

Handling Both-Armed Zero-Event Studies in Meta-Analyses: A Simulation Study

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Outline

- **Background**
 - What, Why, How
 - Objective
- **Methods**
 - Design of the simulation
- **Results**
- **Discussion and conclusion**

- **What** is both-armed zero-event (BA0E)
 - Double-zero event, total zero-event or complete zero-event,
 - No event observed in both treatment and control arms for binary outcomes

- **Why** it is important
 - A combination of small probability and small sample size
 - Rare disease in EU: 1/2000; rare AE in US: 1/1000
 - Median sample size = 102, IQR = (50, 243)¹
 - 41/64 (64.1%) clearly had BA0E presented ²

1: Characteristics of meta-analyses and their component studies in the Cochrane database of systematic review (2011)

2: Systematic review of methods used in meta-analyses where a primary outcome is an adverse or unintended event (2012)

- **How** it is handled
 - 19/41 included BA0E
 - 18/41 excluded BA0E
 - 4/41 unclear
- Reasons for the inconsistency
 - Statistical methods cannot incorporate BA0E for OR or RR
 - No guideline developed on handling BA0E
- **Objective:** conduct a simulation study to evaluate the impact of including and excluding BA0E studies in MA

- Simulation design
 - Effect measures: OR and RR
 - Method to incorporate BA0E
 - Continuity correction: 0.5
 - Parameters fixed
 - Number of studies in each MA: 5
 - Treatment and control group ratio: 1:1
 - Number of data sets generated: 2500

- Parameters varied
 - Control group event rate: 0.001, 0.005, 0.01
 - Treatment effect: 1, 0.8, 0.5, 0.2
 - Number of patients in each study: 50, 100, 200
 - Between study SD: 0.1, 0.5, 1

- Parameter calculated
 - Treatment arm event rate

- Software for generating: R

- Analytical methods investigated
 - Inverse variance (IV) random-effects model
 - Inverse variance (IV) fixed-effects model
 - Mantel-Haenszel (M-H) random-effects model
 - Mantel-Haenszel (M-H) fixed-effects model
 - Peto method (OR only)
- Software for MA: STATA
- Results compared: including and excluding BA0E

- Evaluating performance of simulation
 - **Bias**: Difference between the average of estimated treatment effects and true treatment effect
 - **SQRT-MSE**: Average distance of estimated treatment effects from true treatment effect
 - **Conditional coverage**: Percentage of true treatment effect included in the available 95% CIs over all generated data sets

Results

Comparing bias (treatment effect varies)

Number of studies = 5	Number of patients = 200	Group ratio = 1	Control arm probability = 0.001	Number of simulated data sets = 2500	Between-study SD = 0.5			
Methods	Excluding BAOE studies				Including BAOE studies			
	OR = 1	OR 0.8	OR =0.5	OR = 0.2	OR = 1	OR 0.8	OR =0.5	OR = 0.2
IV Random effects	<-0.001	0.098	0.311	0.860	<0.001	0.195	0.665	1.493
IV Fixed effects	<-0.001	0.097	0.310	0.859	<0.001	0.192	0.662	1.480
M-H Radom effects	<-0.001	0.098	0.311	0.860	<0.001	0.192	0.665	1.493
M-H Fixed effects	<-0.001	0.097	0.310	0.859	<0.001	0.195	0.662	1.480
Peto	-0.007	0.003	0.024	0.295	0.001	0.183	0.653	1.448

Results

Comparing bias (control arm event rate varies)

Number of studies = 5		Number of patients = 200		Group ratio = 1		OR = 0.5		Number of simulated data sets = 2500		Between-study SD = 0.5	
Methods	Excluding BAOE studies			Including BAOE studies							
	pc = 0.001	pc = 0.005	pc = 0.01	pc = 0.001	pc = 0.005	pc = 0.01					
IV Random effects	0.341	0.301	0.251	0.658	0.535	0.414					
IV Fixed effects	0.341	0.299	0.241	0.654	0.522	0.392					
M-H Radom effects	0.341	0.301	0.251	0.658	0.535	0.414					
M-H Fixed effects	0.341	0.299	0.241	0.654	0.522	0.392					
Peto	0.075	0.045	0.011	0.645	0.467	0.287					

pc : Control group probability

Results

Comparing bias (number of patients in each study varies)

Number of studies = 5	Control group probability = 0.001			Group ratio = 1			OR = 0.5			Number of simulated data sets = 2500	Between-study SD = 0.5
	Excluding BAOE studies						Including BAOE studies				
	Methods	n = 50	n = 100	n = 200	n = 50	n = 100	n = 200				
IV Random effects	0.377	0.332	0.311	0.677	0.655	0.620					
IV Fixed effects	0.377	0.330	0.300	0.675	0.650	0.613					
M-H Radom effects	0.377	0.332	0.311	0.677	0.655	0.620					
M-H Fixed effects	0.377	0.330	0.300	0.675	0.650	0.613					
Peto	0.141	0.039	0.024	0.671	0.641	0.592					

n: Sample size in each study

- Summary of findings

- Including BA0E decreased MSE
- Including BA0E increased conditional coverage
- Estimates from both including and excluding BA0E studies showed little bias when no true treatment effect presented
- Including BA0E increased bias when true treatment effect presented

- Summary of findings (continued)
 - Bias increased with
 - Increment of true treatment effect and between-study variance
 - Decrement of control arm event rate and number of patients
 - Peto excluding BA0E had little bias for
 - Small to moderate treatment effects
 - Small to moderate between-study variance
 - Larger sample size

■ Limitations

- The following factors were fixed
 - Number of patients
 - Number of studies
 - Treatment and control group ratio
- One continuity correction factor
- Same numbers of data sets generated

■ Conclusion

- **Including BA0E** when treatment effect unlikely presents
- **Excluding BA0E** when treatment effect clearly presents
- **Peto method** is a safer choice when treatment effect presents
- **Report both** approaches when situation unclear



THANK YOU !

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