Methods to describe treatment effect heterogeneity in individual patient data meta-analysis

Karla Hemming, Jim Hughes, Andrew Forbes, Jo McKenzie

University of Birmingham; Washington University; Monash University

Cochrane Methods Group

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Meta-analysis

- Conventional meta-analysis based on summary level data[1]:
  - For every study an estimate of the treatment effect (SD) is available;
  - These treatment effects are pooled to obtain a single summary estimate of the treatment effect (along with CI).
- IPD meta-analysis using individual level data[2]:
  - These data are pooled either using a two-stage approach (above);
  - Or, the data are analyzed using a one-stage approach using a generalised linear mixed model (details later).
- Two common approaches, fixed or random:
  - Fixed effect meta-analysis (common treatment effect across studies);
  - Random effect meta-analysis (heterogeneity of treatment effects).

[1] Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ. 1997

[2] Higgins JP, Whitehead A, Turner RM, Omar RZ, Thompson SG. Meta-analysis of continuous outcome data from individual patients. Stat Med. 2001

Treatment effect heterogeneity in meta-analysis

- Test-statistic for treatment effect heterogeneity:

$$Q = \sum w_i(\hat{\mu}_i - \hat{\mu}_F)^2 \tag{1}$$

where i: study; $\hat{\mu}_i$: treatment effect for study i; w_i: precision for study i; $\hat{\mu_F}$: weighted pooled estimate.

- If $w_i^{-1} = \hat{\sigma}^2$ (variance of the treatment effect for study i) does not vary across studies the intuitive measure of between study heterogeneity is:

$$\hat{I}^2 = \frac{\hat{\tau}^2}{\hat{\tau}^2 + \hat{\sigma}^2} = \frac{between}{between + within} \tag{2}$$

where $\hat{\tau}^2$ is the (estimated) variance of the distribution of the μ_i's across the studies.

- If w_i is allowed to vary across studies it turns out that:

$$\hat{I}^2 = 100 * \frac{Q - (K-1)}{Q} \tag{3}$$

where K is the number of studies.

Prediction intervals

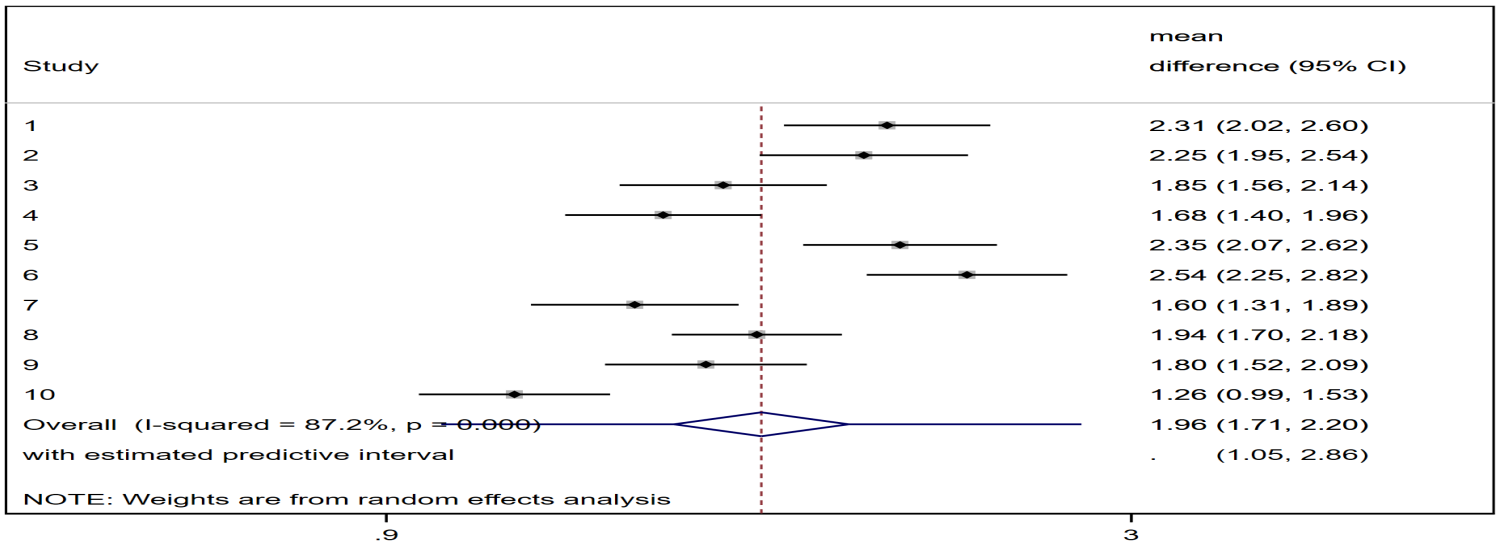
Finally, the predictive interval, which represents a region in which it is expected that 95% of future trial specific treatment estimates will fall, will be:

