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THE ROLE OF META-ANALYSIS IN DESIGNING NEW STUDIES

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CONTEXT

- Systematic review & meta-analysis is widely acknowledged for identifying gaps in the evidence base & providing a quantitative basis for informing new research initiatives.

- Little formal methodology developed on how to use previous evidence when designing a new study.

SAMPLE SIZE FOR META-ANALYSIS

- Will the updated systematic review/meta-analysis be of more interest than the new individual study results?

- Lead to development of simulation framework for sample size calculation for future RCTs based on the results of M-A of existing evidence
  - Power based on the updated meta-analysis

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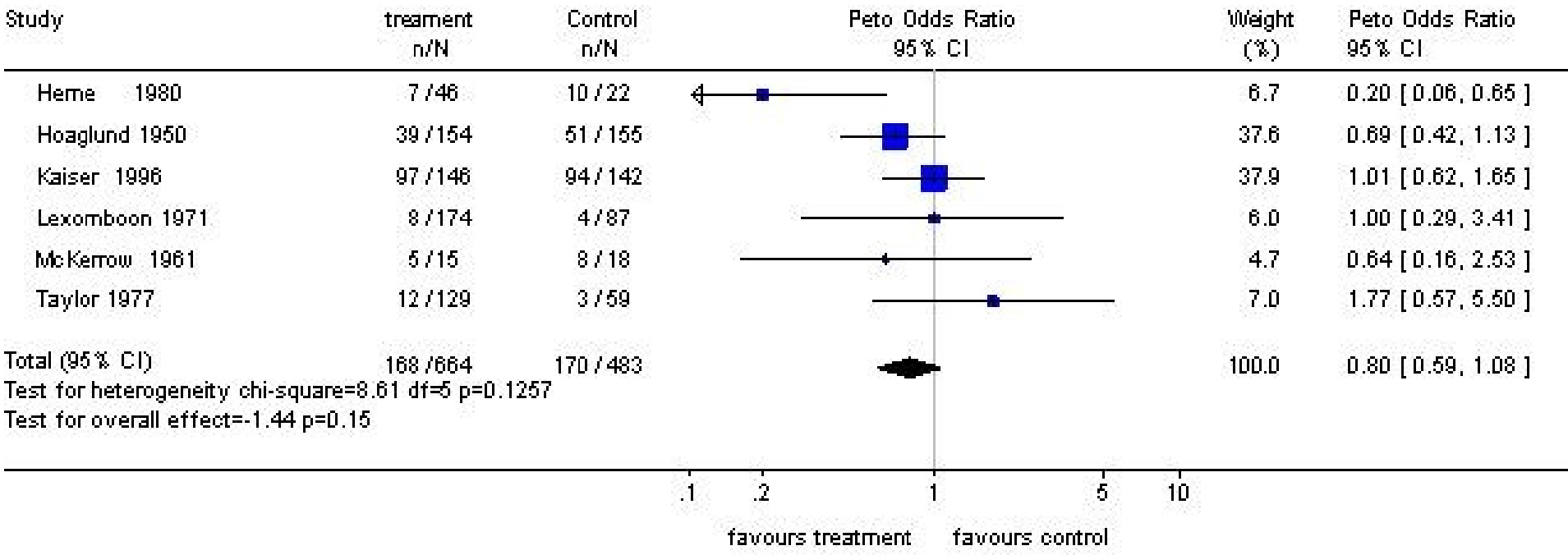
EXAMPLE

From Cochrane Review Antibiotics for Common Cold: Persisting Symptoms 1-7 Days

Review: Antibiotics for the common cold
Comparison: 01 Antibiotic Vs Placebo
Outcome: 01 Persisting symptoms 1 to 7 days



POWER BY SIMULATION

1. A distribution for the effect size expected to be seen in the new study is derived from the M-A of existing evidence. A starting sample size is specified indicating the initial size of the new study considered. Data relating to a new study is generated stochastically.
2. The simulated study is then included in the meta-analysis and a rule used to establish whether the result is "decisive"
3. Steps 1 and 2 are repeated a large (*N*) number of times recording whether the result is "decisive or not"
4. Power is estimated by calculating what proportion of the *N* simulations are deemed to give "decisive" results
5. Procedure is iterative using different sample sizes until the desired level of power is achieved.

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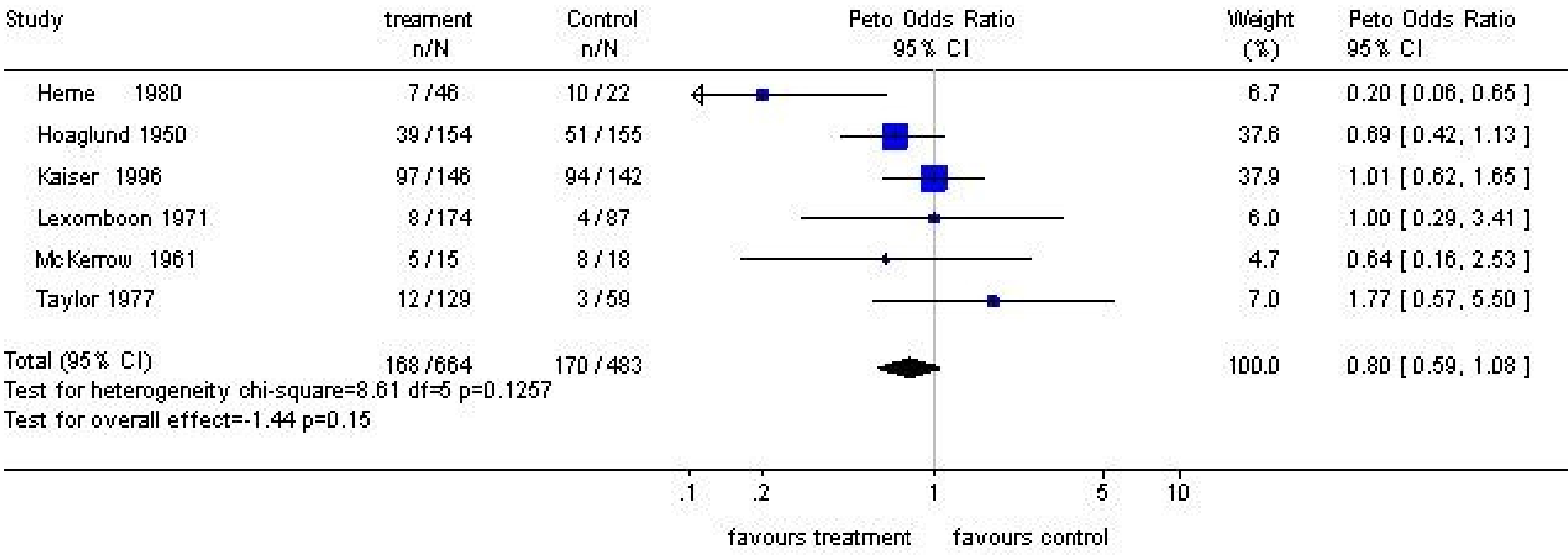
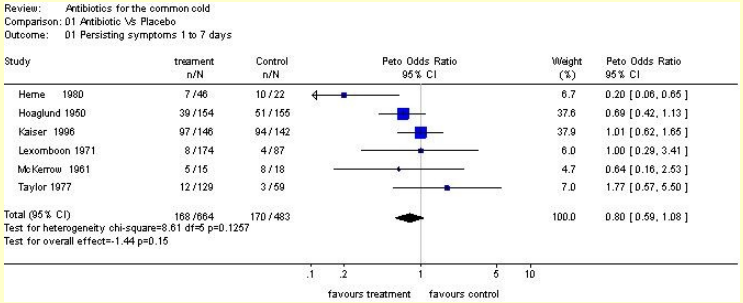


EXAMPLE (Continued)

- **Scenario:** 2 arm RCT with equal patient allocation and binary outcome analysed on odds ratio scale & fixed effect meta-analysis model
- Assume effect seen in a new study is estimated from pooled meta-analysis result (with uncertainty)
- Assume that the control group event rate in the new study is known
- Estimate the event rate in the treatment group
  - Derived directly from effect size (odds ratio) and control group event rate
- Simulate data for a new trial
  - Fix sample size and estimate the number of events in each group based on treatment and control group event rates (estimated above)
- Follow procedure outlined previously: add study to meta-analysis; analyse; assess whether result is decisive; repeat many times; calculate power as proportion of decisive simulations

WORKED EXAMPLE

1) Meta-analysis of current evidence



Pooled OR = 0.80 (0.59 to 1.08)

