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EVIDENCE SYNTHESIS FOR HEALTH TECHNOLOGY ASSESSMENT WITH LIMITED STUDIES

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Background

Meta-analyses using fixed effect and random effects models are used to synthesise evidence from randomised controlled trials in health technology assessment. Fixed effect models are often used because there are too few studies with which to estimate the between-study standard deviation from the data alone. When heterogeneity is expected and inferences are required beyond the sample of studies an analysis using a fixed effect model will underestimate uncertainty.

Aim

To elicit a prior distribution for the between-study standard deviation (SD) in a random effects meta-analysis and to compare the impact on results using alternative approaches.

Methods

We developed an elicitation method using external information and experts' beliefs on the 'range' of treatment effects in order to infer the prior distribution for the between-study SD τ, where the 'range' is the ratio of largest to the smallest treatment effect in a population of treatment effects. We also developed the method to be implemented in R using the `SHELF` package.

Feedback

We propose providing feedback to the expert about the implied distribution of τ, where

- P_L is P(τ<0.1), L for 'low' heterogeneity
- P_M is P(0.1<τ<0.5), M for 'moderate'
- P_H is P(0.5<τ<1), H for 'high'
- P_{EH} is P(τ>1), EH for 'extreme high'

General elicitation framework

Stage 1: confirmation of the need for a random effects model	"Can you be certain that the treatment effects across the studies will be identical, ignoring within-study sampling variability?"
Stage 2: consideration of an upper bound for R	"Let R be the ratio of the largest to the smallest OR. Are you able to judge a maximum plausible value for R? Denoting this limit by R_{max}, this means that you would think values of R above R_{max} are too implausible to be contemplated."
Stage 3: consideration of a full distribution for R Turner RM, et al. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. Int J Epidemiol. 2012;41(3):818–27.	" Can you judges some values in the range $[1, R_{max}]$ to be more likely than others?" • If she is not able to make such judgements, then we propose using external information such as the prior distributions proposed by Turner et al (2012) , but now truncated to $\left[0, \left(\frac{\log(R_{max})}{3.92}\right)^2\right]$. • If she is able to make such judgements, then use standard elicitation approach such as the roulette method.

Example

Re-analyse the data from NICE TA163 of infliximab for treating acute exacerbations in adults with severely active ulcerative colitis. Data were available from 4 studies of 3 treatments (placebo, infliximab and ciclosporin) and two studies to inform each treatment comparison.

Table 1: Comparison of results obtained from fixed effect and random effects models with the prior distribution for heterogeneity as uniform[0,5], lognormal proposed by Turner et al (2012), truncated Turner prior and a elicited prior. Results in bold are from the predictive distributions.

TA163: Colectomy rate at 3 months treatment effect on log OR scale	OR, median (95% CrI) ciclosporin vs. placebo	OR , median (95% CrI) infliximab vs. placebo	P_L	P_M	P_H	P_{EH}	Conclusions
Fixed effect	0.13 (0.03, 0.44)	0.72 (0.18, 2.70)	0	0	0	0	
Random effects with $\tau_{OR} \sim uniform\,[0,5]$	0.02 (0, 1.46) **0.03 (0, 33.02)**	0.70 (0.01, 84.59) **0.69 (0, 2498.82)**	0.01	0.05	0.07	0.87	Implausible wide CrI
Random effects with $\tau^2_{OR} \sim \log normal\,(0.256, 1.74^2)$	0.11 (0.01, 0.48) **0.12 (0.01, 0.62)**	0.71 (0.14, 3.25) **0.71 (0.10, 4.83)**	0.11	0.62	0.18	0.08	8%l extreme heterogeneity
Random effects with $\tau^2_{OR} \sim$ truncated $\log normal\,(0.256, 1.74^2)$ $I(0, 0.345)$	0.12 (0.03, 0.48) **0.12 (0.03, 0.54)**	0.69 (0.17, 2.77) **0.69 (0.15, 3.14)**	0.15	0.78	0.07	0	Eliminated the possibility of extreme heterogeneity
Random effects with $(R_{OR} - 1) \sim gamma(2.62, 0.721)$ and $\tau_{OR} = \log(R_{OR} + 1)\,/3.92$	0.12 (0.03, 0.47) **0.12 (0.02, 0.56)**	0.71 (0.17, 2.97) **0.71 (0.14, 3.69)**	0.01	0.85	0.14	0	Eliminated the possibility of extreme heterogeneity

Discussion

The choice between using a fixed effect or random effects meta-analysis model depends on the inferences required and not on the number of available studies. Our elicitation framework captures external evidence about heterogeneity and overcomes the often implausible assumption that studies are estimating the same treatment effect, thereby improving the quality of inferences in decision making.

The three-stage procedure could be used for any scale-free outcome measure such as a hazard ratio or relative risk. When the outcome measure is continuous or ordinal a modified version of the procedure can be used. A pre-print version of the manuscript is available.

Publication: A manuscript "Incorporating genuine prior information about between-study heterogeneity in random effects pairwise and network meta-analyses" is in submission. The pre-print can be downloaded from https://arxiv.org/abs/1708.01193

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