Advanced IPD meta-analysis methods for clinical trials

Part 3

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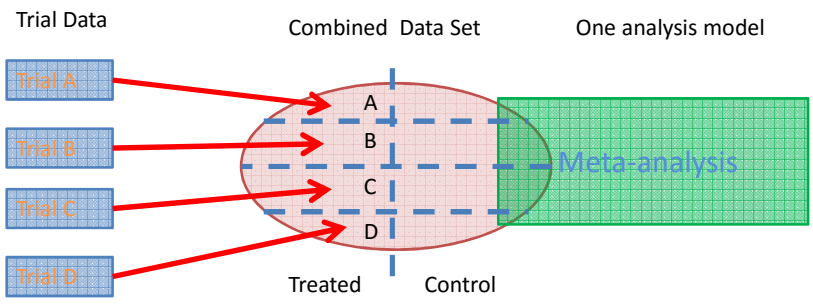
The one-stage approach



- All data analysed in one model
  - Account for trial and treatment

Extending the two-stage approach

Linear (continuous)

$$y_i = \alpha + \theta x_i$$

Logistic (binary)

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

Extend these models to include multiple trials (subscript *s*)

$$y_{si} = \alpha_s + \theta x_{si}$$

$$\log\left(\frac{p_{si}}{1-p_{si}}\right) = \alpha_s + \theta x_{si}$$

Outcome for patient i in trial s

Control group average in trial s

Common treatment effect in all trials

Stratified studies, common treatment

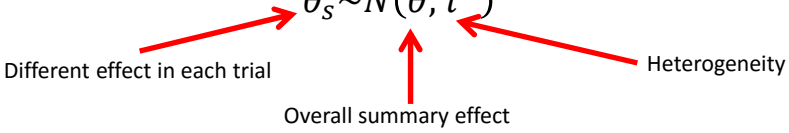
$$g(y_{si}) = \alpha_s + \theta x_{si}$$

General link function

- Separate baseline effect for each trial
  - Trials are kept separated
  - Randomisation respected
- Common treatment effect in all trials
  - Fixed effect meta-analysis

Random effects

$$g(y_{si}) = \alpha_s + \theta_s x_{si}$$
$$\theta_s \sim N(\theta, \tau^2)$$



- Random treatment effects
- (Generalised) Linear Mixed Effect Model

Random study effects

$$g(y_{si}) = \alpha_s + \theta_s x_{si}$$
$$\begin{pmatrix} \alpha_s \\ \theta_s \end{pmatrix} \sim N\left(\begin{pmatrix} \alpha \\ \theta \end{pmatrix}, \begin{pmatrix} \tau_\alpha^2 & \rho \\ \rho & \tau_\theta^2 \end{pmatrix} \right)$$

- Can assume random effects on baseline parameters
- Useful for:
  - Small trials
  - Trials using similar protocols

Advantages of one-stage approach

- Highly flexible: broad range of models
  - Linear / logistic / Poisson / survival regression
  - Fixed or random effects
  - Add covariates and interaction parameters
  - Multivariate analysis
- BUT
  - More statistically complex
  - Different approach from standard meta-analysis

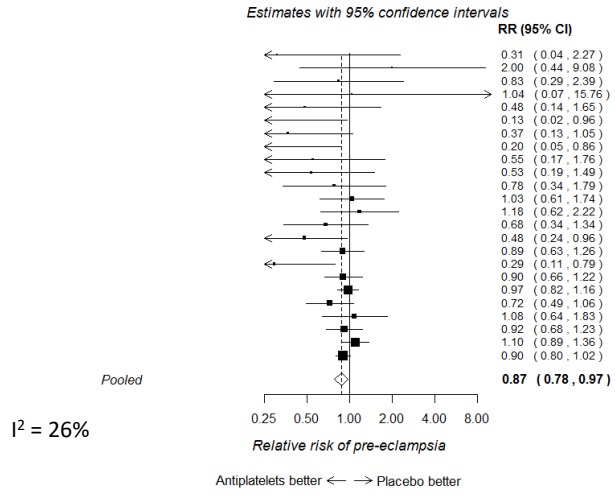
Software

- Mixed effect regression
- Needs specialist statistical software
- SAS
  - PROC MIXED, PROC GLIMMIX
- R
  - lme4 library (lmer, glmer)
- Stata
  - mixed, melogit

