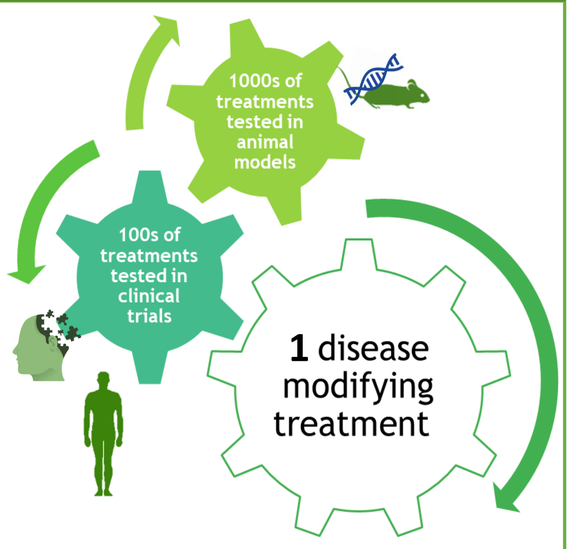
META-ANALYSIS OF PRECLINICAL DATA IN DRUG DISCOVERY RESEARCH

Ezgi Tanriver-Ayder[1], Christel Faes[2], Tom Van De Casteele[3], Sarah K. McCann[4], Malcolm R. Macleod[1]
[1] University of Edinburgh, [2] Hasselt University, [3] Janssen Pharmaceutica NV, [4] Charité Universitätsmedizin Berlin
ezgi.tanriverayder@ed.ac.uk

1. Objective

Meta-analysis of preclinical animal studies is vital in evaluating the internal and external validity. This informs the design and conduct of future preclinical studies and translation to a clinical setting. Investigating causes of heterogeneity between studies and choosing appropriate methods for estimation and modeling is crucial to perform a meta-analysis.



Assuming aggregate level data for a continuous primary outcome variable, we focus on two topics:

- Estimation of heterogeneity using three methods: method of moments (Dersimonian-Laird, DL), maximum likelihood (REML) and Bayesian approach (FB).
- Univariable versus multivariable meta regression for adjusting heterogeneity and exploring relative impact of multiple covariates on study level treatment effects.

2. Methodology

In random effects meta-analysis model, the treatment difference in studies are a random sample of independent observations.

$$\widehat{\theta_i} = \theta + b_i + \epsilon_i \qquad (1)$$

where $b_i \sim N(0, \tau^2)$ and $\epsilon_i \sim N(0, \xi_i^2)$ implying $\widehat{\theta_i} \sim N(\theta, \xi_i^2+\tau^2)$.

Classical Estimation of Between Study Heterogeneity:

1) REML estimator: A maximum likelihood-based method, where estimates of τ^2 and θ are obtained through an iterative procedure.
2) DL estimator: A method of moments-based estimate, where τ^2 can be derived by using the observed value of Q statistics and its expectation.

Frequentist Approach to Meta Regression:
Heterogeneity between studies can be explored based on study design and characteristics by meta regression with $\alpha_i = \beta_2 X_{2i}$ where X_{2i} is a covariate, $b_i \sim N(0, \tau^2)$ and $\epsilon_i \sim N(0, \xi_i^2)$.

$$\widehat{\theta_i} = \beta_1 + \alpha_i + b_i + \epsilon_i \qquad (2)$$

Bayesian Approach to Meta-Analysis and Heterogeneity Estimation:
$\widehat{\theta_i}$ are the estimates for effect size $N(\theta_i, \xi_i^2)$, where prior for θ_i is $N(\theta, \tau^2)$ with hyperpriors $\theta \sim N(\theta_0, \sigma_0^2)$, $\tau^2 \sim IG(\alpha, \lambda)$.

Bayesian Meta Regression:
Prior for θ_i is $N(\mu_i, \tau^2)$, where $\mu_i = \beta_1 + \beta_2 x_{2i}$.

