# IPD Meta-Analysis of Clinical Trials

## Part 1

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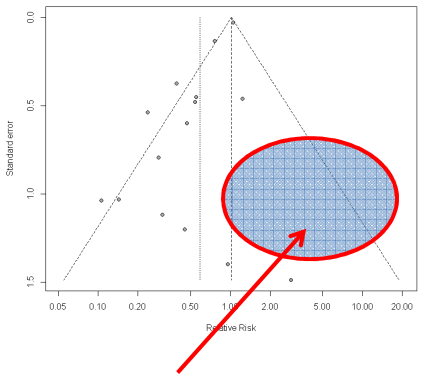
## Standard Meta-Analysis

- 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- Include unpublished trials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

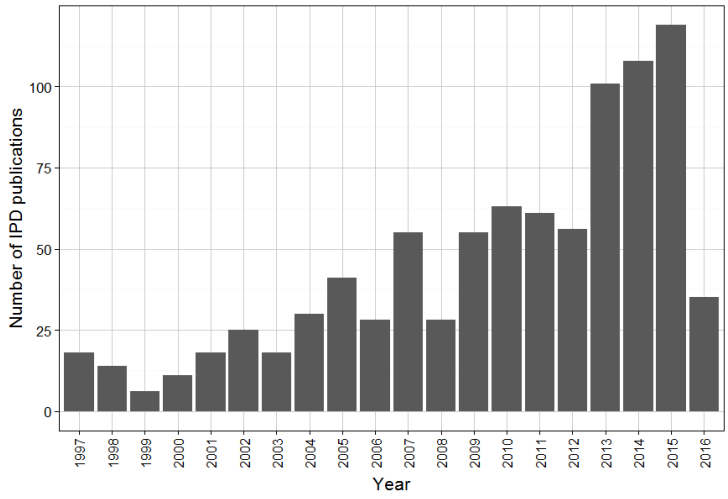
- May not get all data
  - Refusal of collaboration, loss of data, high cost of data
- Needs more collaboration
  - Time consuming and expensive
- Multiple data formats and codings
  - Complex data management and security
- More difficult to analyse



## 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

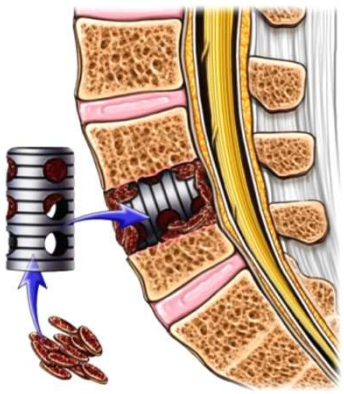
## Popularity of IPD






## Spinal fusion using rhBMP2 protein

- 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?

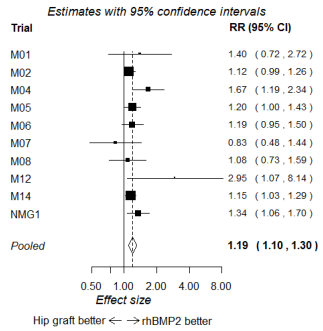


## Obtaining the IPD

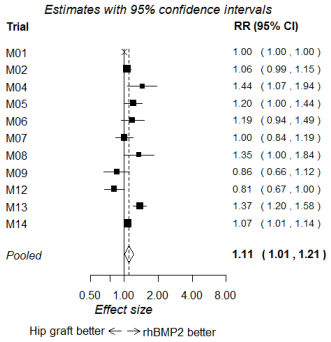
- Medtronic made all trial data available
  - To Yale Open Data Access (YODA)
- YODA authorised York team to perform an IPD meta-analysis
- 17 trials
  - Only a subset were eligible for primary analyses
- All clinical study reports, protocols, etc.
- Around 1800 files in total
- Over 400 SAS data files

