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UMC Utrecht
Julius Center

IPD-MA of RCTs: one-stage meta-analysis

Valentijn de Jong[1,2], PhD
1. Julius Center for Health Sciences and Primary Care
2. Data Analytics and Methods Task Force, European Medicines Agency

Cochrane
MSC EPIDEMIOLOGY
University Medical Center Utrecht

One-stage meta-analysis

Analyze all trials simultaneously by specifying an appropriate statistical model that accounts for clustering of subjects within trials.

When accounting for clustering, these models are also known as:

- Multilevel models
- Hierarchical models
- Mixed effects models
- Random intercept models

Overview of statistical methods

- Summarizing treatment effect(s)
- Investigating subgroups
- Exploring treatment effect modifiers

Clinical example

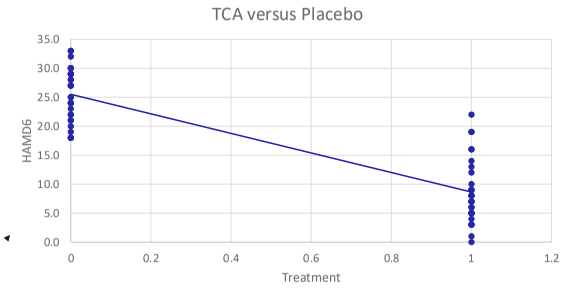
Meta-analysis of antidepressant trials

- 5 randomized trials
  - Patients diagnosed with major depressive disorder
  - Tricyclic antidepressant (TCA) versus Placebo (Plac)
- Outcome measurements
  - Hamilton Depression (HAMD) score, ranging from 0 to 54
  - Measured at baseline and after 6 weeks

Clinical example

Linear regression (clustering ignored)

$$HAMD6_{ik} = \alpha + \delta\ TREAT_{ik} + \varepsilon_{ik}$$



One-stage meta-analysis

Simultaneous analysis of trials and evidence synthesis

- We assume that parameters are somehow related or identical across trials.
  - Fixed effects (stratification; makes no assumptions about how effects differ across trials)
  - Random effects
  - Common effect (same for all trials)

Reduce # unknown parameters (as compared to two-stage MA)

- Different types of effects can be specified for each variable

Clinical example

How would you analyze the IPD from the antidepressant trials?

Patient	Study	Treatment	HAMD0	HAMD6
1	1	Placebo	26	15
2	1	TCA	24	18
3	1	Placebo	29	19
…				
439	5	TCA	21	22
440	5	placebo	24	15

Specifying the statistical model

Implementation of generalized linear *mixed* regression models (GLMM):

$$g\big(E(y_{ik})\big) = \alpha_k + \delta_k x_{ik}$$

Where

- Index i denotes the subject and k denotes the study
- $E(y_{ik})$ denotes the expected value of y_{ik}
- α_k denotes the study effect (e.g. baseline risk)
- δ_k represents the relative treatment effect
- $g(\cdot)$ represents the link function

Specifying the statistical model

Common statistical models

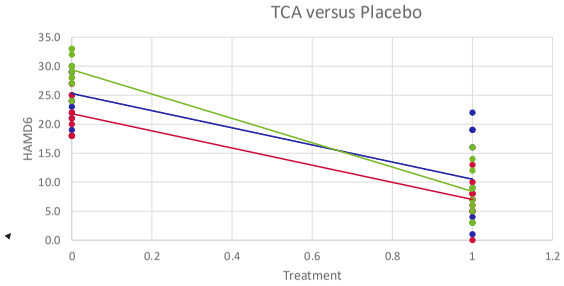
- Continuous outcomes
  - Normal distribution with identity link (linear regression)
- Binary outcomes
  - Bernoulli distribution with a logistic link (logistic regression)
- Count data
  - Poisson distribution with a log-link
- Time-to-event data
  - Hierarchical Cox PH model (with strata or frailty terms)
  - Poisson GLMM

Ref: Debray TPA, et al. (2015). Get real in individual participant data (IPD) meta-analysis: a review of the methodology. *Research Synthesis Methods*, (November 2014), n/a–n/a.
Ref: de Jong VMT, Moons KGM, Riley RD, Tudur Smith C, Marson AG, Eijkemans MJC, Debray TPA. Individual participant data meta-analysis of intervention studies with time-to-event outcomes: A review of the methodology and an applied example. Research Synthesis Methods. 2020 Mar;11(2):148-68. https://doi.org/10.1002/jrsm.1384

Clinical example

Linear regression accounting for clustering

$$HAMD6_{ik} = \alpha_k + \delta_k\, TREAT_{ik} + \varepsilon_{ik}$$



Specifying the statistical model

Implementation of generalized linear *mixed* regression models (GLMM):

$$g\big(E(y_{ik})\big) = \alpha_k + \delta_k x_{ik}$$

Where each δ_k may be taken as

- Fixed effects (estimated separately in each study)
- A common effect (so $\delta_k = \delta$ for all trials)
- Random effects (so δ_k is drawn from a certain, e.g. Normal, distribution)

Note: It is common to assume fixed effect**s** for α_k.