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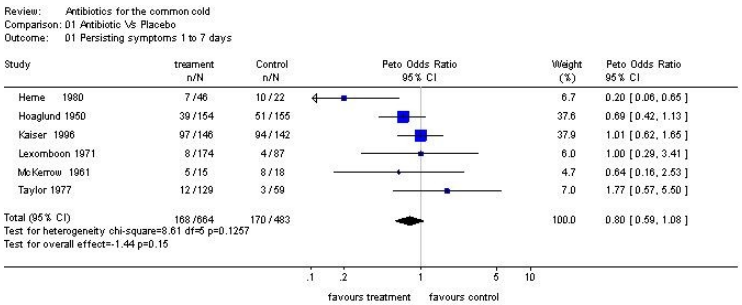

Pooled OR = 0.80 (0.59 to 1.08)

2) Simulate a new study:

ln(OR.new) ~ N(-0.22, 0.024)

= *-0.15*

Set *pc.new* = 0.20 &

derive *pt.new* = *0.18*

events.c.new ~ Bin(0.20, 200) = *38*

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Subjects in each group

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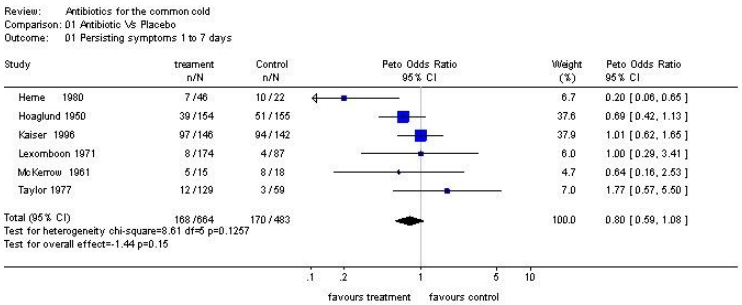

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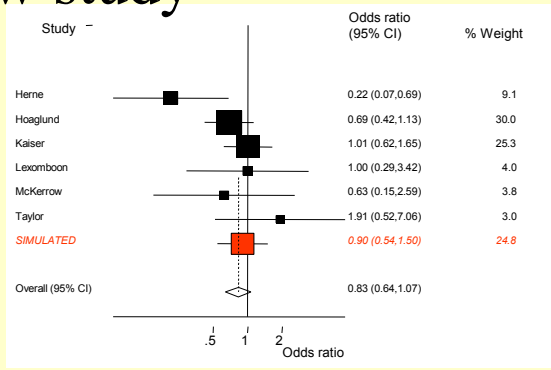

Test treatment effect: *p* = *0.15*

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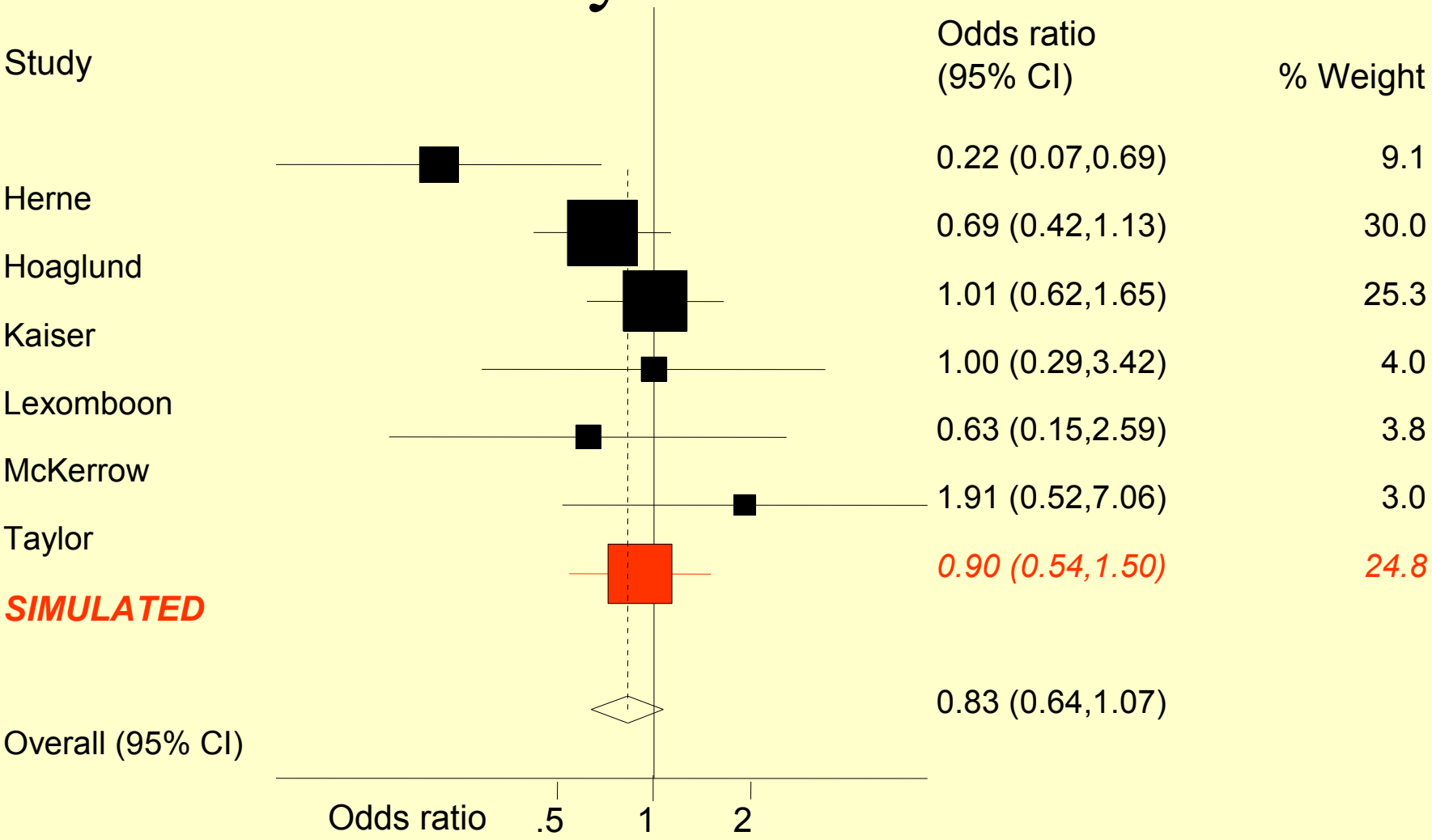

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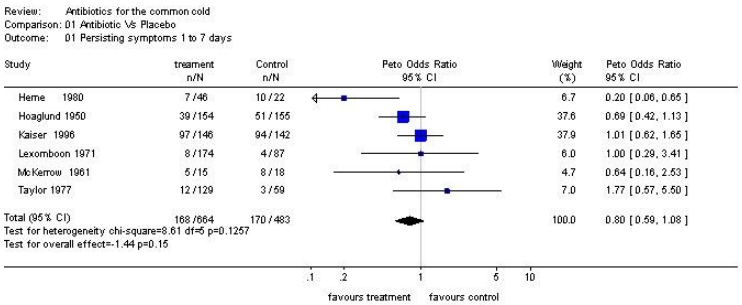

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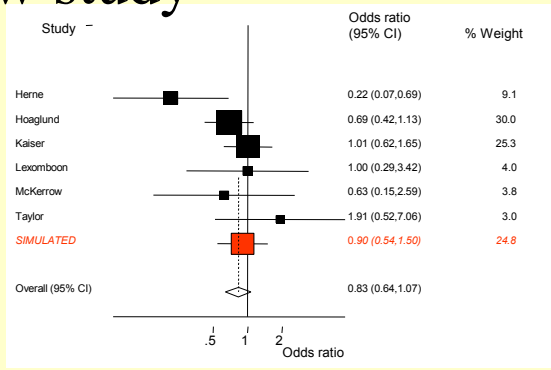

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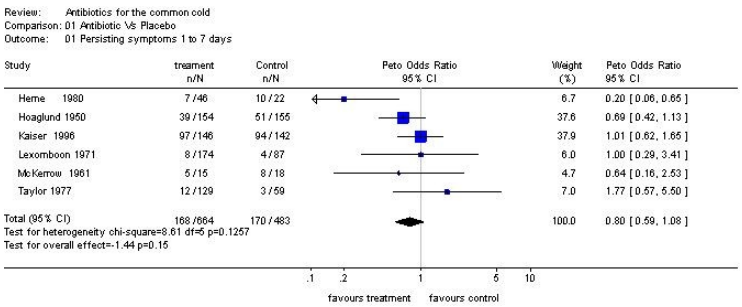

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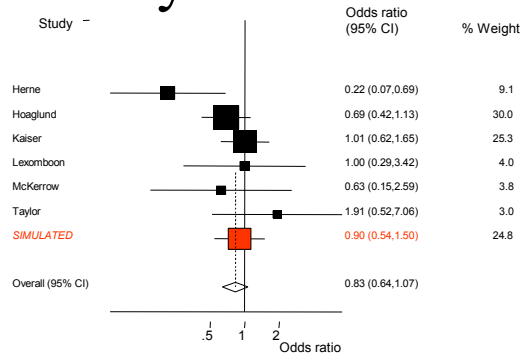

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4) Steps 2 & 3 repeated a large number of times (1000).

