

Two Comparators, Twice the Fun!

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Statistical Revelations

The Problem

- Need an estimate of A vs B
- A and B are different therapies for a given indication
- Desire to show A better than B

The Information

- Have 3 studies with a direct comparison of A vs B
- Numerous studies with other information, especially vs D

Comparison	Number of studies
A vs C	5
B vs C	2
A vs D	6
B vs D	10

Possible Approaches

- **Combine direct results for estimate of A vs B**
- **Adjusted indirect analysis using C as common comparator**
- **Adjusted indirect analysis using D as common comparator**
- **Which do we present?**

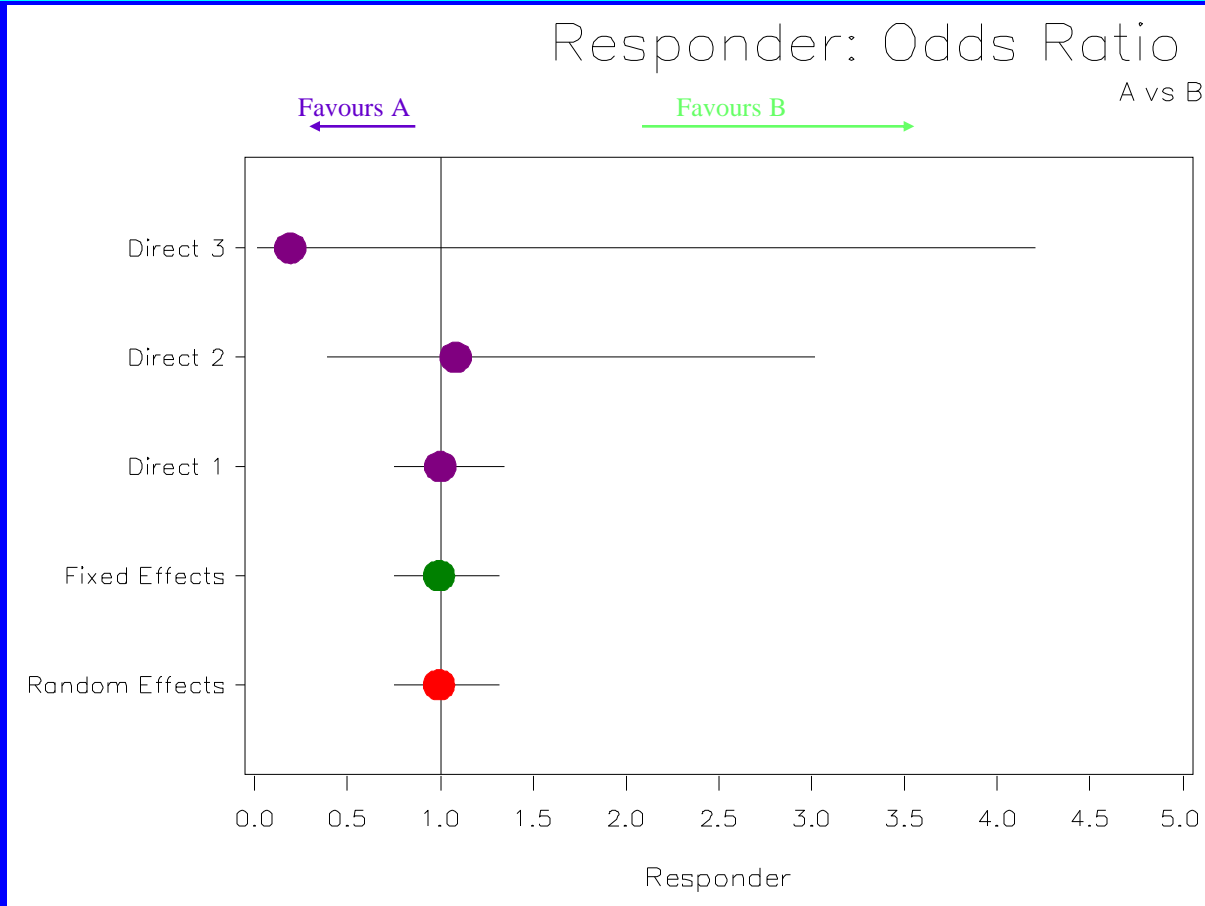
The Studies

- **Published information and internal reports from various clinical trials**
- **All in the same indication**
- **Similar patient populations**
 - **Adults**
 - **Moderately severe disease**
 - **Similar prior treatment**
 - **Similar definitions of endpoints**