Clinical example

Mean treatment difference of HAMD score after 6 weeks

Trial	N	δ (1-stage)	δ (2-stage)
1	51	-6.98	-6.42
2	53	0.95	1.24
3	78	-5.92	-6.88
4	63	-3.86	-3.22
5	16	-0.98	-0.90

In one-stage MA, study-specific treatment effects are shrunk towards the overall mean

Comparison	$\widehat{D}$	SE($\widehat{D}$)	$\widehat{\tau}^2$
Two-stage	-3.44	1.60	11.05
One-stage	-3.36	1.68	12.01

Investigating effect modification

Statistical model

$$y_{6ik} \sim N(\mu_{ik}, \sigma_k^2)$$
$$\mu_{ik} = \alpha_k + \delta_k x_{ik} + \gamma_k y_{0ik} + \theta_{AW} x_{ik} y_{0ik}$$
$$\delta_k \sim N(D, \tau^2)$$

Adjust for treatment-covariate interaction

Adjust for baseline imbalance.

Note that a common effect is estimated for interaction at the patient level and at the trial level (as mean values of y_{0ik} may vary across trials and be correlated with study-level characteristics such as level of blinding)

=> risk for ecological bias!

Clinical example

Calculate mean treatment difference of HAMD score after 6 weeks in each trial:

$$y_{ik} = \alpha_k + \delta_k \, TREAT_{ik} + \varepsilon_{ik}$$
$$\varepsilon_{ik} \sim N(0, \sigma_k^2)$$
$$\delta_k \sim N(D, \tau^2)$$

Pooled treatment effect

Random effects for the treatment effect

Extending the model

It is fairly straightforward to extend the statistical model to:

- Correct for baseline imbalance
- Adjust for prognostic factors
- Explore interaction with trial-level covariates
- Explore interaction with patient-level covariates
- Explore non-linear associations

Investigating effect modification

Statistical model

$$y_{6ik} \sim N(\mu_{ik}, \sigma_k^2)$$

$$\mu_{ik} = \alpha_k + \delta_k x_{ik} + \gamma_k (y_{0ik} - \bar{y}_{0i}) + \theta_W x_{ik} (y_{0ik} - \bar{y}_{0k}) + \theta_A x_{ik} \bar{y}_{0k}$$

$$\delta_k \sim N(D, \tau^2)$$

Within-trial interaction

Across-trial interaction; quantifies the presence of ecological bias.

Centering y_{0ik} about the mean covariate value $\bar{y}_{0k}$ is necessary to separate within-trial interaction from between-trial interaction !

Recall: two-stage meta-analysis

Distinct steps for the analysis of individual trials and the synthesis of corresponding results.

- Stratification of *all* model parameters by study (i.e. fixed effects for treatment, study, confounders, interactions, etc.)
  - Automatically uses within-trial information!
- Meta-analysis is based on estimates of treatment effect and may assume a fixed or a random treatment effect

Danger of ecological bias

Treatment effect can be affected by:

- Individual covariate values (e.g. due to effect modification)
- A covariate mean value (e.g. due to study-level confounding)

θ_{AW} represents an amalgamation of within- and across-trial interactions!

Ref: Hua H, Burke DL, Crowther MJ, Ensor J, Tudur Smith C, Riley RD. One-stage individual participant data meta-analysis models: estimation of treatment-covariate interactions must avoid ecological bias by separating out within-trial and across-trial information. Statistics in Medicine. 2017;36(5):772–789.

Investigating effect modification

Statistical model

$$y_{6ik} \sim N(\mu_{ik}, \sigma_k^2)$$

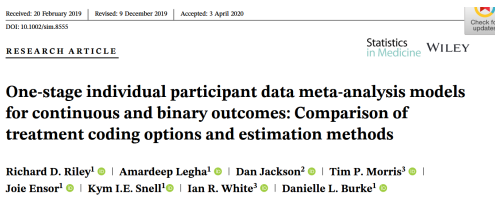
$$\mu_{ik} = \alpha_k + \delta_k x_{ik} + \gamma_k (y_{0ik} - \bar{y}_{0i}) + \theta_W x_{ik} (y_{0ik} - \bar{y}_{0i}) + \theta_A x_{ik} \bar{y}_{0i}$$

$$\delta_k \sim N(D, \tau^2)$$

If $\theta_k = 0$ and $\theta_A \neq 0$, we have the situation where treatment effects vary according to whether trials included *older* participants ($\bar{y}_{0i}$). However, within trials, there is no relation between participant *age* (y_{0ik}) and treatment effect; the (expected) relative change in HAMD score is the same for all participants.

- Estimates for θ_A can also be obtained from meta-regression
- Estimates for θ_W can also be obtained by pooling of within-trial covariate interactions.
- We can allow for heterogeneity in interaction by replacing θ_W with $\theta_{W,k}$ and assuming random effects for $\theta_{W,k}$

Estimation methods



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RESEARCH ARTICLE

Statistics in Medicine WILEY

One-stage individual participant data meta-analysis models for continuous and binary outcomes: Comparison of treatment coding options and estimation methods

Richard D. Riley[1] | Amardeep Legha[1] | Dan Jackson[2] | Tim P. Morris[3] | Joie Ensor[1] | Kym I.E. Snell[1] | Ian R. White[3] | Danielle L. Burke[1]

- Use REML and/or center the intervention variable within studies
- Use CI based on t-distribution instead of z-distribution