$$[\hat{\mu}_F - t_{\alpha/2,K-1} * \sqrt{((\hat{\tau}^2 + SE(\hat{\mu}_F)^2)} \text{ to } \hat{\mu}_F + t_{\alpha/2,K-1} * \sqrt{(\hat{\tau}^2 + SE(\hat{\mu}_F)^2)}] \quad (4)$$

Illustration of treatment heterogeneity in meta-analysis

Simulated IPD data (true I-squared 91%)

10 trials; High treatment effect heterogeneity (I-squared = 87.2%; Q-statistic=70.13 (d.f=9) p=0.000; $\hat{\tau}^2 = 0.14$); two-stage approach.



We will go on to consider how this analysis could be conducted using a one-stage approach.

Linear mixed model with treatment effect heterogeneity

Model treatment effect heterogeneity using an "interaction" term and allowing for a covariance term:

$$y_{ijs} = \beta_0 + x_{ijs}\theta + \alpha(S)_j + x_{js}\alpha(ST)_j + e_{ijs} \quad (5)$$

$$\boxed{i : individual; j : study; s : arm \ (m \ per \ arm)}$$

and that

$$\begin{pmatrix} \alpha(S)_j \\ \alpha(ST)_j \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \tau_S^2 & \sigma_{ST}^2 \\ \sigma_{ST}^2 & \tau_{ST}^2 \end{pmatrix}\right)$$

$$\boxed{S : Study \ effect; ST : Study \ by \ Treatment \ effect}$$

Relationship to MA

τ_{ST}^2 represents the variation between studies in their response to treatment (and so is akin to τ^2 in a meta-analysis).

[3] Hemming K, Taljaard M, Forbes A. Modeling clustering and treatment effect heterogeneity in parallel and stepped-wedge cluster randomized trials. Stat Med. 2018

Proposed I-squared one-stage

Recap: I-squared

The between study variability of the treatment effect divided by the sum of the between-study variability and the within-study variability

When analysing using a one-stage approach an intuitive estimate of I-squared is thus:

$$I^2 = \frac{\tau^2_{ST}}{\tau^2_{ST} + \frac{2\sigma^2_e}{\bar{m}}}$$

$$\boxed{\bar{m} : average\ (harmonic\ mean)\ study\ size\ per - arm}$$

Prediction interval:

$$[\hat{\theta} - t_{\alpha/2,K-1}\sqrt{((\hat{\tau}^2_{ST} + SE(\hat{\theta})^2)} \text{ to } \hat{\theta} + t_{\alpha/2,K-1}\sqrt{(\hat{\tau}^2_{ST} + SE(\hat{\theta})^2)}] \quad (6)$$