Power is calculated as proportion of "sig" p-values.

= *304/1000* = *30.4%* power

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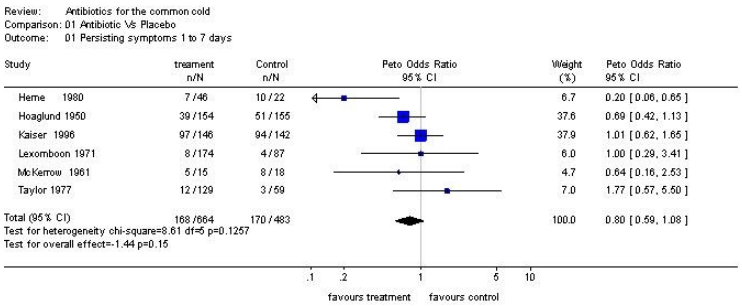

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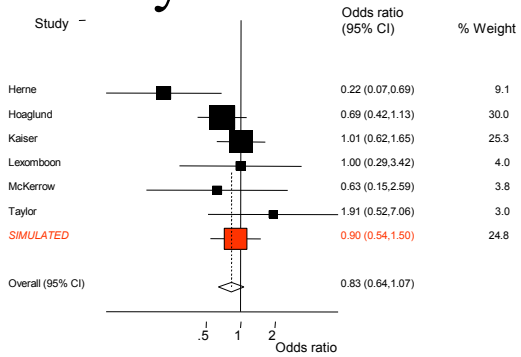

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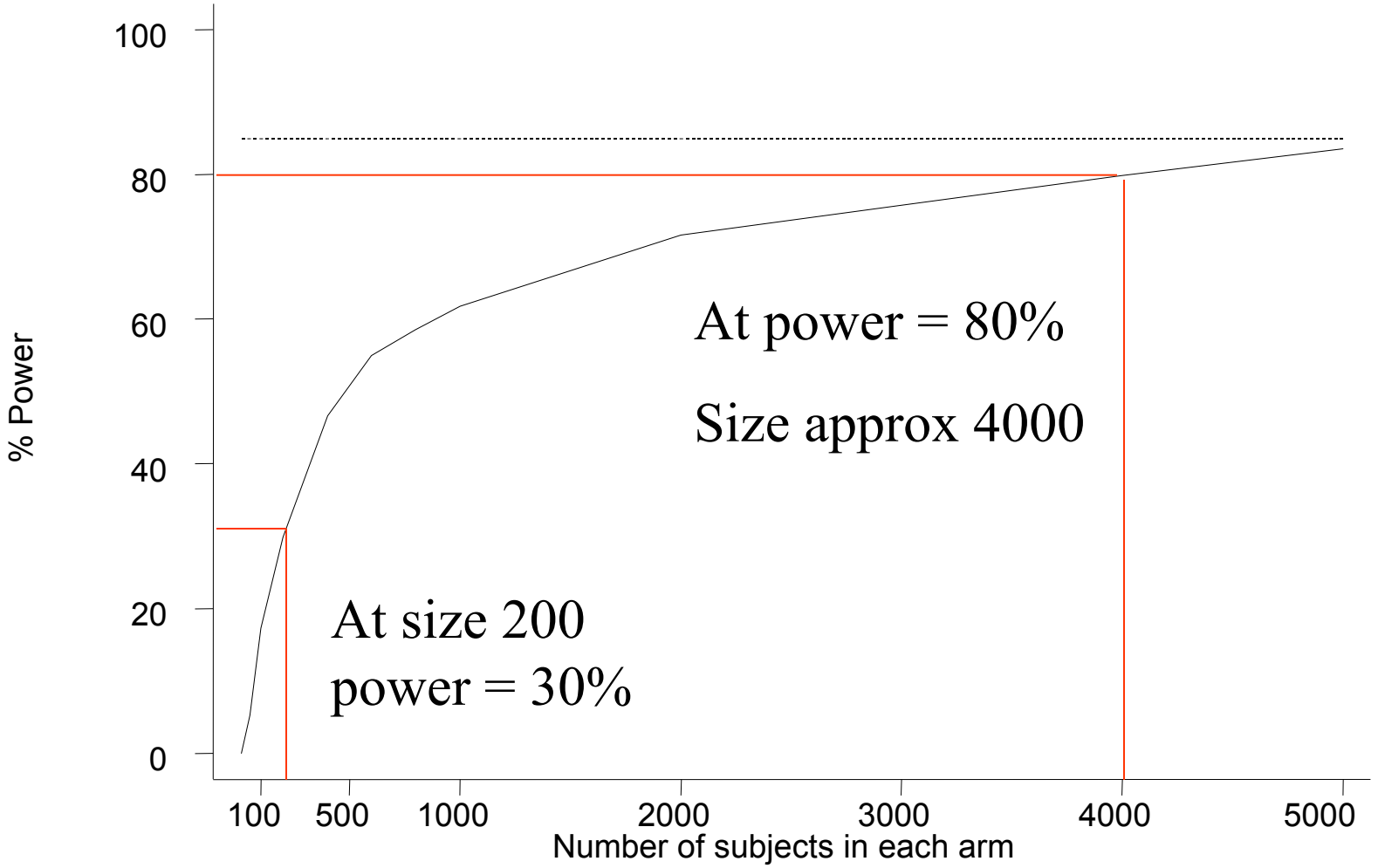
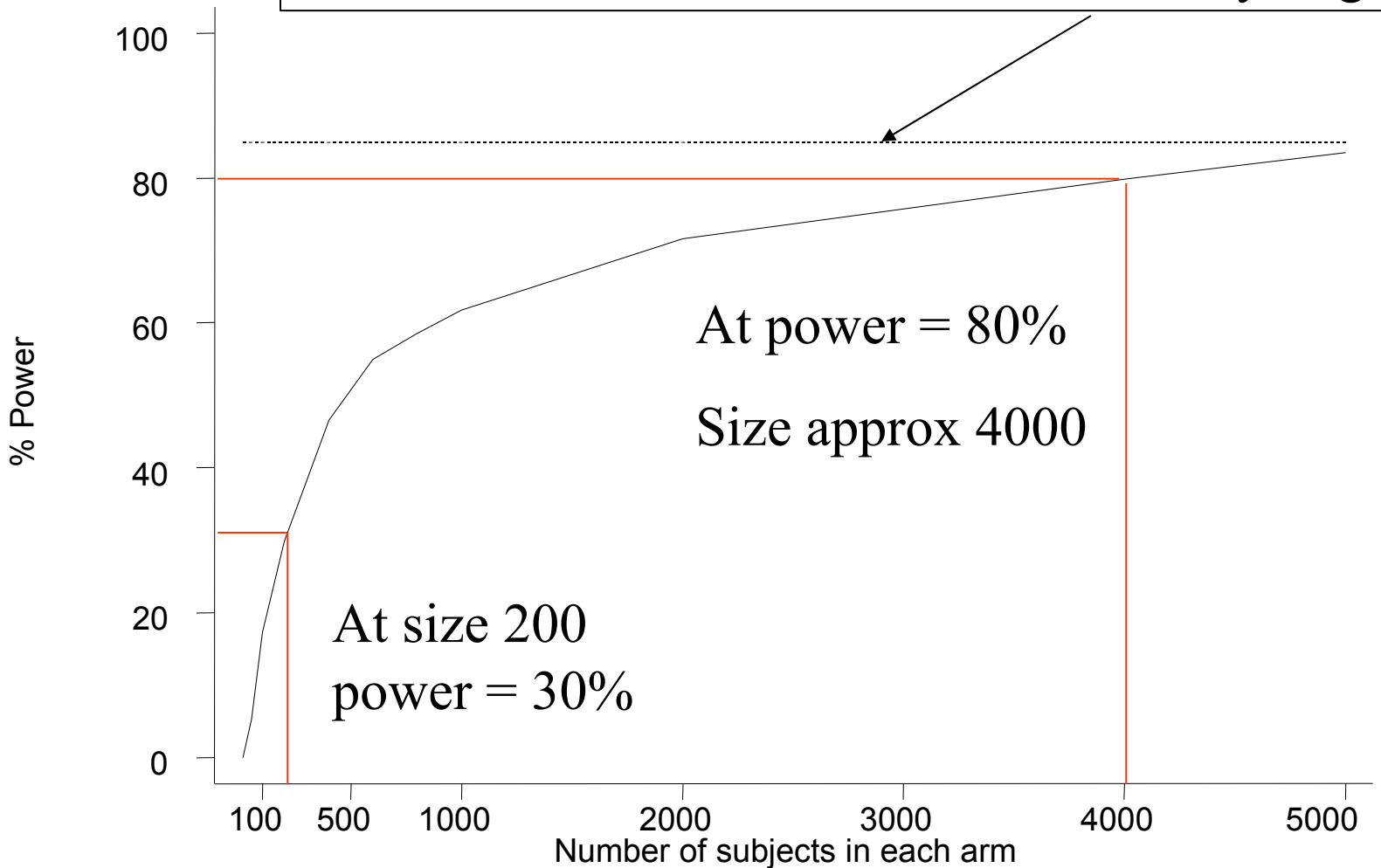
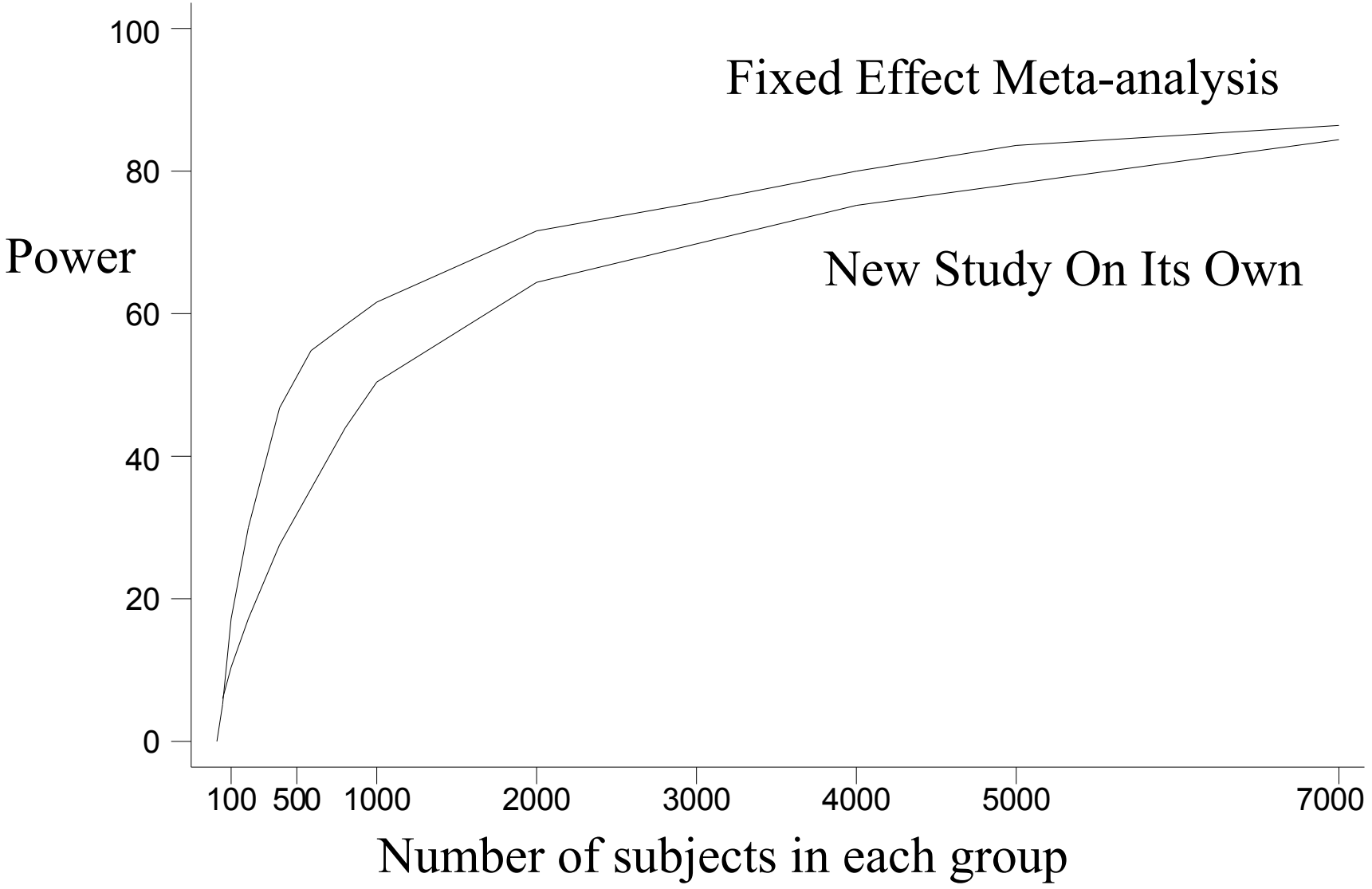