# Meta-analysis: fusion after 2 years

Published data

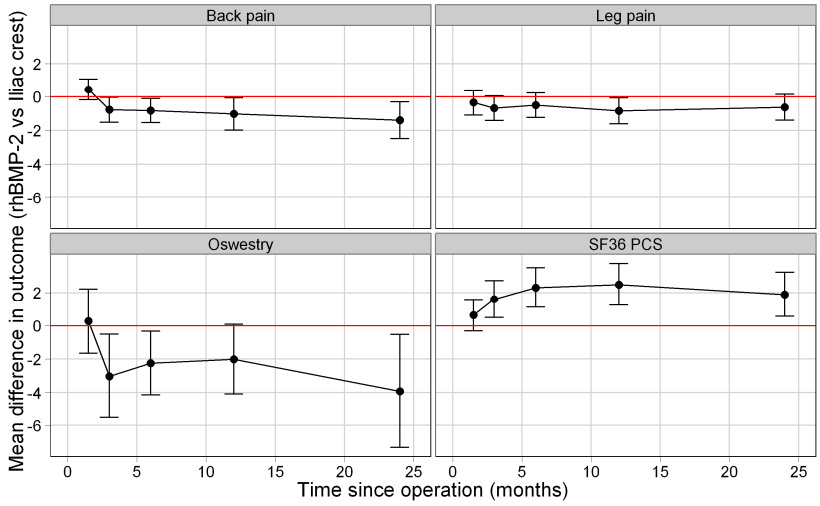



IPD

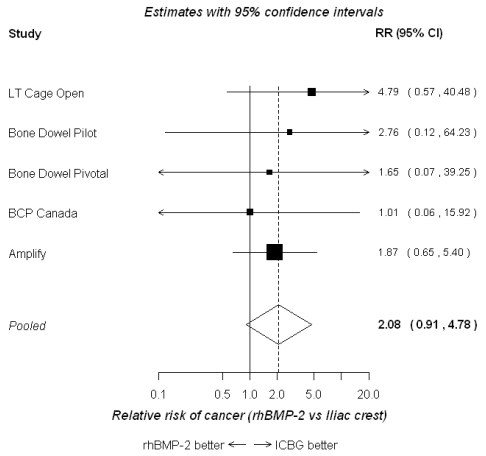





# The real outcome: Pain



# Cancer

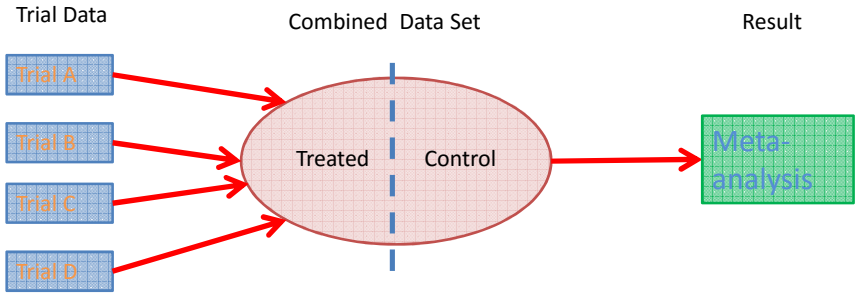





# Methods of IPD Meta-Analysis

"One-stage" and "Two-stage"

