Trial design and Value of Information based on a meta-analysis

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Summary

- Part 1 (Hayley) –

  Trial design & analysis based on a meta-analysis

- Part 2 (Jason) –

  Implications for cost effectiveness analysis and Value of Information

Background

- Funders often require a systematic review as part of an application.
- Spiegelhalter *et al* (1994) encouraged formal incorporation of external evidence in trial design and analysis, using a Bayesian framework.
- But how should we use the MA in study design?
- And how should we interpret new results in the context of a previous MA?

Meta-analysis models

- Fixed effect: $\theta_i = \theta$ in all studies

  Use mean & se for θ from this MA as basis of prior distribution for new trial.

- Random effects: $\theta_i \sim \text{Normal}(\mu, \tau^2)$

  The causes of heterogeneity, and the target of inference in the new trial, require careful consideration.

Inference based on RE mean

- Sutton *et al* (1995): *Sometimes* results of updated MA will be of more interest than results of new trial alone.

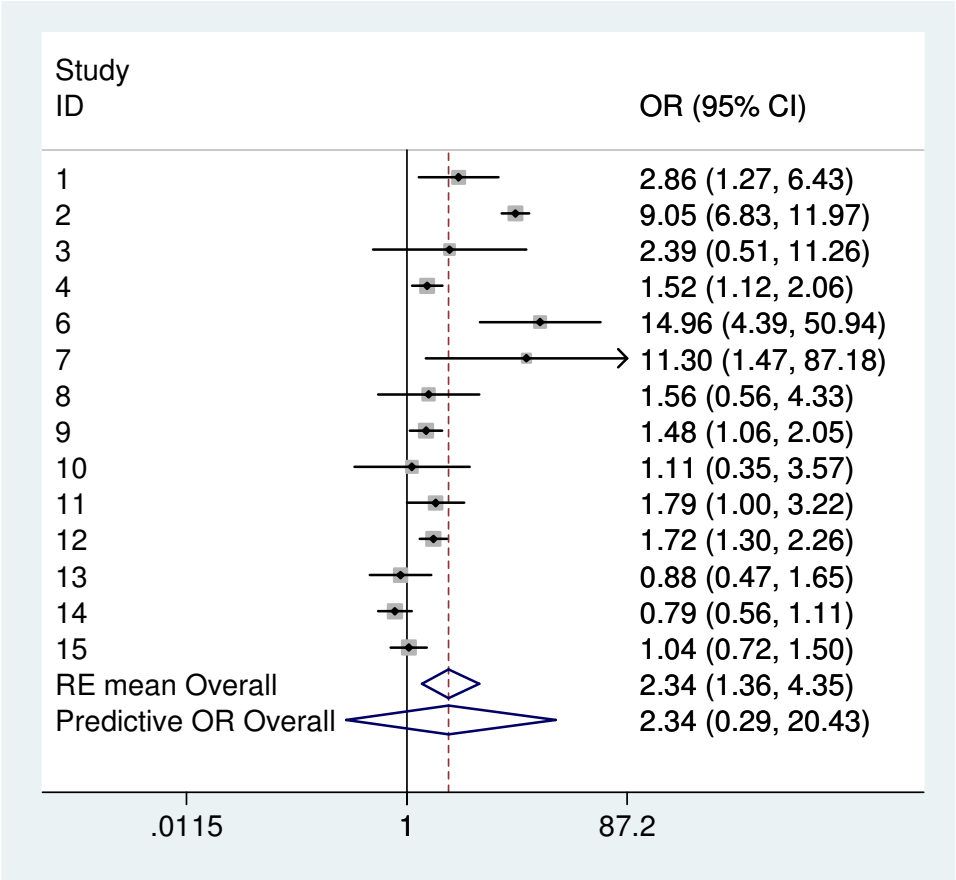
→ Base sample size calculations for new RCT on ability to affect inference about RE mean.

- But, if considerable heterogeneity:
  - Even very large study may have little power
  - Multiple smaller studies may be more powerful than one larger study

Target of inference

- The updated RE mean may be of some interest in certain situations.
- But great care is taken over trial design: seems unlikely a trial designer would ever plan just to contribute another point to the RE distribution.
- We consider a few alternative scenarios using an example.