PARIS antiplatelet meta-analysis

- Preventing pre-eclampsia in pregnant women
- Treatment with antiplatelets (e.g. aspirin)
- 31 placebo-controlled trials with 32,217 women

Two-stage meta-analysis



I^2 = 26%

One-stage analysis

$$log(p_{si}) = \alpha_s + \theta_s x_{si}$$
$$\theta_s \sim N(\theta, \tau^2)$$

1: Antiplatelet
0: Placebo

Log link for relative risk

Log relative risk

Model	Effect estimate	95% CI	Heterogeneity (τ^2)
Two-stage RR	0.871	0.78 to 0.97	0.014 (I^2 = 26%)
One-stage RR	0.898	0.84 to 0.97	0
Two-stage OR	0.849	0.75 to 0.97	0.021 (I^2 = 29%)
One-stage OR	0.886	0.82 to 0.96	0

Extending the one-stage model

- Adding covariates:

$$g(y_{si}) = \alpha_s + \theta_s x_{si} + \gamma_s z_{si}$$
$$\theta_s \sim N(\theta, \tau^2)$$

A covariate:
Age
Sex
Drug dose
Severity

- Can correct for imbalance in poorly randomised trials

The impact of covariates on treatment

- Do covariates alter the treatment effect?

$$g(y_{si}) = \alpha_s + \theta_s x_{si} + \gamma_s z_{si} + \delta_s x_{si} z_{si}$$
$$\theta_s \sim N(\theta, \tau^2)$$

Interaction between treatment and covariate

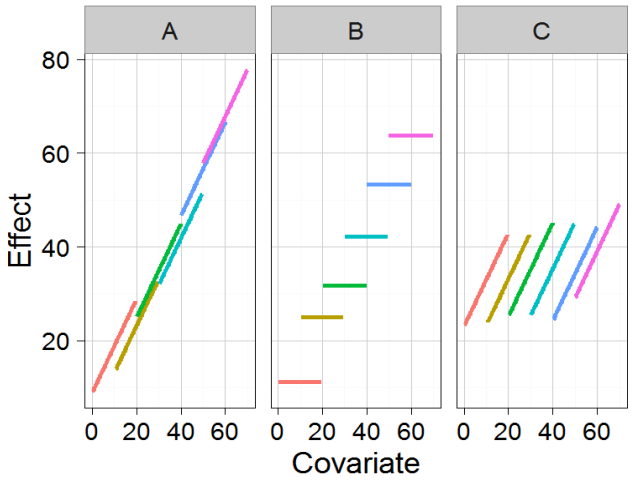
- δ (and γ, θ, α) can be:
  - Fixed effect: $\delta_s = \delta$
  - Random effects: $\delta_s \sim N(\delta, \tau_\delta^2)$
  - Different in each trial
    - Will need to meta-analyse these δ_s
    - A two-stage approach

Covariate effects in the PARIS analysis

Covariate	Odds ratio of interaction with antiplatelets	95% CI
Previous pregnancy (Yes vs no)	1.022	0.86 to 1.21
Gestational age (per week)	1.004	0.99 to 1.02
Maternal age (per year)	1.001	0.99 to 1.01

Assumed a common δ across all trials: i.e. a fixed effect regression

Aggregation bias: within and between trials



Separating within and between trials data

$$g(y_{si}) = \alpha_s + \theta_s x_{si} + \gamma_s z_{si} + \delta_W (z_{si} - \bar{z}_s) + \delta_B x_{si} \bar{z}_s$$