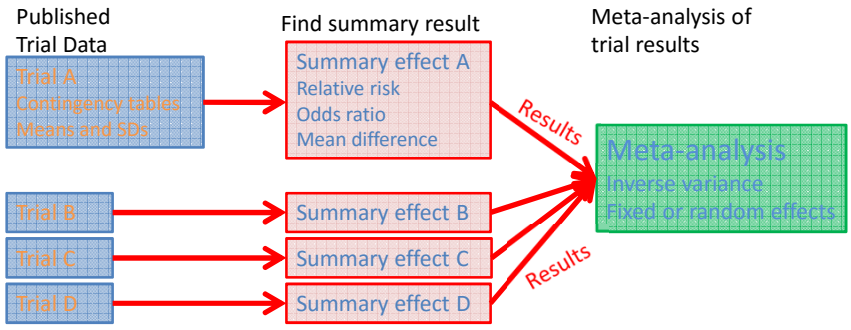
## Treat IPD like a trial




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

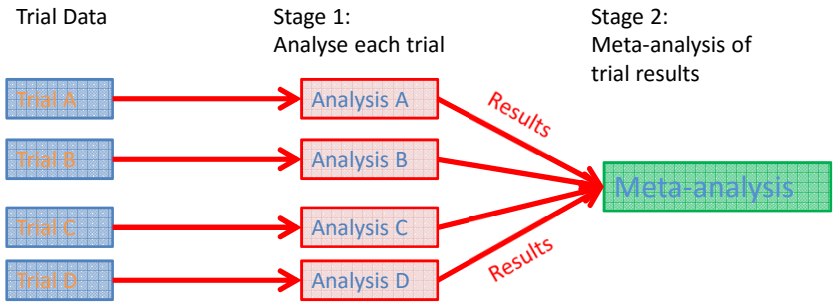


## Standard meta-analysis




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

## Two-stage meta-analysis




1. Use IPD to estimate summary effect from each trial
2. Combine in a meta-analysis

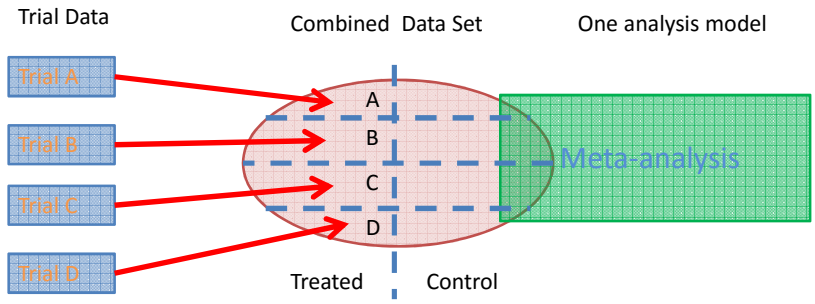
- Similar to an analysis of published data



## 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



## Two-stage MA: Stage 1

Binary data: successful fusion at 24 months

| Trial A | Fusion | No fusion |
|---|---|---|
| rhBMP2 | 123 | 7 |
| Control | 106 | 13 |

Log relative risk: 0.060
Standard error: 0.038

Log odds ratio: 0.768
Standard error: 0.487

| Trial B | Fusion | No fusion |
|---|---|---|
| rhBMP2 | 24 | 0 |
| Control | 13 | 6 |

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:

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

Treatment
1: rhBMP2
0: Control

Probability of fusion in person i

Log odds ratio

| Trial | 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 $\widehat{\theta_s}$ and variance $\sigma_s^2$

$$\hat{\theta} = \frac{\sum_s w_s \widehat{\theta_s}}{\sum_s w_s} \qquad var(\hat{\theta}) = \frac{1}{\sum_s w_s} \qquad w_s = \frac{1}{\sigma_s^2 + \tau^2}$$

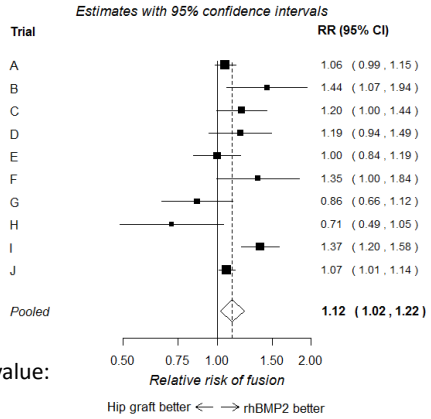
- For a fixed effect analysis $\tau^2 = 0$
- For random effects need an estimate of $\tau^2$
  - E.g. DerSimonian-Laird