Example: Smoking cessation



Individual counselling vs self support (15 trials)

Data from Hasselblad *et al,* 1998

Between trials sd = 0.94 (0.59, 1.62)

3 types of variation

Assuming we have failed to explain heterogeneity using meta-regression etc... we suggest there are broadly 3 possible types of variation:

1) True variation

2) Fixed effect + bias with random noise

3) Distribution of effects

(1) True variation

- Variation may be real, e.g. due to different participant populations / different protocols.
- But the setting / conditions of interest to us are the ones *in our new trial.*
- Inference should be based on a FE model for treatment effect in new trial.
- Use predictive distribution from previous MA as prior.

(2) FE + bias with random noise

Variation may alternatively be due to problems with internal validity. In reality there is a single FE.

(a)Assume biases random with mean 0: base prior for true FE in new trial on RE mean

(b)Or, if have markers of risk of bias, possible to perform bias-adjusted MA and base prior on this (Welton *et al*, 2009; Turner *et al*, 2009).

If new trial has marker of risk, incorporate this.

(3) Distribution of effects

- Or there may be a real distribution of treatment effects, due to random deviations from protocol / varying (unknown) staff skill levels
- E.g. effectiveness might vary by counsellor
- Arguably, target of inference is then the whole distribution of treatment effects
- Updated MA is therefore of interest

A new large trial

Say a new trial produced OR = 1.00 (0.87, 1.15). How should we interpret this in the context of the previous evidence?

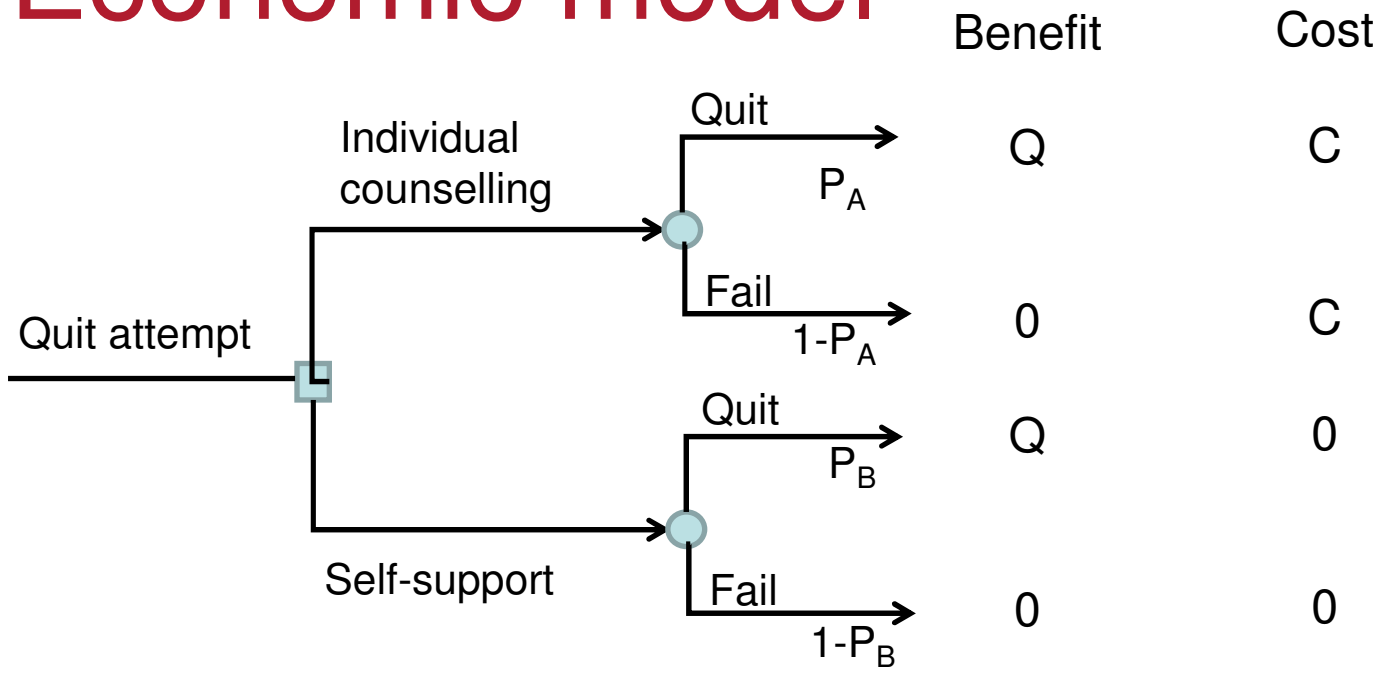
	Prior OR from MA	Posterior OR
(1) True variation	2.34 (0.29, 20.42)	1.00 (0.87, 1.16)
(2) FE + random bias (no bias adjustment)	2.34 (1.36, 4.35)	1.05 (0.92, 1.21)