POWER CURVE: FIXED EFFECT MA

P-value for original meta-analysis = 0.15, therefore for power to go beyond 85% need to get "sig" treatment effects in the harmful direction – need very large numbers!



POWER OF TRIAL v META-ANALYSIS



RANDOM EFFECTS APPROACH

- Although same approach as fixed effect – heterogeneity does make things more complicated.
- Need to specify and sample from predictive distribution for a new study
  - Should take into account uncertainty in estimation of the between study variance
  - Can be done using Bayesian methods in WinBUGS software
- Producing a wider distribution of effect sizes to sample from than fixed effect
- Proceed as before but using random effect meta-analysis model in the simulations

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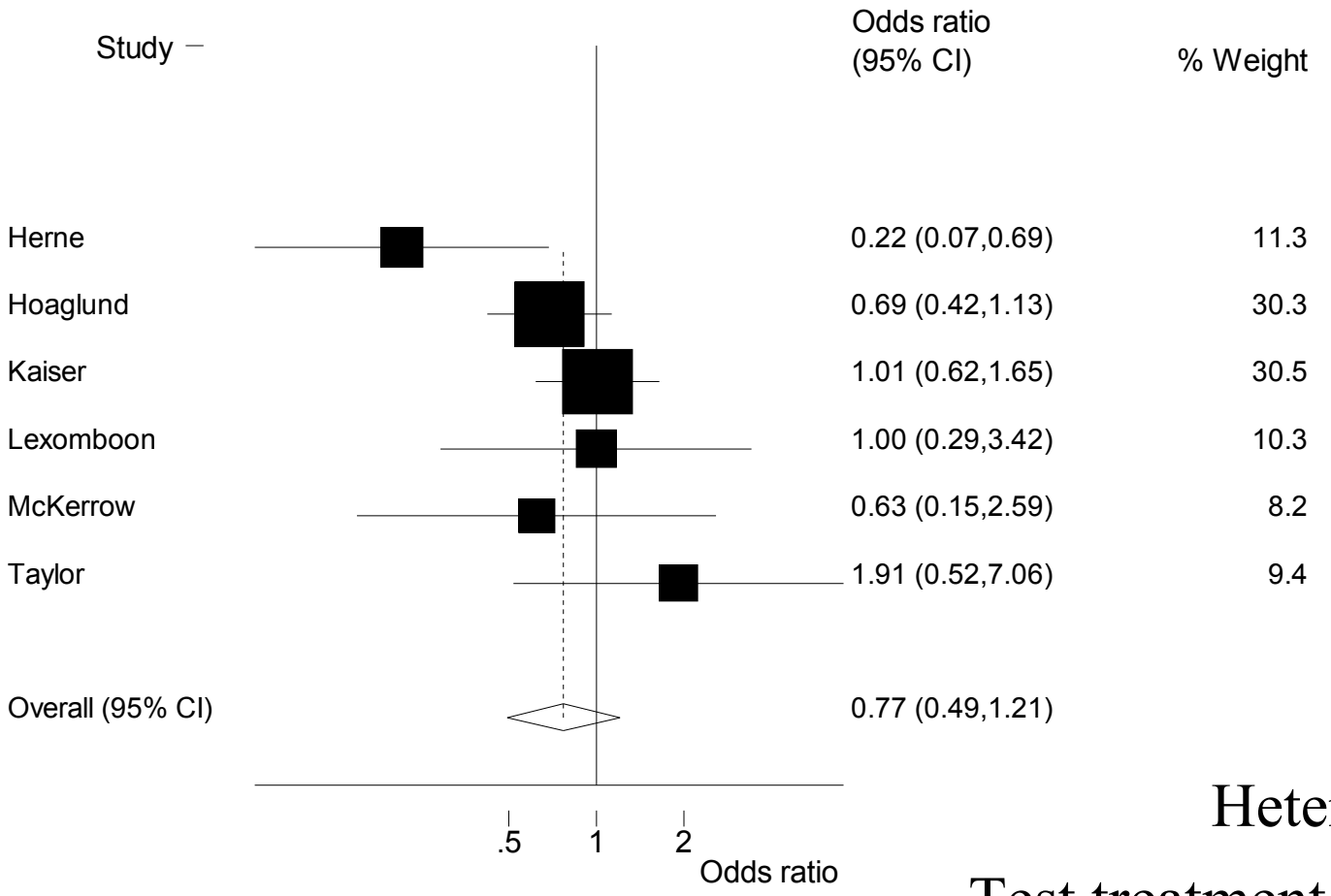
EXAMPLE