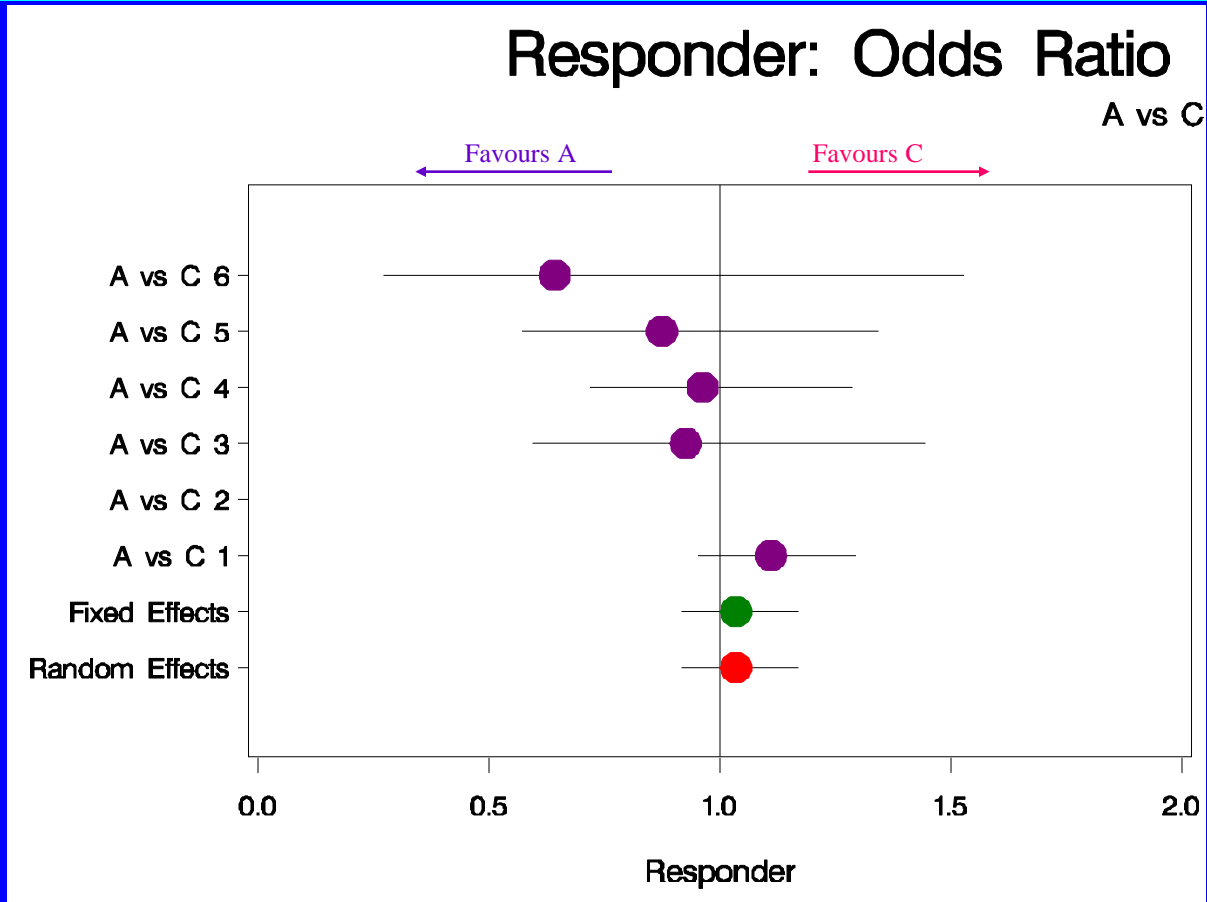
Simple Approach - Methods

- Extract results as number 'responders' and total number at risk each treatment
- A 'response' is an undesirable event
- Obtain fixed and random effects meta-analysis results as log odds ratio
- RE using Dersimonian and Laird methods
- Re-exponentiate to obtain OR with CI
- Plot