Or in scenario (3) update the MA:
OR = 2.19 (1.31, 3.91), sd = 0.92 (0.59, 1.55)

Meta-analysis in a policy context

- HTA organisations (e.g. NICE) assess costs v benefits of new treatments:
  - Adopt A if net benefit (NB) of A vs B > 0.
  - NB is a measure that combines outcomes and costs.
- NB estimates require a cost-effectiveness model
  - Meta-analysis informs treatment effects in the model
  - Model translates uncertainty in efficacy into uncertainty in NB
- Uncertainty in NB implies current decision may be wrong
- Value of information (VoI) analysis of a study considers:
  - Chance decision will change after study
  - Benefit from doing so

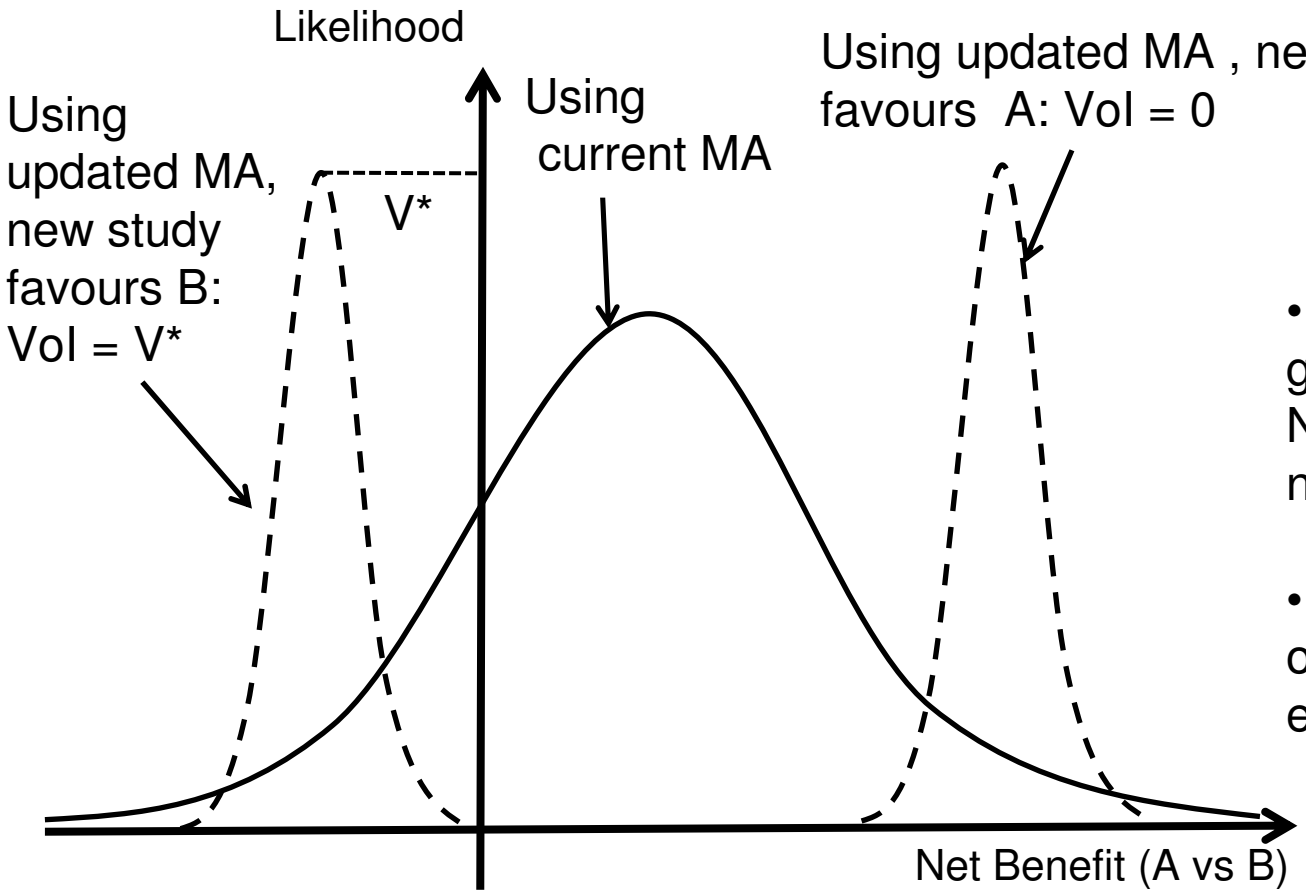
Smoking Cessation Economic model



$$NB_A - NB_B = (P_C - P_S) \cdot Q \cdot W - C$$

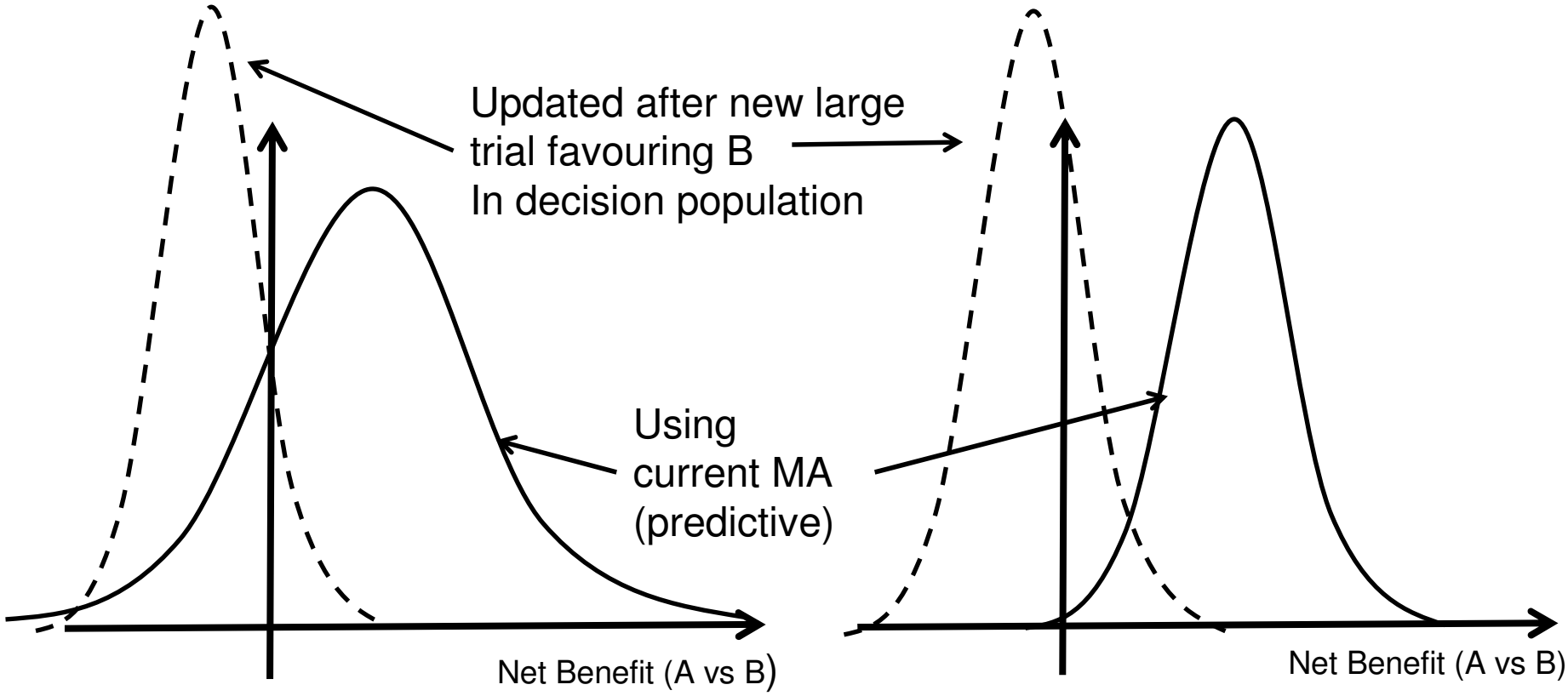
W= Willingness to Pay for intervention leading to gain of 1 QALY