Random Effects: Antibiotics for Common Cold



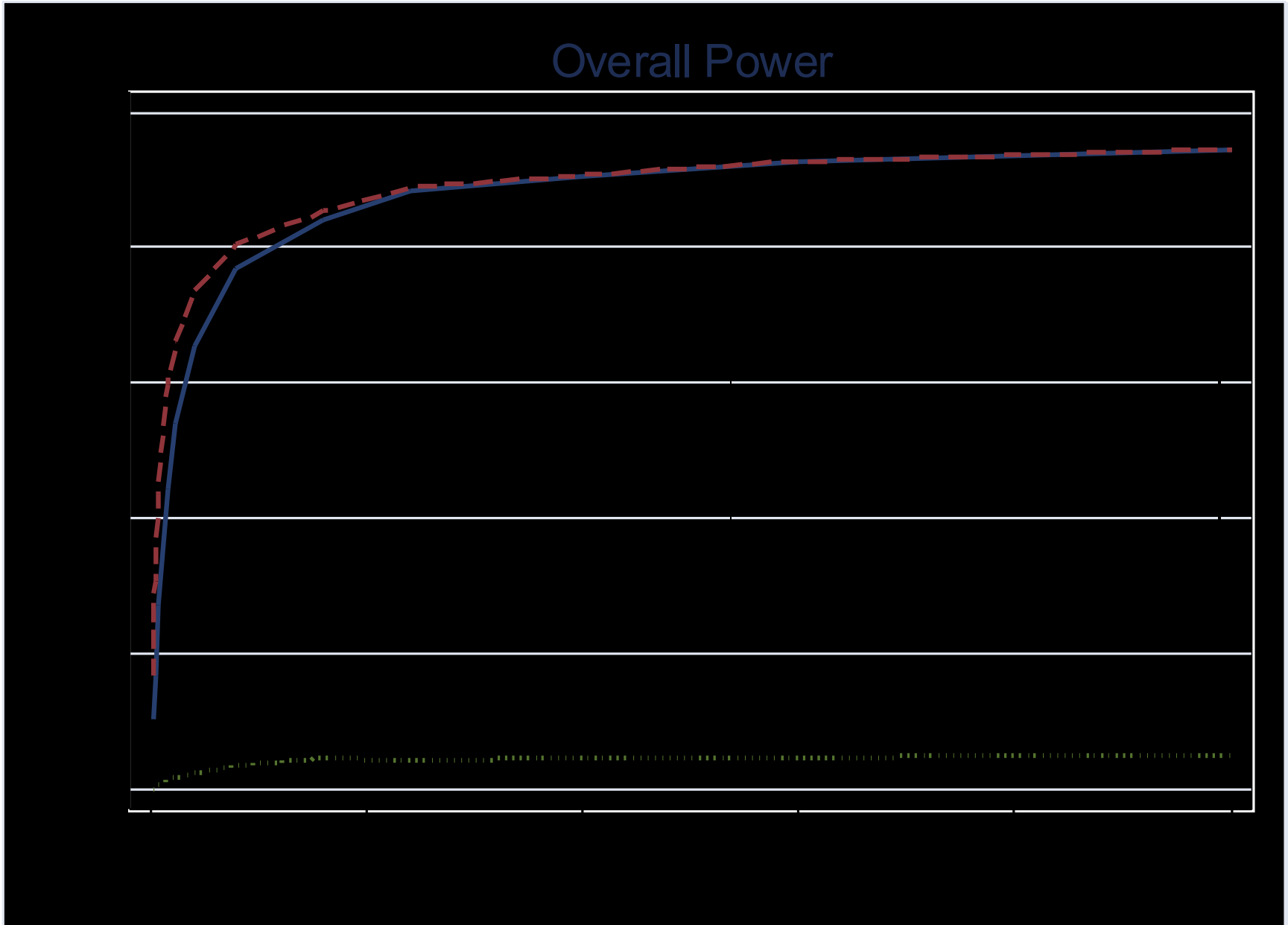
$\tau^2 = 0.11$

Hetero test: $p = 0.15$

Test treatment effect: $p = 0.26$

Predictive effect in new study: 0.77 (95% CI 0.25 to 2.34)

POWER CURVES FOR NEW STUDY



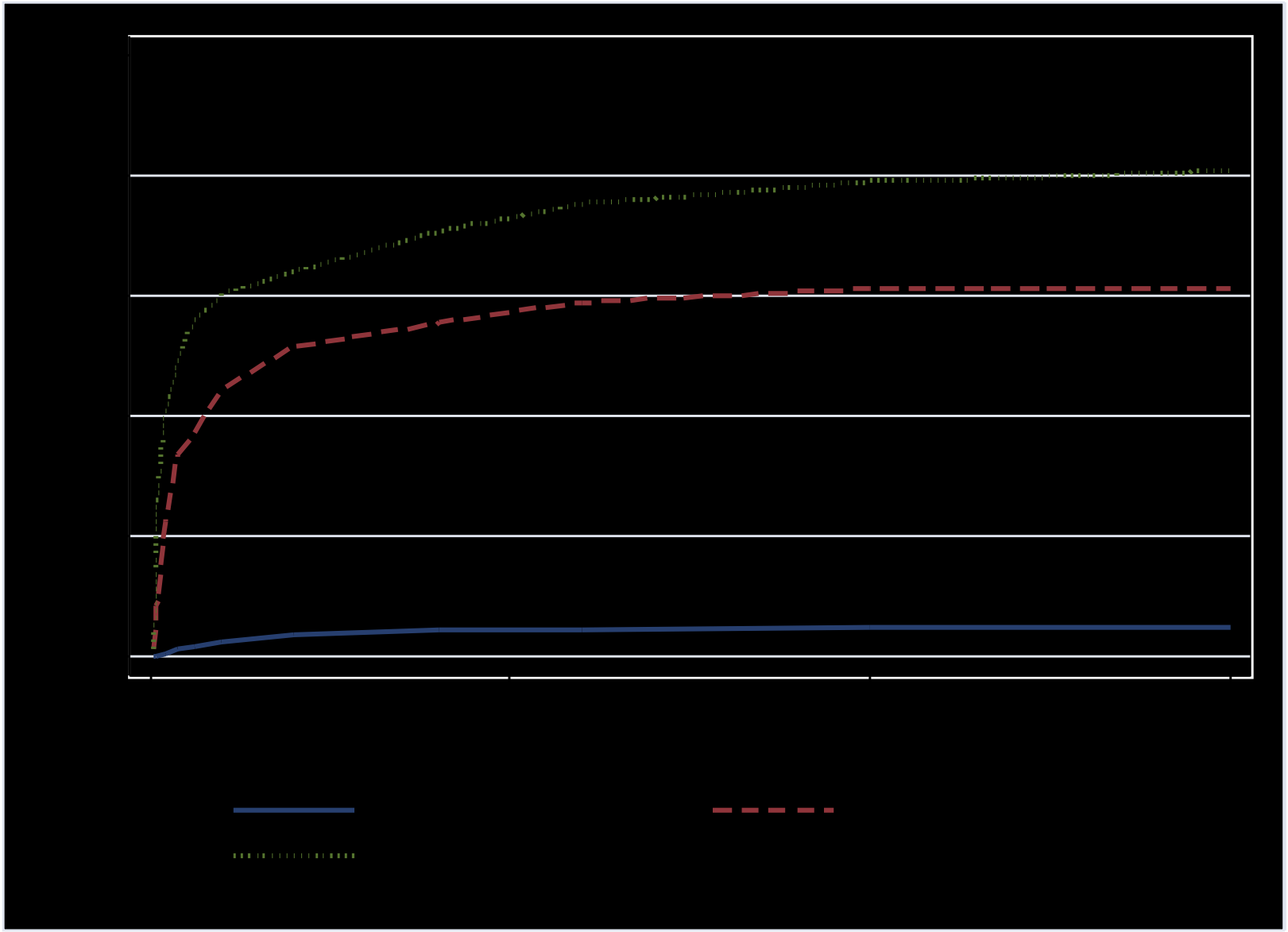
IMPACT OF RANDOM EFFECTS MODEL

- Weighting in random effect model = $1/(\text{var.ln.or} + \tau^2)$
- Therefore even for a huge study with essentially 0 variance – maximum weighting is $1/\tau^2$
- Therefore power of 100% may be impossible to reach with addition of only one study if heterogeneity is large.