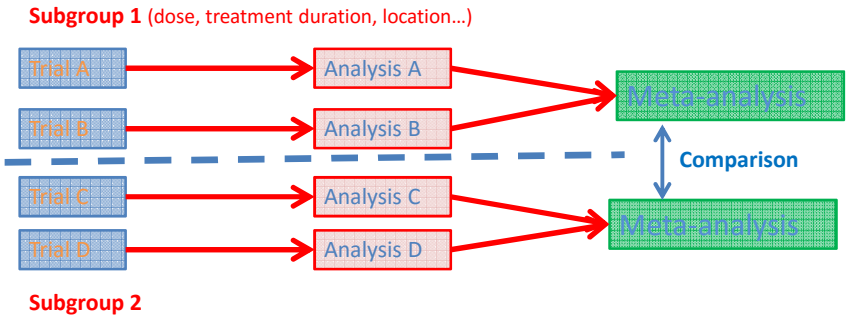
$$\theta_s \sim N(\theta, \tau^2)$$

Mean value in trial

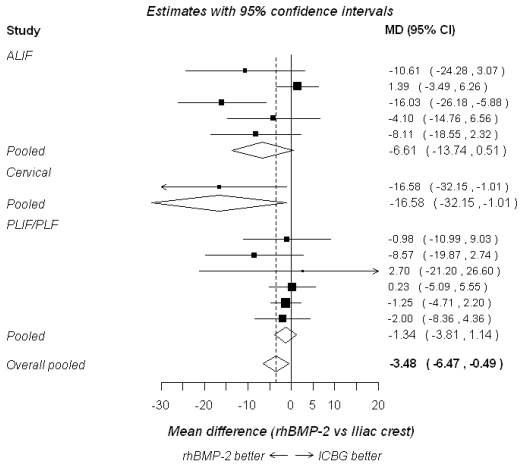
- δ_W gives within-trial estimate
- δ_B gives between-trial estimate
- Can examine if these are inconsistent
  - Evidence of bias

Two-stage approach

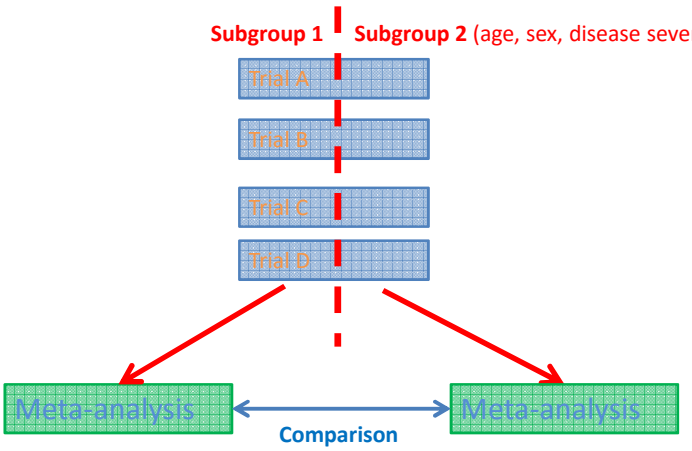
- Subgroup by trials



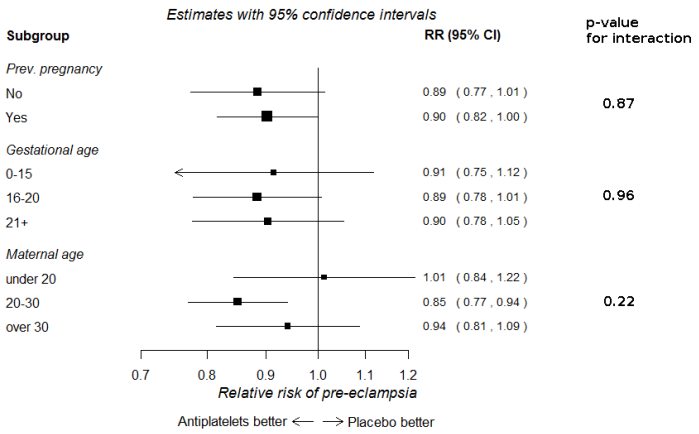
Oswestry score improvement by type of rhBMP2 surgery



Subgroup by patients



Subgroup analysis in PARIS



Survival data analysis and IPD

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Why use IPD?