3. Motivating Dataset

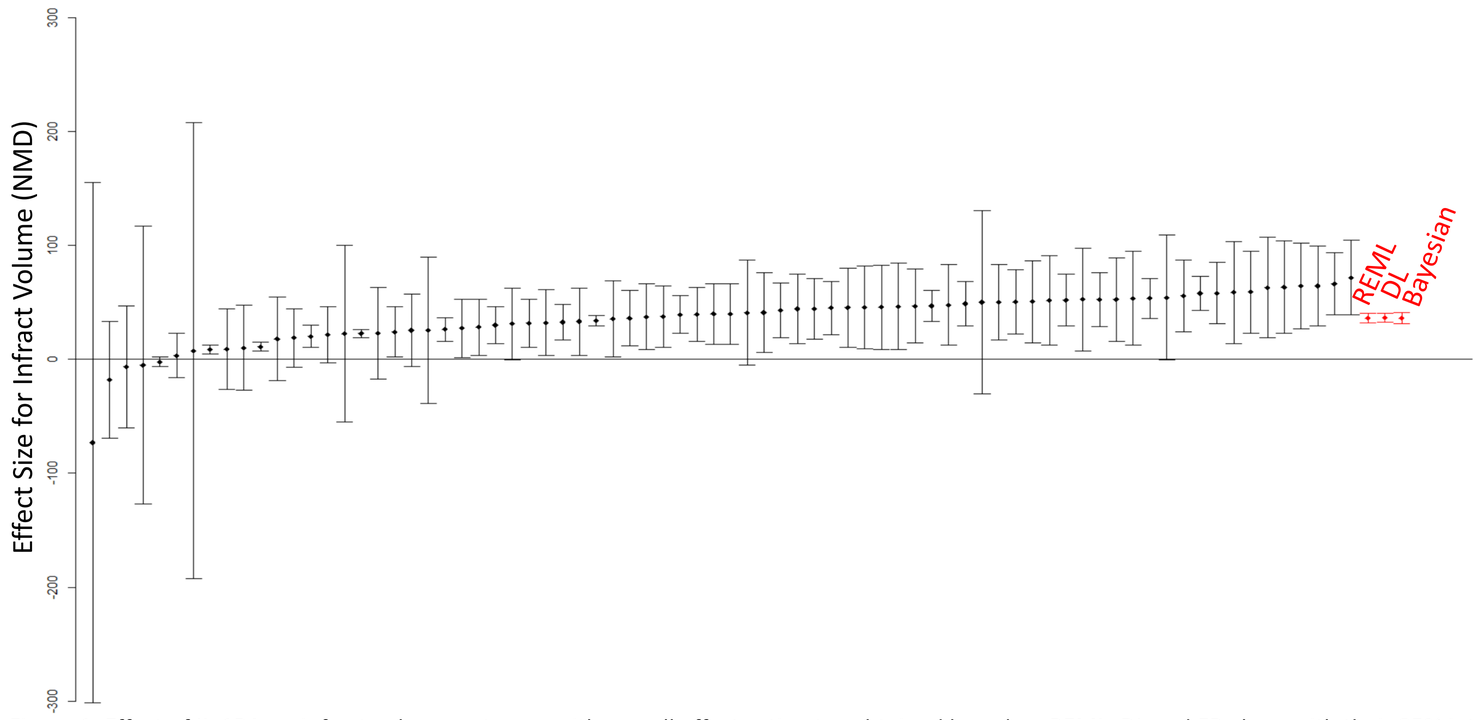


Figure 1: Effect of IL-1RA on infract volume outcome with overall effect estimates obtained based on REML, DL and FB along with their 95% intervals.

- To exemplify the suggested methodology for meta-analysis, we reassess the study quality and design characteristics of systematic review data relating to the efficacy of Interleukin-1 Receptor Antagonist (IL-1RA) in animals exposed to focal cerebral ischaemia (modelling human with stroke).
- The difference in the effects of IL-1RA compared to a control group exposed to vehicle or to no treatment in animal studies of focal cerebral ischaemia is the outcome of interest. The primary endpoint was infarct volume.

4. Results

Table 1: (a) Summary of the selected univariate meta regression results using each study characteristic variables as a moderator to explain the extra heterogeneity present in infarct volume data, (b) Parameter estimates from multivariable meta regression model, where * represents significant effect of a moderator. (FB noninformative priors: $\beta \sim N(0, 10^4)$, $\tau^2 \sim IG(0.001, 0.001)$ ran for 10000 iterations with 1000 burn-in period)

Method	Variable	Estimate (SE/MC Error)	95% CI	p-value	τ^2	I^2	R^2
REML	No covariate	35.5(2.35)	(30.8, 40.2)	<.0001	213.9	82.4%	-
	Time to Outcome Measure(Intercept)	37.7(2.75)	(32.3, 43.2)	<.0001	206.4	80.8%	3.50%
	Time to Outcome Measure	-0.03(0.02)	(-0.06, 0.01)	0.12			
	Route of Drug Del.(Intercept)	31.5(3.27)	(24.9, 38.0)	<.0001	120.1	69.6%	43.9 %
	Route of Drug Del.(ICerebVentricular)	20.3(5.54)	(9.25, 31.4)	0.001			
	Route of Drug Del. (Other)	-14.6(5.67)	(-26.0,-3.31)	0.01			
	Route of Drug Del.(Ivenous)	5.79(4.99)	(-4.19, 15.8)	0.25			
	Dose(Intercept)	38.0(2.91)	(32.2, 43.8)	<.0001	221.9	81.7 %	0 %
	Dose	-0.02(0.02)	(-0.05, 0.01)	0.17			
DL	No covariate	35.7(2.35)	(31.0, 40.4)	<.0001	235.2	83.7%	-
	Time to Outcome Measure(Intercept)	38.0(2.75)	(32.5, 43.5)	<.0001	253.3	83.8%	0%
	Time to Outcome Measure	-0.03(0.02)	(-0.06, 0.01)	0.13			
	Route of Drug Del.(Intercept)	32.4(3.31)	(25.8, 39.1)	<.0001	177.8	77.2%	24.4 %
	Route of Drug Del.(ICerebVentricular)	19.3(5.49)	(8.28, 30.3)	0.001			
	Route of Drug Del. (Other)	-15.5(5.99)	(-27.4,-3.50)	0.01			
	Route of Drug Del.(Ivenous)	4.48(5.02)	(-5.57, 14.5)	0.38			
	Dose(Intercept)	38.4(2.91)	(32.5, 44.2)	<.0001	263.5	84.2 %	0 %
	Dose	-0.02(0.02)	(-0.05, 0.01)	0.15			
Bayesian	No covariate	35.5(0.09)	(30.3, 40.7)	-	224.2	-	-
	Time to Outcome Measure(Intercept)	37.6 (0.05)	(31.7, 37.6)	-	215.2	-	-
	Time to Outcome Measure	-0.03 (0.0004)	(-0.07, 0.01)	-			
	Route of Drug Del.(Intercept)	31.5 (0.10)	(24.4, 39.3)	-	127.7	-	-
	Route of Drug Del.(ICerebVentricular)	20.2(0.15)	(7.78, 32.3)	-			
	Route of Drug Del. (Other)	-14.6 (0.12)	(-27.7, -1.99)	-			
	Route of Drug Del.(Ivenous)	5.85 (0.13)	(-5.50, 16.9)	-			
	Dose(Intercept)	37.9 (0.06)	(31.7, 44.7)	-	232.9	-	-
	Dose	-0.02 (0.0003)	(-0.05, 0.01)	-			