IS ONE LARGE STUDY OPTIMAL?

- Fixed effect model:
  - Makes little difference whether one large or multiple smaller studies (adding up to the same number of patients randomised) are carried out.
- Random effect model:
  - Since each study contributes information to both the pooled estimate and the between study variance parameter there are gains for carrying out multiple smaller studies.
  - Issue over whether multiple studies done by same investigators can be considered sampled from the population of theoretical studies.
  - Goes against the notion of big well powered individual studies!

POWER CURVES FOR THE COMBINED EFFECT OF MULTIPLE NEW STUDIES



HAVE THE METHODS A ROLE IN PRIORITISING UPDATING OF COCHRANE REVIEWS?

- Although Cochrane *should* be able to influence design/prioritisation of future trials – may not always be possible
- Methods could still be used as a guide as to when 'sufficient' new evidence would make updating a review worthwhile
- Ultimately could be programmed into Rev Manager?

THE HEART OF THE MATTER

Assumes the existing meta-analysis is the best description of current knowledge.

Specification of random effects distribution is critical

Is there inconsistency if you are willing to analyse but not design using the same statistical model?

"Any sample size calculation is either arbitrary or infinite"

Karl Claxton, San Francisco, June 2003

A DECISIVE RESULT REVISITED

- Possible options are
  1. Conventional: statistical significance of the pooled treatment effect – say 5% level
  2. Variance minimisation: reduce the variance of the pooled treatment effect to a specified level (irrespective of statistical significance)
  3. Limits of equivalence (minimal clinical worthwhile benefit): decisive when pooled treatment effect and (95%) confidence interval lie completely within, or outside, pre-specified limits of equivalence within which the two interventions are considered, for practical purposes, to be equivalent.

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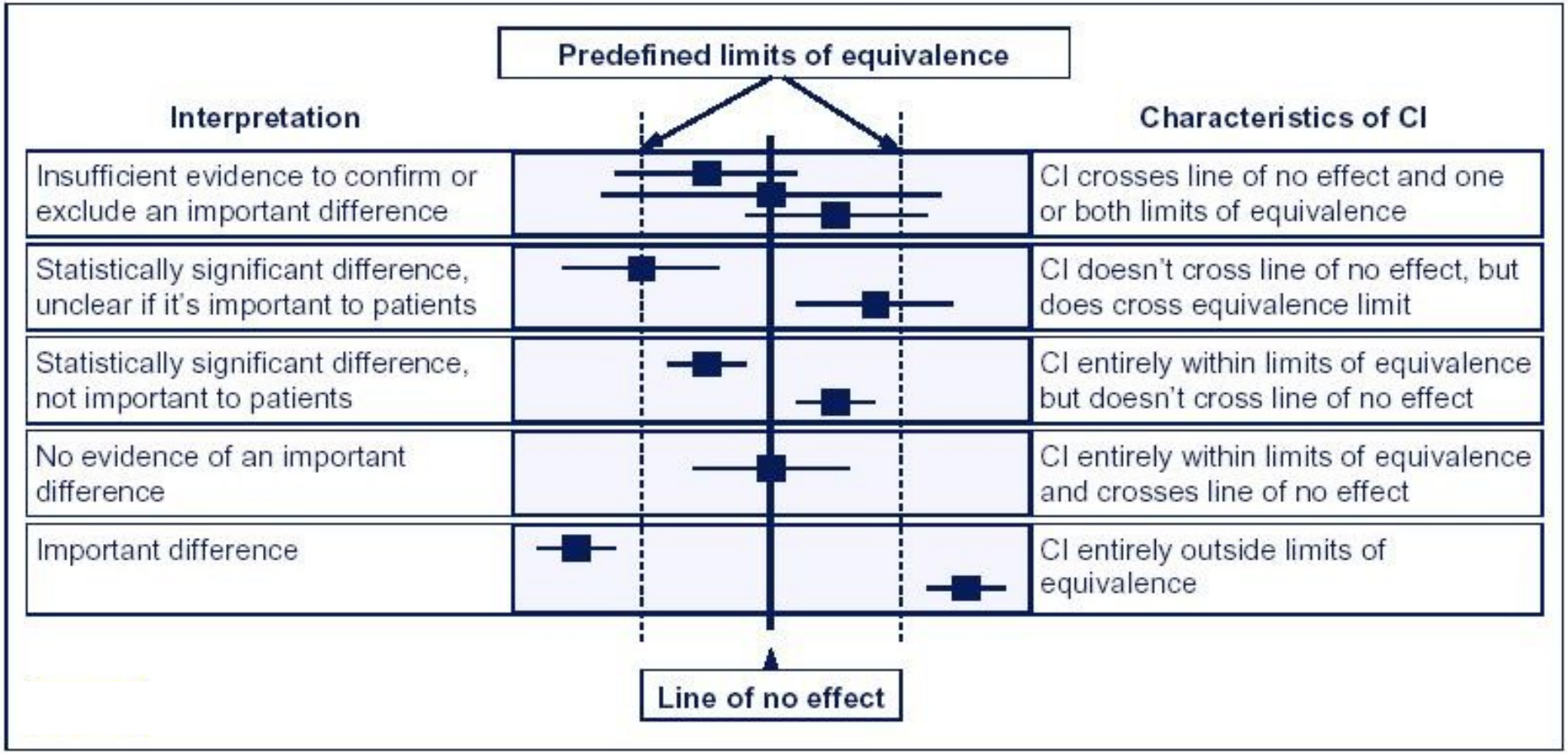
DECISION RULES IN PRACTICE

(Modified from Alderson, Cochrane News 2002)



LINKS TO RELATED AREAS

- Prospective meta-analysis
- Cumulative meta-analysis
- Bayesian sample size calculations
- Sample size for multi-centre trials
- Trial monitoring
- EVI decision theory

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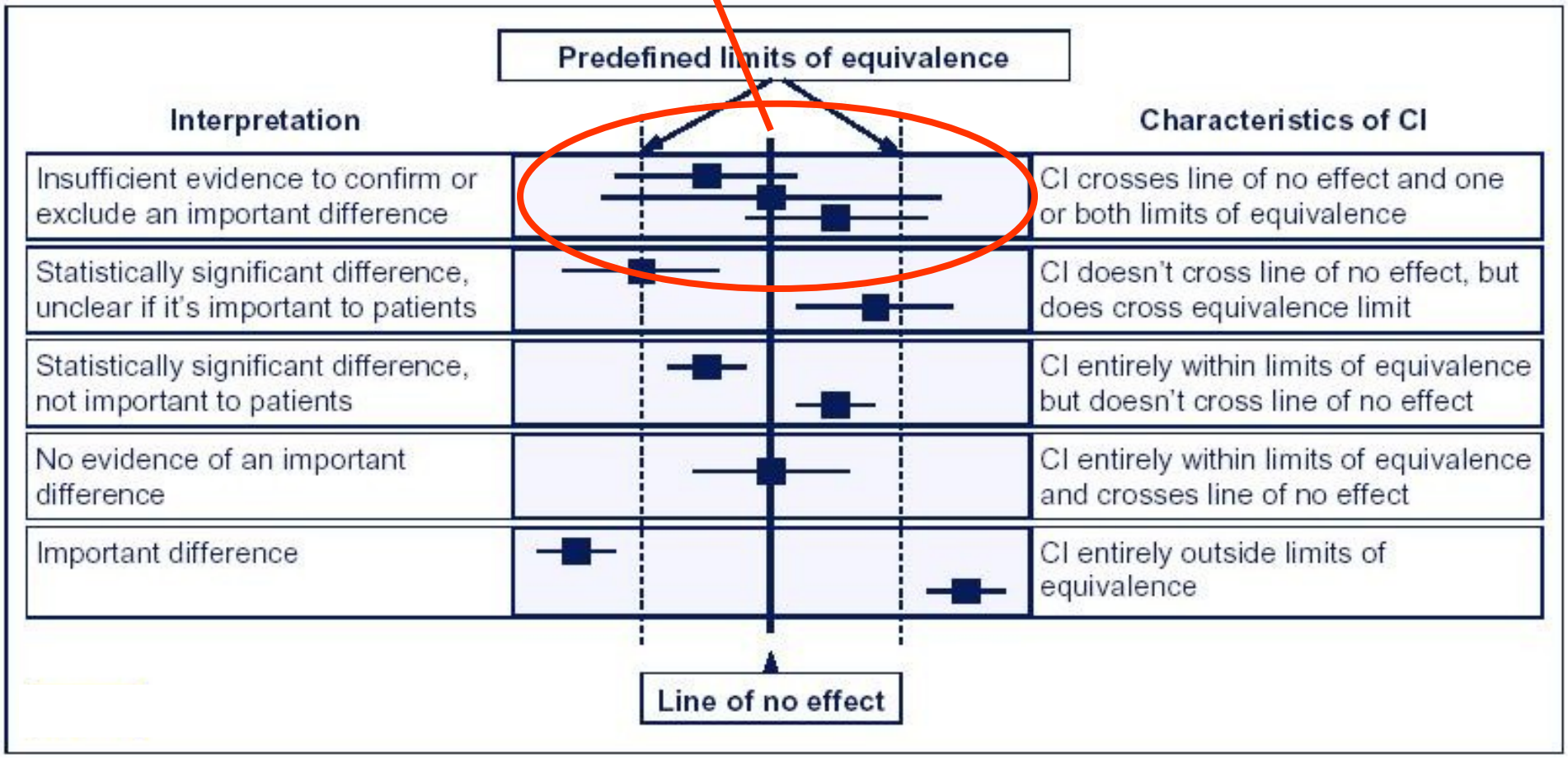
DECISION RULES IN PRACTICE