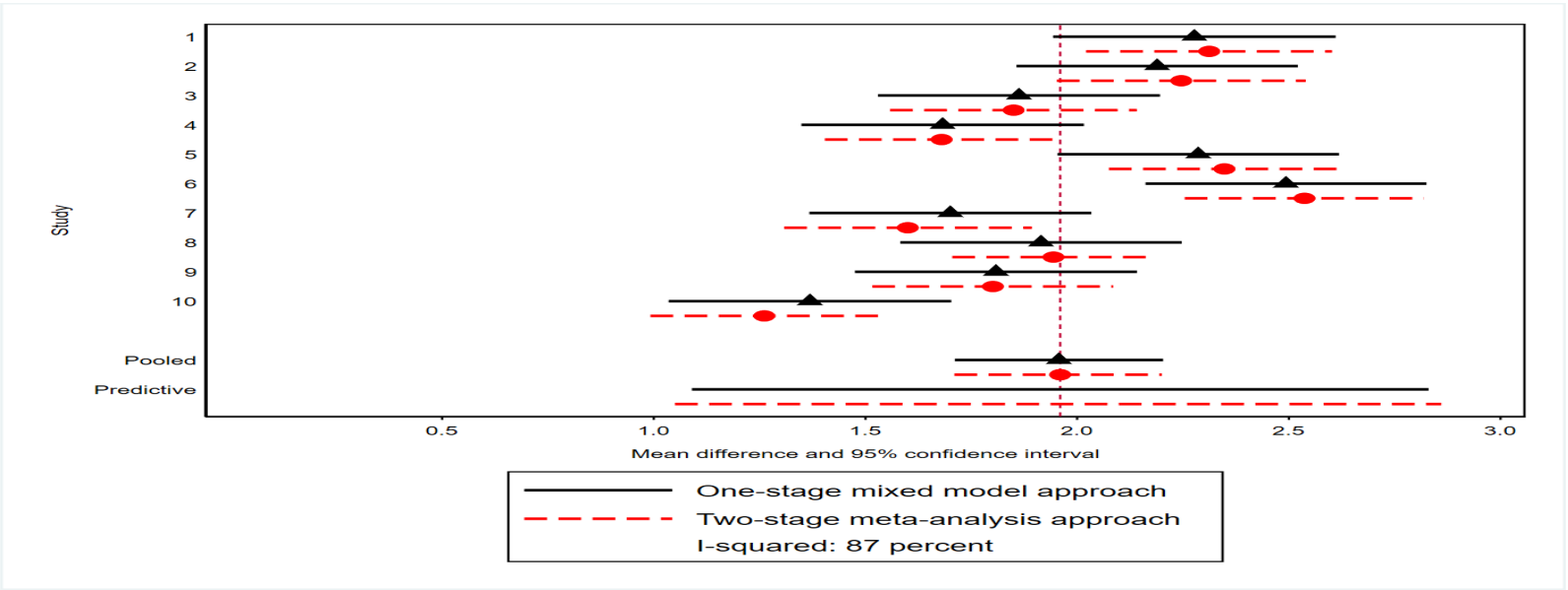
Illustration of one-stage approach using simulated IPD data

Recap: Simulated IPD meta-analysis

10 trials; High treatment effect heterogeneity (True I-squared = 91%; Q-statistic=70.13($d.f = 9$)$p = 0.000$; $\hat{\tau}^2 = 0.14$);

I-squared

Using one-stage approach $\hat{I}^2$ is 91.7% (87% using two-stage approach).