- Summary data is usually insufficient
  - We need the time of each event
- Reporting of survival analyses is not consistent
  - Kaplan-Meier curves, hazard ratios, log rank tests, parametric models
- IPD is usually needed for a consistent meta-analysis

One-stage approach

- Extend the Cox model:

$$h_{si}(t) = h_{0s}(t)\exp(\theta_s x_{si})$$
$$\theta_s \sim N(\theta, \tau^2)$$

Completely stratified baseline hazards

$$h_{si}(t) = h_0(t)\exp(\alpha_s + \theta_s x_{si})$$
$$\theta_s \sim N(\theta, \tau^2)$$

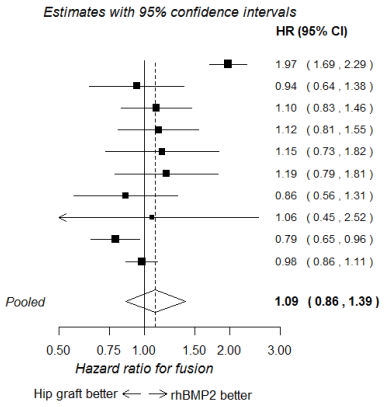
Baseline hazards have same "shape" but different scaling

- Limited software options for RE models
  - coxme library in R, WinBUGS

Parametric models and alternatives

- Can approximate Cox model with a logistic regression or Poisson model
  - Have to assume baseline hazard is "piecewise constant"
  - It changes only at end of every month / year
- Use parametric models
  - E.g. Weibull model
  - Limited random effects software

Time to spinal fusion (artificial)



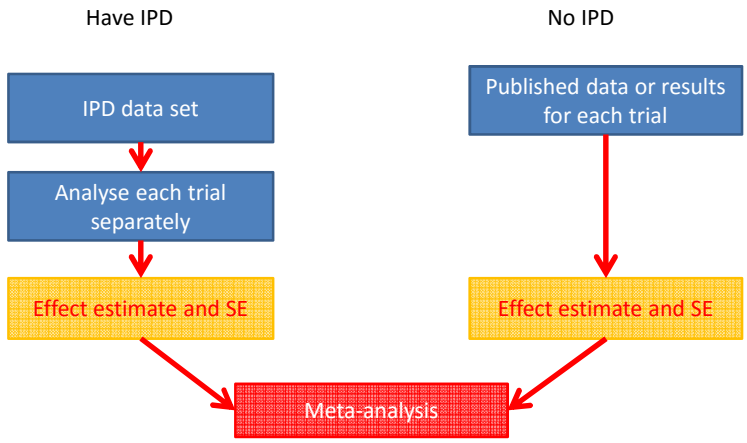
Method	Hazard ratio	95% CI
Two-stage Cox model (RE)	1.09	0.86 to 1.39
One-stage Cox model (FE)	1.14	1.06 to 1.24
One-stage Cox model (RE)	1.10	0.91 to 1.33

Missing data in IPD analyses

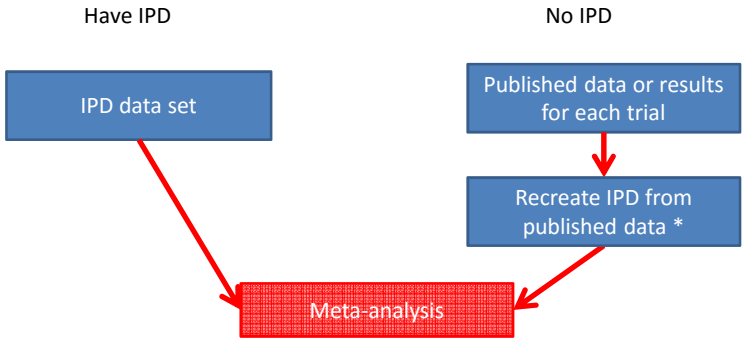
Trials not supplying IPD

- Trials may not provide IPD
  - Refusal to cooperate
  - Loss of original data
- May still have summary data
  - From publications or authors
- Can we combine summary data with IPD?