Conventional: collect more data
Equivalence: collect more data



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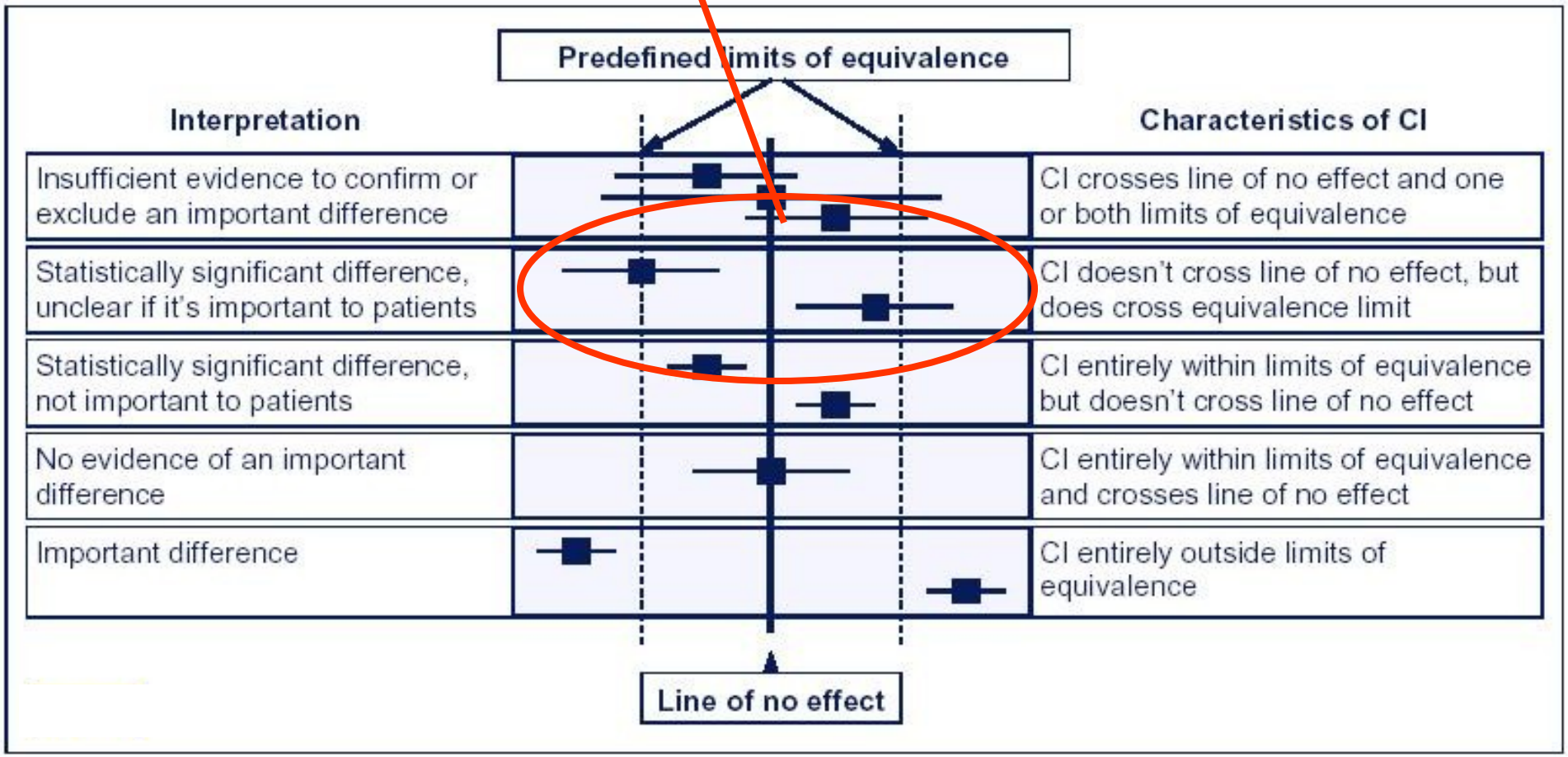
DECISION RULES IN PRACTICE

Conventional: stop collecting data
Equivalence: continue collecting data



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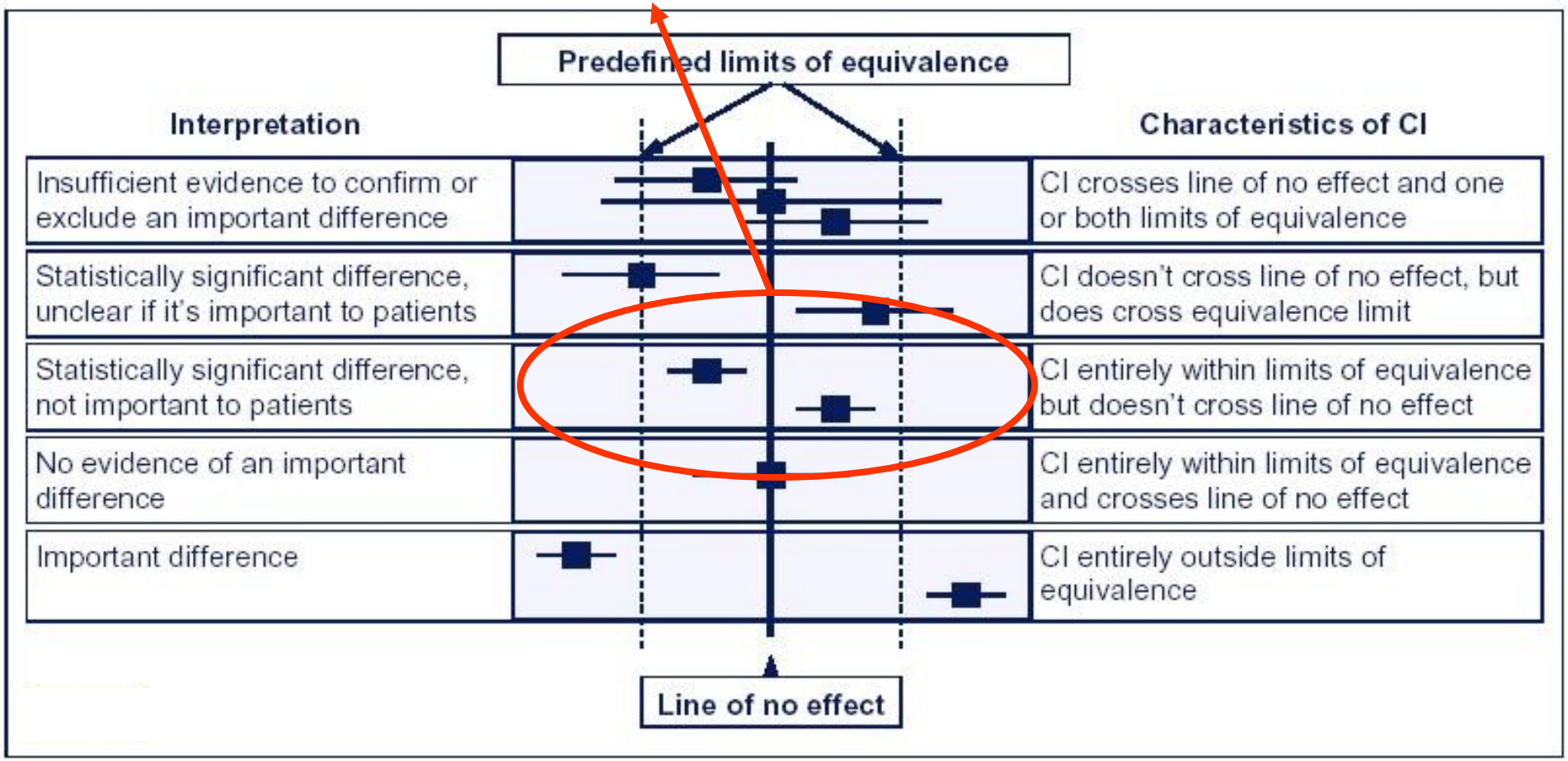