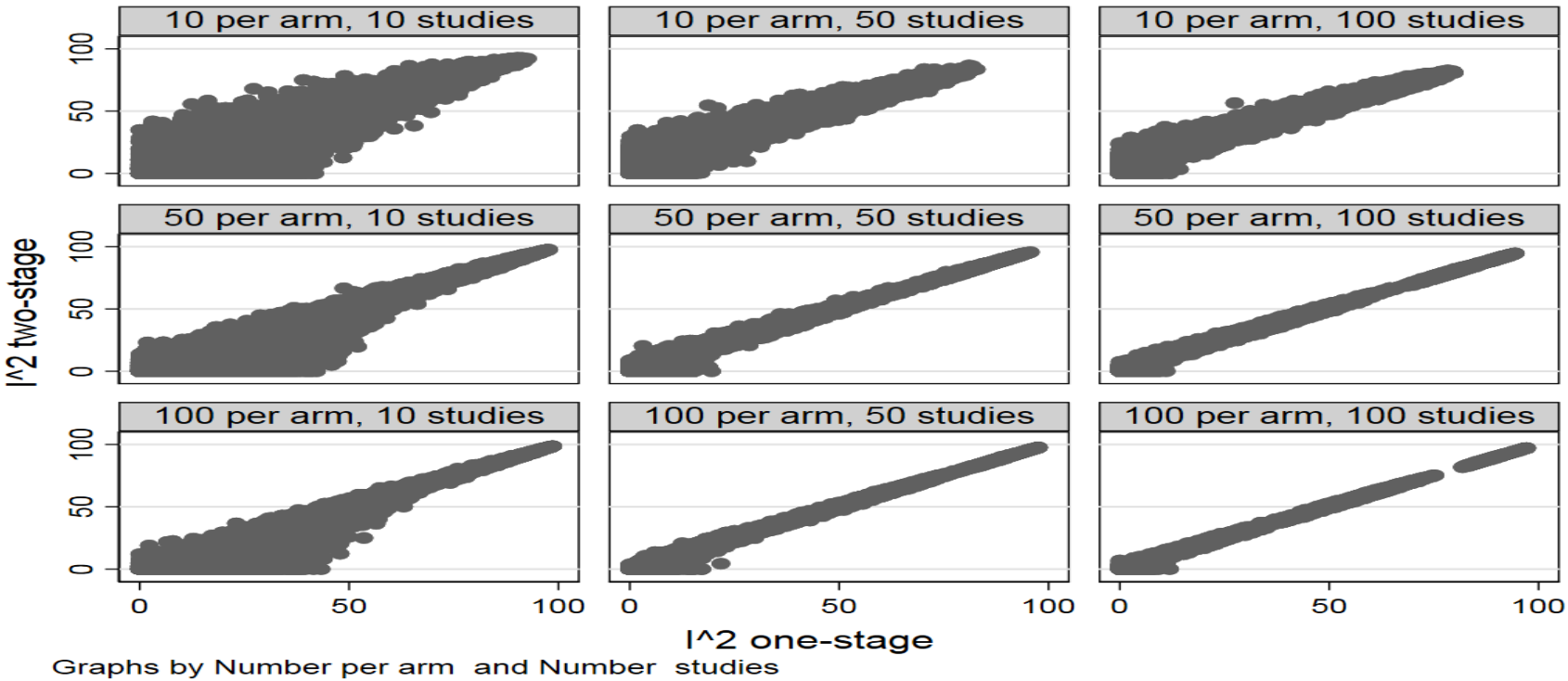


Simulation study

- Performance measures: correlation and bias;
- $N = 10,000$ data-sets simulated for each scenario;
- Data simulated from a linear mixed model with random study and random study by treatment interaction.
- Scenarios considered: 108:
  - REML and DL methods;
  - Number of studies: 10, 50, 100;
  - Study size per arm: 10, 50, 100;
  - Treatment effect 0; total variance 1;
  - Varying study sizes (zero-truncated negative binomial, CV=0.7);
  - Approximate (true) I-squared's high: 80% to 97%[1] [2]; moderate: 60% to 75%[2] [3]; low: 5% to 20% [3] [4].

[1] Equivalent $\tau^2_{CT} = 0.25$; $\tau^2_C = 0.125$; $\sigma^2_e = 0.625$.
[2] Equivalent $\tau^2_{CT} = 0.125$; $\tau^2_C = 0.125$; $\sigma^2_e = 0.75$.
[3] Equivalent $\tau^2_{CT} = 0.025$; $\tau^2_C = 0.125$; $\sigma^2_e = 0.85$.
[4] Equivalent $\tau^2_{CT} = 0.0025$; $\tau^2_C = 0.125$; $\sigma^2_e = 0.8725$.

