>GLMM and survival using ML, REML and EM</td>
</tr>
</tbody>
</table>

For further details see Debray et al *Res. Syn. Meth.* 2015, 6 293–309
Interactions between treatment and covariate
No treatment x covariate interaction (absolute scale)

- Experimental Treatment
- Control Treatment

Qualitative treatment x covariate interaction (absolute scale)

- Control Treatment
- Experimental Treatment

Quantitative treatment x covariate interaction (absolute scale)

- Experimental Treatment
- Control Treatment
Investigating interactions

- Does treatment effect differ according to particular patient level characteristics?
  
  e.g. Is carbamazepine more effective for focal seizures and valproate more effective for generalised seizures?

- Can we explain heterogeneity in treatment effects?

- To explore this we need to examine treatment – covariate interactions (also referred to as treatment effect modifier or subgroup analyses)
Investigating interactions

Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials

Why not AD?

Detailed exploration of participant level covariates influence on treatment effect

- Meta-regression based on AD can only tell us about the across trial relationships between treatment effect and aggregated trial level covariate (e.g., mean age)
  - Will only identify differences if large variation in aggregated trial level covariate values
  - Ecological bias (relationship across trials doesn’t necessarily reflect within trial relationship)
  - Confounding (e.g., an observed relationship between treatment effect and mean age may be due to higher dose of treatment given to older patients)
Why not AD?

**Detailed exploration of participant level covariates influence on treatment effect**

- **Lambert et al., 2004** simulated 1000 meta-analyses, each with 5 trials and treatment effective for high risk patients but ineffective for low risk patients.
- Each meta-analysis analysed first using IPD, and then using meta-regression; treatment-covariate interactions estimated in both cases.
  - IPD approach has a power of 90.8% to detect interactions.
  - AD approach (meta-regression) has a power of 10.8% to detect interactions.
Investigating interactions: two stage approach

Stage 1: Simmonds and Higgins, 2007

Estimate the treatment effect (and variance) and interaction between covariate and treatment effect, (and variance), in each trial separately

\[ y_{k(i)} = \alpha_{(i)} + \beta_{(i)} x_{k(i)} + \mu_{(i)} z_{k(i)} + \gamma_{(i)} x_{k(i)} z_{k(i)} + e_{k(i)} \]

\[ e_{k(i)} \sim N(0, \sigma_{(i)}^2) \]

\( x_{k(i)} \): treatment indicator variable (1: treated, 0: control)

\( z_{k(i)} \): covariate value (eg 1: male, 0: female)

\( \gamma_{(i)} \): Interaction between treatment and covariate (change in treatment effect for male compared to female)
Investigating interactions: two stage approach

Simmonds and Higgins, 2007

\[ y_{k(i)} = \alpha_{(i)} + \beta_{(i)} x_{k(i)} + \mu_{(i)} z_{k(i)} + \gamma_{(i)} x_{k(i)} z_{k(i)} + e_{k(i)} \]
\[ e_{k(i)} \sim N\left(0, \sigma_{(i)}^2\right) \]

Stage 2:

i. Take the treatment effect estimates (\( \hat{\beta}_{(i)} \)) and variance for each trial and combine them in a usual fixed-effect or random-effects meta-analysis

ii. Take the interaction estimates (\( \hat{\gamma}_{(i)} \)) and variance for each trial (within trial estimates), and combine them in a usual fixed-effect or random-effects meta-analysis
Investigating interactions: one stage approach

Simmonds and Higgins, 2007

\[ y_{ik} = \alpha_i + \beta_i x_{ik} + \mu_i z_{ik} + \gamma_i x_{ik} z_{ik} + e_{ik} \]

\[ e_{ik} \sim N(0, \sigma_i^2) \]

\[ \beta_i \sim N(\beta, \tau^2) \]

Important:
(i) Account for clustering within trial

Assumptions about \( \gamma_i \)

i) Fixed (separate in each trial)
ii) Common (\( \gamma_i = \gamma \))
iii) Random (\( \gamma_i \sim N(\gamma, \theta^2) \))
Investigating interactions: one stage approach


\[ y_{ik} = \alpha_i + \beta_i x_{ik} + \mu_i z_{ik} + \gamma_W x_{ik} (z_{ik} - m_i) + \gamma_A x_{ik} m_i + e_{ik} \]

\[ e_{ik} \sim N(0, \sigma_i^2) \]

\[ \beta_i \sim N(\beta, \tau^2) \]

Important:
(i) Account for clustering within trial
(ii) Separate the within and across trial interaction
Further topics
IPD unavailable.... ?

- Could studies with IPD represent a biased sample?
  - Yes if reason is related to treatment effect e.g. if IPD denied from all studies that favour control

- Can suitable AD be extracted from studies with missing IPD?
  - Undertake separate analysis of AD and compare to IPD
  - Combine if reasonable
NMA of IPD


Sarah Donegan, Paula Williamson, Umberto D’Alessandro, Paul Garner and Catrin Tudur Smith

Network meta-analysis of individual and aggregate level data

References

References 2

- Stewart LA, Tierney JF. To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. *Eval Health Prof* 2002;25(1):76-97.
Practical

• Undertake a two-stage and one-stage meta-analysis of IPD in R (see separate worksheet)

Please do contact me for further information

cat1@liv.ac.uk