## Assessing heterogeneity

- Cochran's Q test
  - $Q = \sum_s w_s \left(\widehat{\theta_s} - \hat{\theta}_{FE}\right)^2$ compared to $\chi^2_{S-1}$
- $I^2$
  - Proportion of variation attributable to heterogeneity
  - $I^2 = \frac{Q-(S-1)}{Q} = \frac{\tau^2}{\tau^2 + \widetilde{\sigma^2}}$

# Random-effects analysis of relative risk

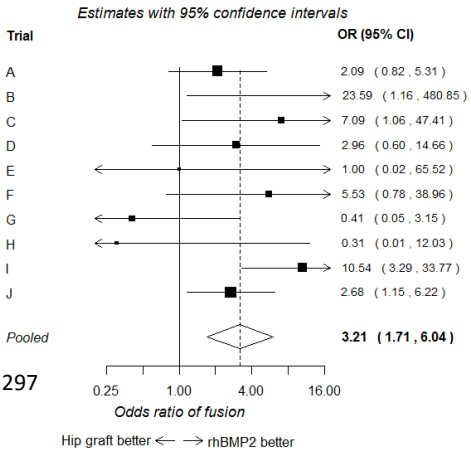



$I^2$: 45%
Cochran P-value: 0.068

*Using contingency table approach*
*With continuity corrections*



# Random-effects analysis of odds ratios




$I^2$: 16%
P-value: 0.297

*Using penalised logistic regression approach*

## Continuous outcomes

- Change in Oswestry score after 24 months

| Trial A | Number | Mean | SD |
|---|---|---|---|
| rhBMP2 | 132 | -27.80 | 20.01 |
| Control | 121 | -29.19 | 21.40 |

Mean difference: 1.39
Standard error: 2.61

Standardised MD: 0.07
Standard error: 0.13

| Trial B | Number | Mean | SD |
|---|---|---|---|
| rhBMP2 | 24 | -33.33 | 17.91 |
| Control | 20 | -17.30 | 17.20 |

Mean difference: -16.03
Standard error: 5.31

Standardised MD: -0.89
Standard error: 0.32



## Alternative: linear regression

- Fit a linear regression in each trial:

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

Error term

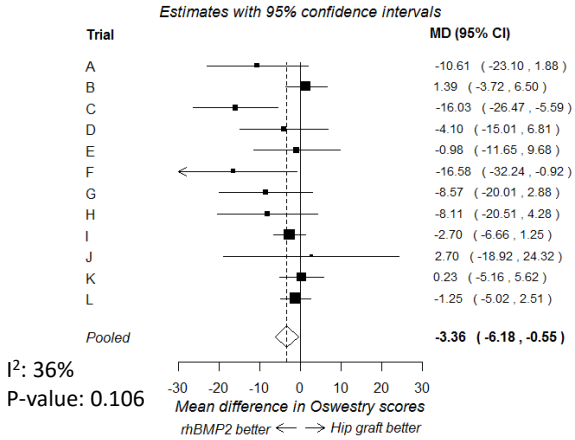
Change in score in person i

Mean difference

Treatment
1: rhBMP2
0: Control

| Trial | Mean difference | Standard error |
|---|---|---|
| A | 1.39 | 2.61 |
| B | -16.03 | 5.33 |

## 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

Simmonds M, Stewart G, Stewart L. A decade of individual participant data meta-analyses: A review of current practice. *Contemporary Clinical Trials 2015*; **45**: 76-83.

Stewart LA, Clarke MJ. Practical methodology of meta-analyses (overviews) using updated individual patient data. *Statistics in Medicine* 1995; **14**: 2057-79.

Stewart LA, Clarke M, Rovers M, et al. Preferred reporting items for a systematic review and meta-analysis of individual participant data: The prisma-ipd statement. *JAMA* 2015; **313**(16): 1657-65.

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