Predicting the VoI of an additional study



- MA of existing studies gives prior uncertainty in NB and predictions for new study
- Need to consider source of variation between existing studies

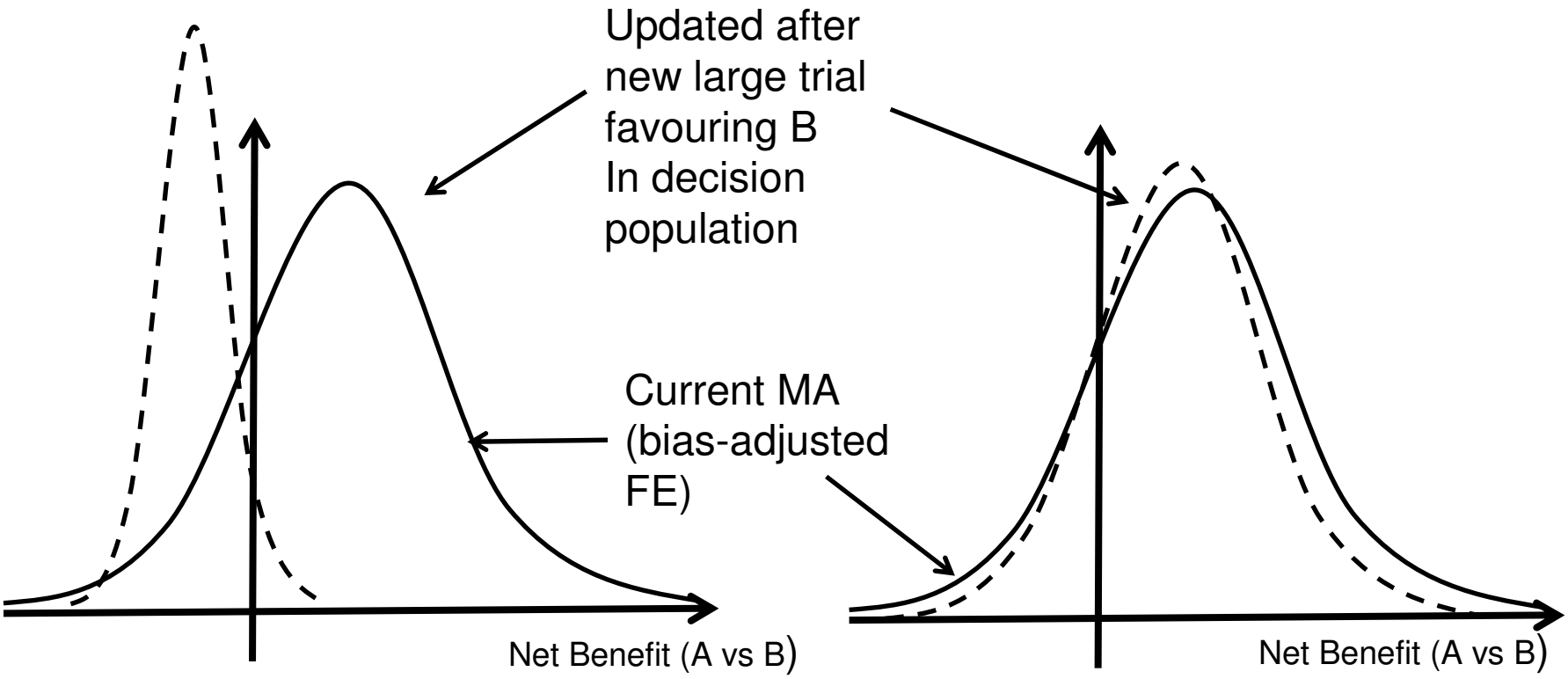
Type 1: True variation



High heterogeneity

Low heterogeneity

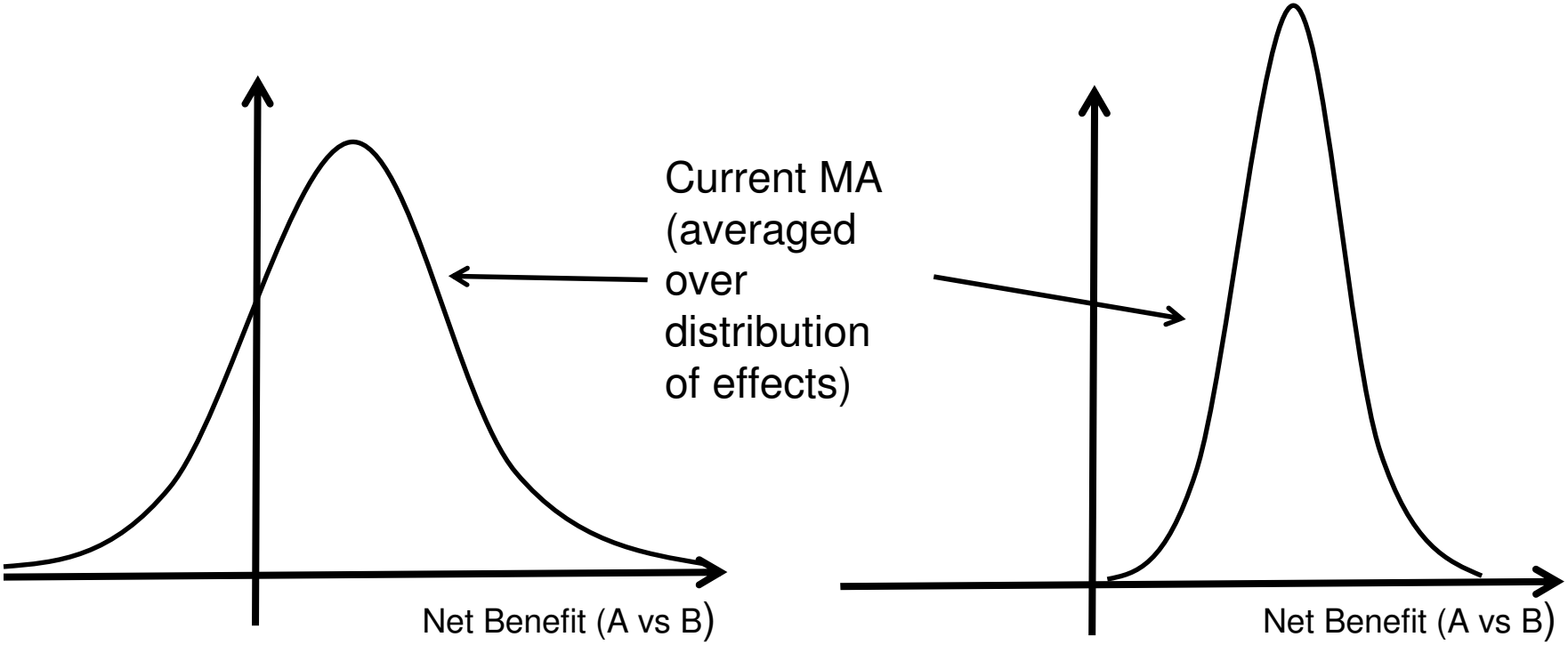
Type 2: Bias