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DECISION RULES IN PRACTICE

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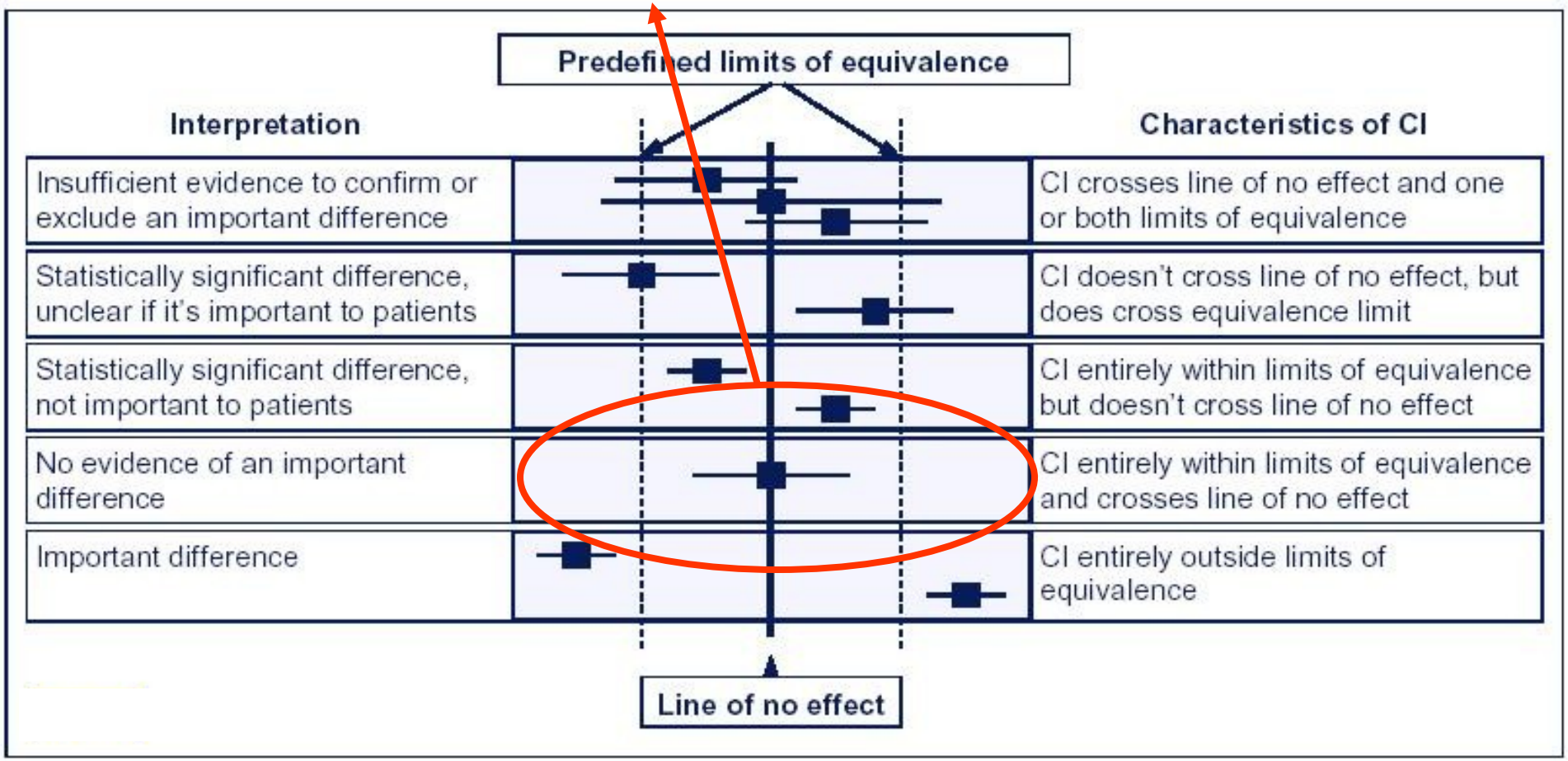
Equivalence: stop collecting data



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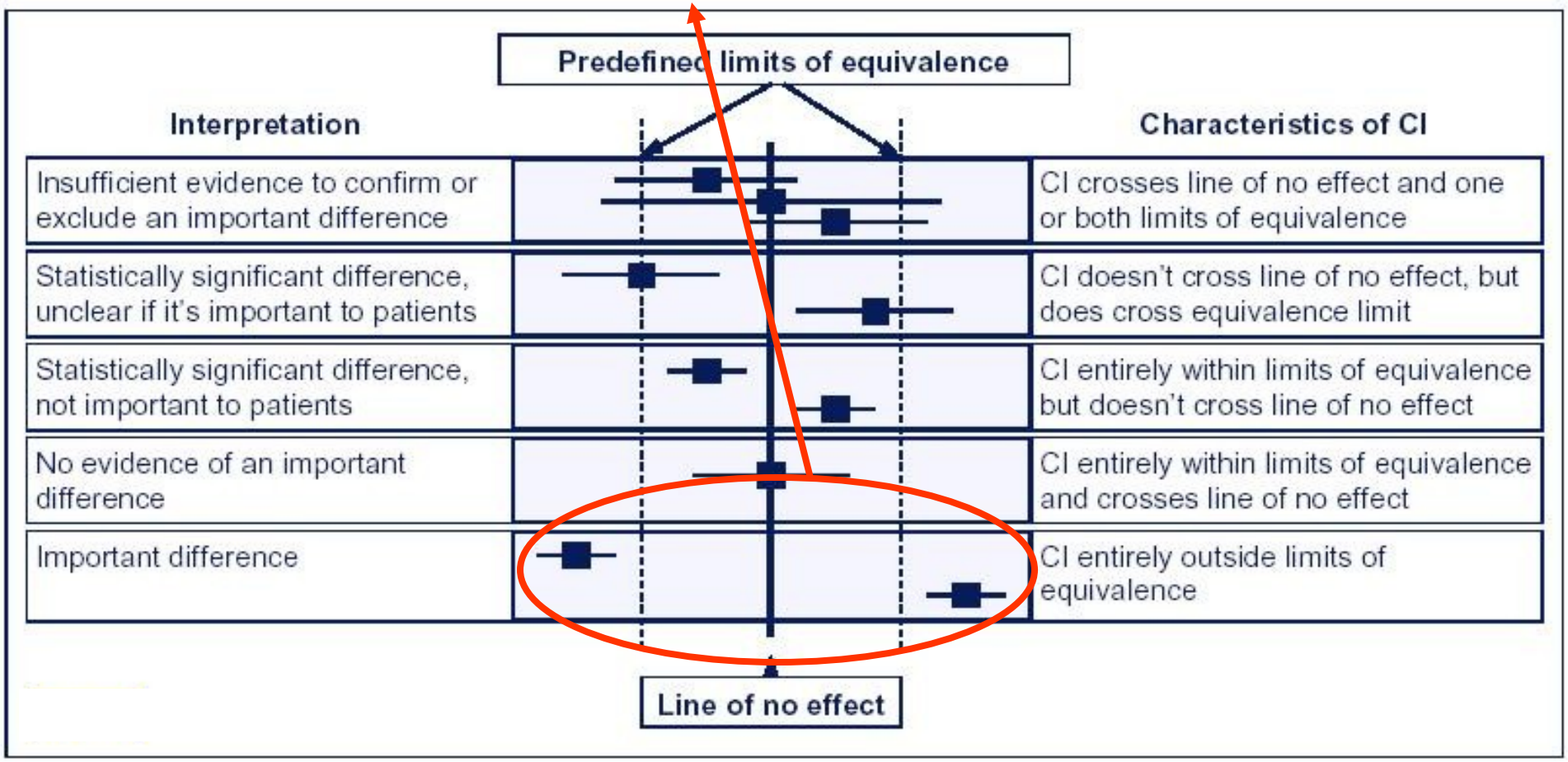

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DECISION RULES IN PRACTICE

Hence in 2 situations decision to stop or continue is reversed when conventional or equivalence considered