Correlation between I-squared one-stage and I-squared two-stage



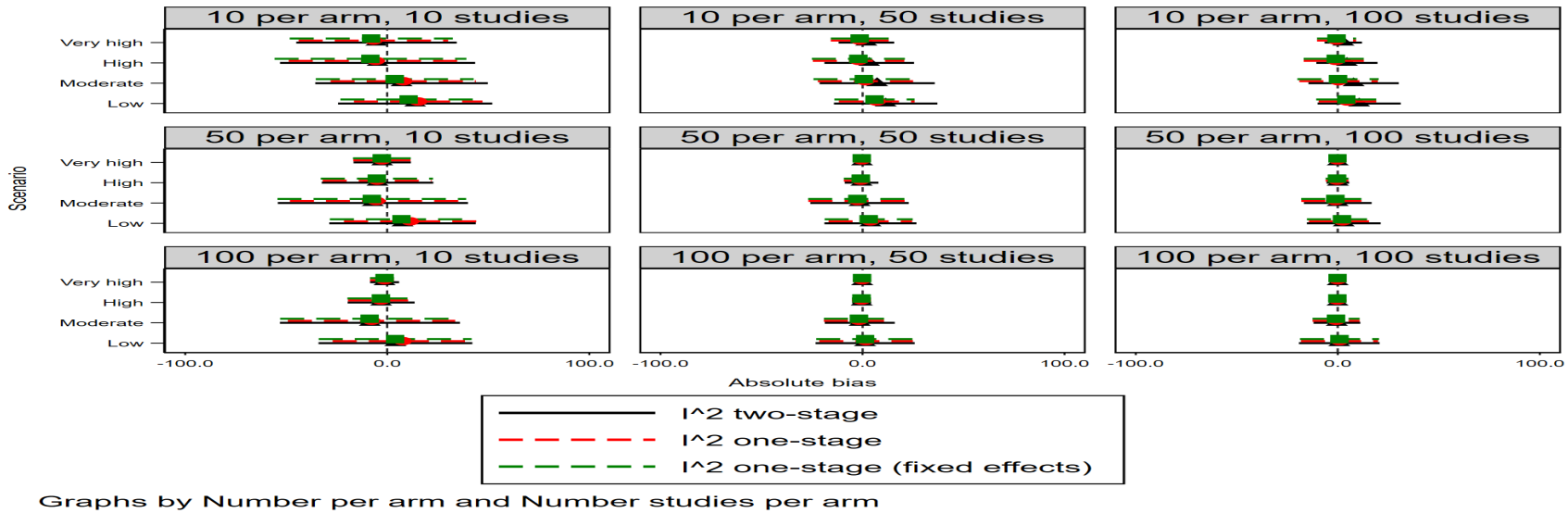
- Good correlation in large samples or when I-squared high [1];
- Models failed to converge for some scenarios with very low I^2.

[1] Austin (2018) The effect of number of clusters and cluster size on statistical power.

Investigation of bias in small sample settings

No clear method preferable

I-squared known to exhibit bias (upward for low I-squared, downward for high I-squared)[1]; no clear differences identified between two metrics.



[1] The heterogeneity statistic I2 can be biased in small meta-analyses Paul T von Hippel BMC Med Res Methodol. 2015;

Points for discussion

- Quantifying treatment effect heterogeneity:
  - Caution: Low I-squared can indicate no treatment heterogeneity or insufficient evidence to make conclusive statements.
  - Caution: High I-squared can indicate clinically important treatment effect heterogeneity or very large sample sizes[1].
  - Caution: I-squared can provide ball-park descriptions of magnitude of heterogeneity; best used in conjunction with a predictive interval.
- The proposed I-squared has the potential to be used in:
  - In cluster trials where treatment is crossed with cluster (to describe treatment effect heterogenity across clusters);
  - In individually randomised trials (to describe treatment effect heterogeneity across sites).

[1] Rucker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I2 in assessing heterogeneity may mislead BMC Med Res Methodol. 2008

[2] Chen B, Benedetti A. Quantifying heterogeneity in individual participant data meta-analysis with binary outcomes Syst Rev. 2017; 6: 243.

Thank you!

Poor man's estimate of the variance of the average within cluster treatment effect