New bias-free trial

New trial with unavoidable bias

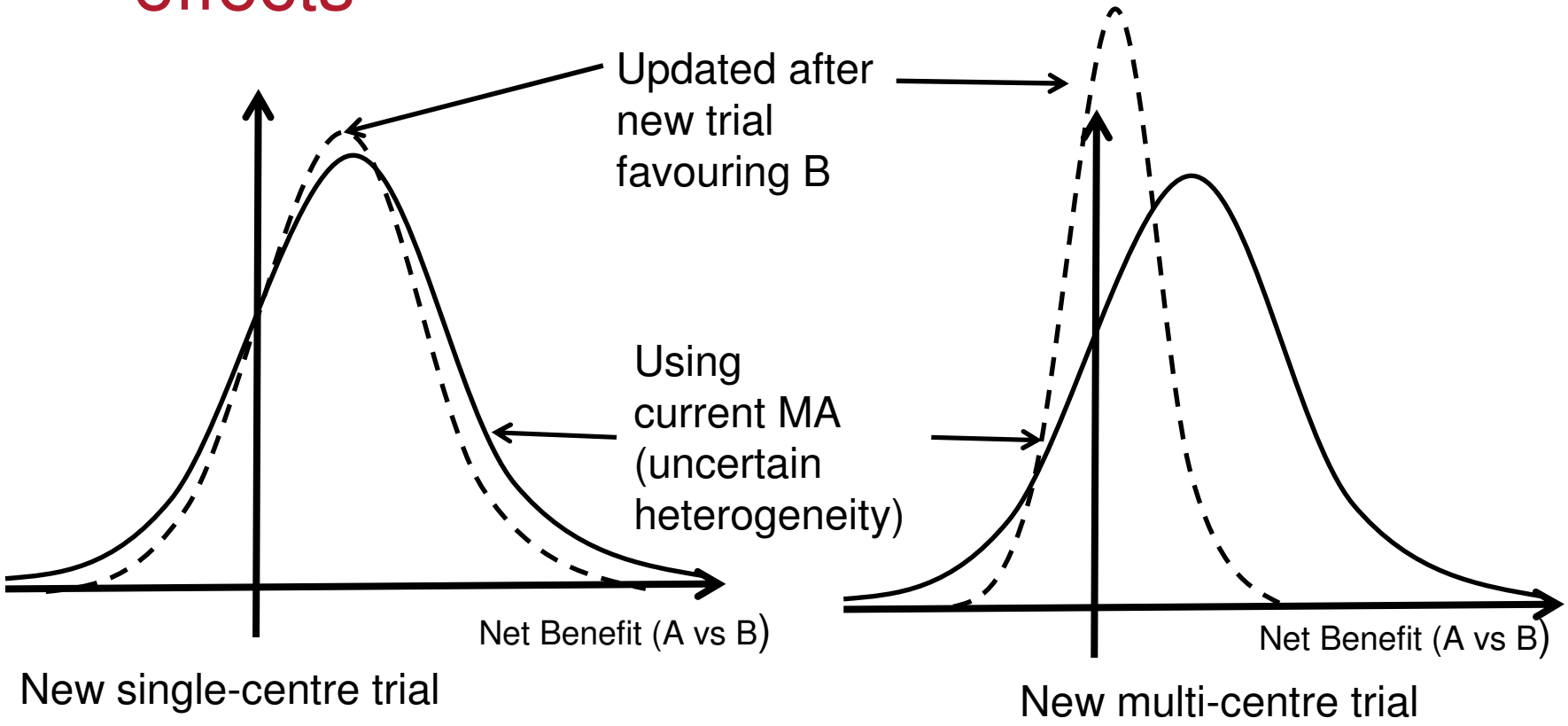
Type 3: Distribution of effects



Uncertainty in heterogeneity: high

Uncertainty in heterogeneity: low

Impact of new study given distribution of effects



Conclusions

- To evaluate the benefit of a proposed study, need to consider:
  - Target of inference
  - Source(s) of variation in current evidence base.
- VoI helps design and prioritise trials to maximise their value to a decision-maker
- Uncertainty around mean of random-effects distribution unlikely to coincide with uncertainty around treatment-effects for decision-making.

References

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