Two-stage approach

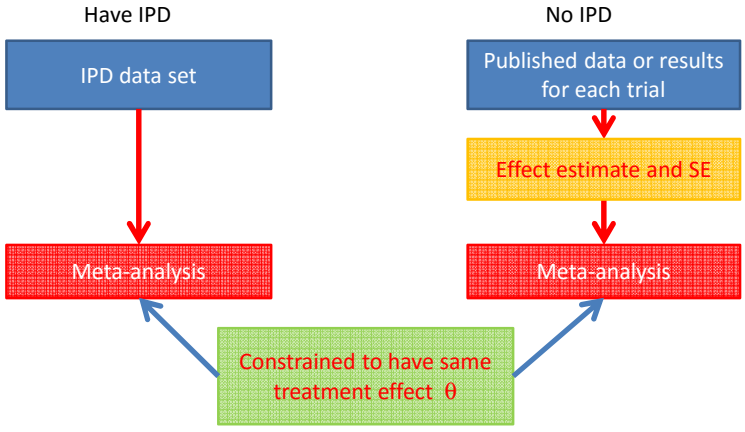


Reconstruct IPD



* Binary data: from contingency tables
* Survival data: from Kaplan Meier curves (using Guyot's method)

Joint modelling



Currently only possible in Bayesian framework (WinBUGS)

Sensitivity analysis

- Published data may be reported differently to IPD
- May not be analysed consistently
- Should compare results from IPD and published data in a sensitivity analysis
- No methods allow for investigation of covariate effects

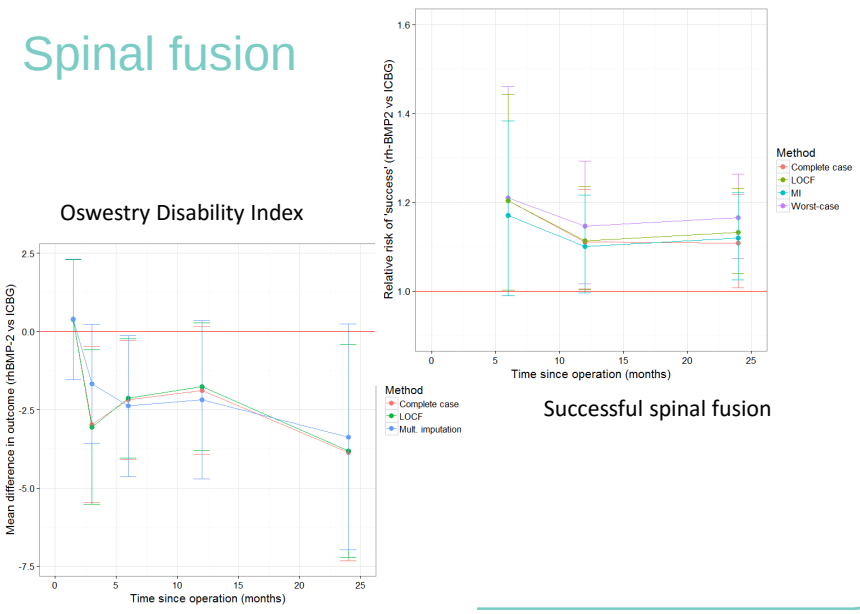
Missing outcome data

- What if some outcome data are missing?
  - Incomplete follow-up
  - Patient withdrawal
  - Loss of records

Imputation methods

- Complete case analysis
  - Exclude patients with missing data
- Last observation carried forward
- Multiple imputation
  - From earlier time points
  - From other similar patients within the trial
  - Across trials?
  - Correct for imputation (Rubin's rules) in each trial before meta-analysis

Spinal fusion



Completely missing outcomes

- Outcomes not reported in some trials
  - Need to impute across trials
- Multiple imputation with chained equations (MICE)
  - Impute missing data for multiple outcomes
  - Use correlations between outcomes in imputation

Summary

- IPD meta-analysis has two forms:
- Two-stage
  - Analyses within trials then pool across trials
  - Simper to perform
  - Can use standard meta-analysis methods
  - More limited when considering covariates
  - Best option if data are missing
- One-stage
  - Pool all data in one regression model
  - Offers more flexibility
  - Software more technical and limited
  - More scope for investigating impact of covariates

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