Recall, for trials where treatment is crossed with cluster:

$$I^2 = 100 * \frac{\tau^2}{\tau^2_{CT} + \frac{4\sigma^2_e}{S\bar{m}}}$$

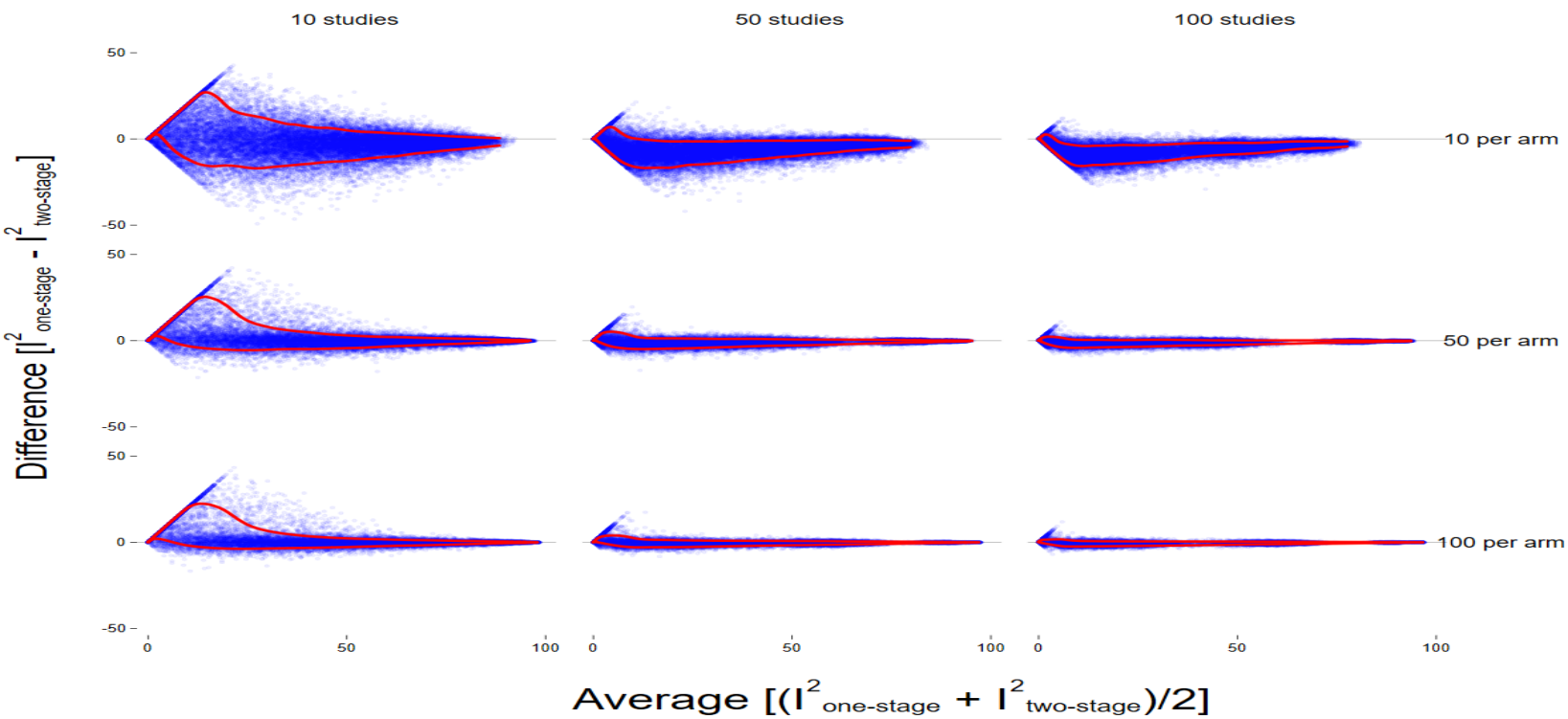
The (average) within-cluster estimate of the variance of the treatment effect is estimated by:

$$\frac{4\sigma^2_e}{S\bar{m}}$$

But....

Whilst this is correct for large sample continuous outcomes where there are no time effects, it should ideally be the average of the variance of within-cluster treatment effects. These are not a direct estimate of the modeling.

Bland Altman plot



Modification for time imbalanced designs

Recall, for trials where treatment is crossed with cluster:

$$I^2 = 100\% * \frac{\hat{\tau}^2_{CT}}{\hat{\tau}^2_{CT} + \hat{\sigma}^2_e \sum_j \frac{1}{\bar{m}_j}(\frac{1}{s_j} + \frac{1}{(S-s_j)})} \tag{7}$$

where s_j denotes the number of time periods that cluster j is observed under the intervention condition.