Method	Variable	Estimate (SE/MC Error)	95% CI
REML	β_1 (Intercept)	42.9 (5.53)*	(31.8, 54.0)
	β_2 (Blinded Induction of Ischemia:True)	-11.5(7.03)	(-25.5, 2.60)
	β_3 (Route of Delivery: Intracerebroventricular)	10.1(6.80)	(-3.55, 23.7)
	β_4 (Route of Delivery: Intravenous)	-2.85(6.10)	(-15.1, 9.37)
	β_5 (Route of Delivery: Other)	-24.4 (6.66)*	(-37.8, -11.1)
	β_6 (Time to Outcome Measure)	-0.03(0.02)	(-0.07,0.01)
	β_7 (Dose)	0.01 (0.02)	(-0.03, 0.05)
DL	β_1 (Intercept)	43.6 (5.47)*	(32.6, 54.5)
	β_2 (Blinded Induction of Ischemia:True)	-10.9(6.92)	(-24.7, 2.97)
	β_3 (Route of Delivery: Intracerebroventricular)	9.28(6.69)	(-4.12, 22.7)
	β_4 (Route of Delivery: Intravenous)	-3.71(6.04)	(-15.8, 8.39)
	β_5 (Route of Delivery: Other)	-24.7 (6.84)*	(-38.4, -11.0)
	β_6 (Time to Outcome Measure)	-0.03(0.02)	(-0.07,0.01)
	β_7 (Dose)	0.01 (0.02)	(-0.03, 0.04)
Bayesian	β_1 (Intercept)	39.0 (0.22)	(27.4, 50.2)
	β_2 (Blinded Induction of Ischemia:True)	-13.7(0.34)	(-31.1, 3.83)
	β_3 (Route of Delivery: Intracerebroventricular)	12.6(0.23)	(-1.67,27.2)
	β_4 (Route of Delivery: Intravenous)	0.05(0.22)	(-13.1, 12.9)
	β_5 (Route of Delivery: Other)	-20.9(0.21)	(-35.3, -6.25)
	β_6 (Time to Outcome Measure)	-0.003(0.001)	(-0.05,0.05)
	β_7 (Dose)	0.01 (0.001)	(-0.03, 0.06)

Three methods yielded similar estimates for overall treatment effect, but between study variabilities vary.

Proportion of heterogeneity explained by a variable is larger for REML and FB than for DL.

Substantial drop in heterogeneity using multiple meta regression (Table 1 (b)):

- τ^2_{REML}=109.3, I^2_{REML}=68.3%, R^2_{REML}=50.2%
- τ^2_{DL}=168.5, I^2_{DL}=76.9%, R^2_{DL}=28.8%
- τ^2_{FB}=123.6

5. Conclusions

1. DL gives higher τ^2 than REML and FB; it is negatively biased when there is high heterogeneity due to false assumption that within study variabilities are known.
2. REML reduces bias by excluding the summary effect parameter in τ^2 estimation but due to its iterative process, convergence is not guaranteed.
3. Bayesian approach accounts for uncertainty in estimation and does not assume that within study variances are known akin to DL and REML.
4. Multivariable meta-regression explains more heterogeneity between studies and leads to more generalisable results than simple random effects meta-analysis or univariate meta-regression.

6. Acknowledgements

This project is supported by IMI2 European Quality in Preclinical Data (EQIPD) under grant agreement No 777364 (**https://quality-preclinical-data.eu/**). This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. This poster reflects only the authors' views neither IMI JU nor EFPIA nor the European Commission are liable for any use of the information contained therein.