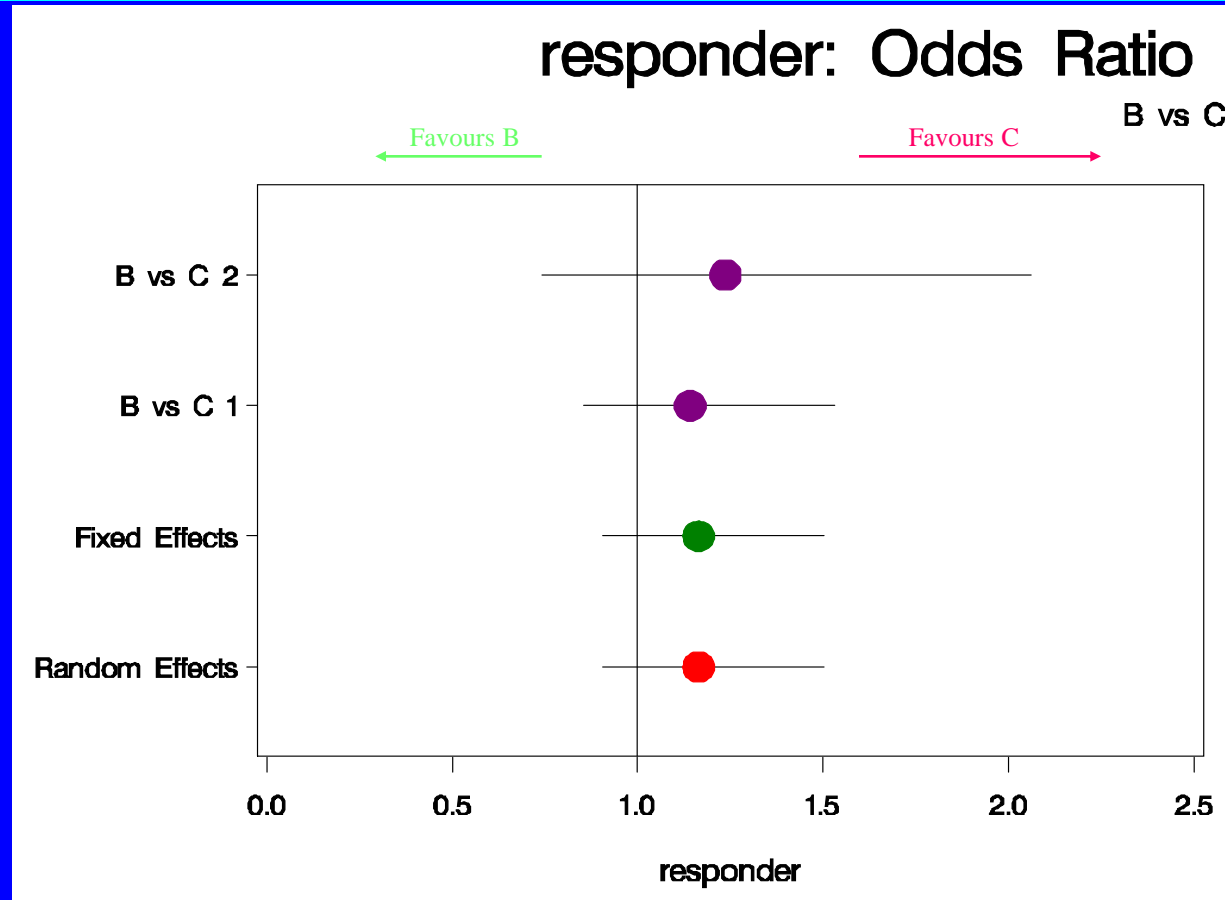
Direct Results



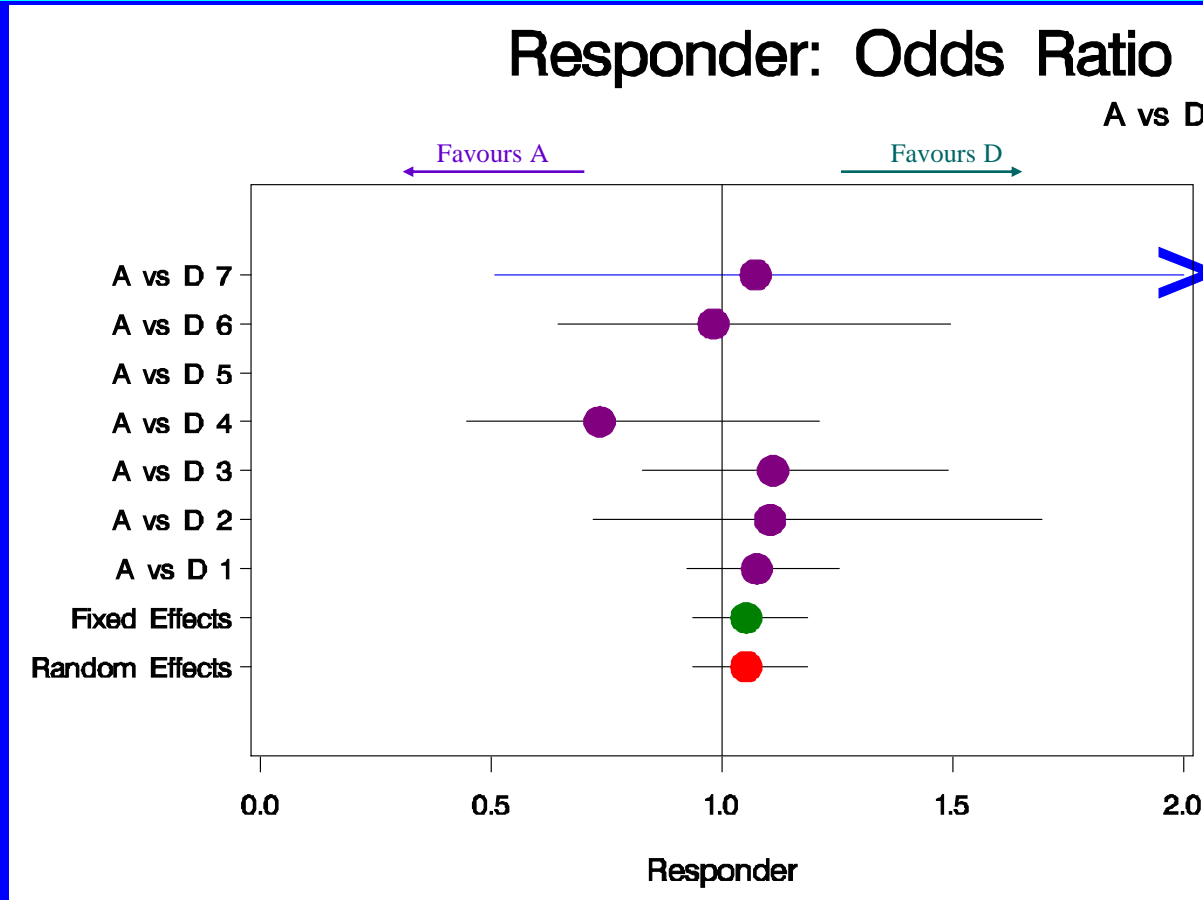
Meta Analysis for A vs C



B vs C

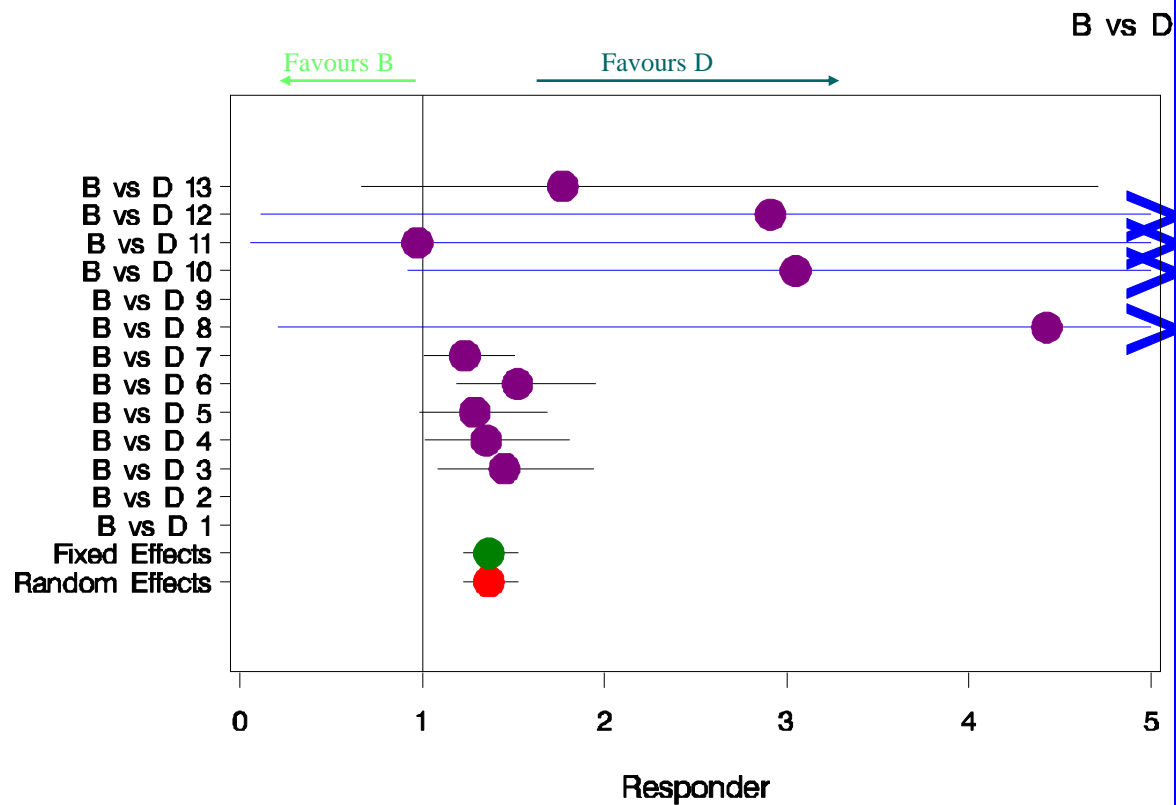


A vs D



B vs D

Responder: Odds Ratio



Summary So Far

Drug	Comparator	Number of studies	Meta analysis model	Estimated effect size	Lower 95% CL	Upper 95% CL	Direction of effect	Statistically sig?
A	B (direct)	3	Random effects model	0.994	0.75	1.32	Essentially no diff	No
A	B (direct)	3	Fixed effects model	0.994	0.75	1.32	Essentially no diff	No
A	C	5	Random effects model	1.04	0.92	1.17	Essentially no diff	No
A	C	5	Fixed effects model	1.04	0.92	1.17	Essentially no diff	No
A	D	6	Random effects model	1.05	0.94	1.19	Essentially no diff	No
A	D	6	Fixed effects model	1.05	0.94	1.19	Essentially no diff	No
B	C	2	Random effects model	1.17	0.9	1.5	In favour of C	No
B	C	2	Fixed effects model	1.17	0.9	1.5	In favour of C	No
B	D	10	Random effects model	1.37	1.22	1.53	In favour of D	Yes
B	D	10	Fixed effects model	1.37	1.22	1.53	In favour of D	Yes

Indirect Analyses

- Adjusted indirect analysis with C as common comparator
- Adjusted indirect analysis with D as common comparator

Example Using C as a Common Comparator

- Method described in Song et al
- Combine trials using meta-analysis
- Use RE variance estimate
- Calc CI as $\pm 1.96 * SE(T_{AB})$

$$T_{AB} = T_{AC} - T_{BC}$$

where

T_{AC} = effect for A vs C

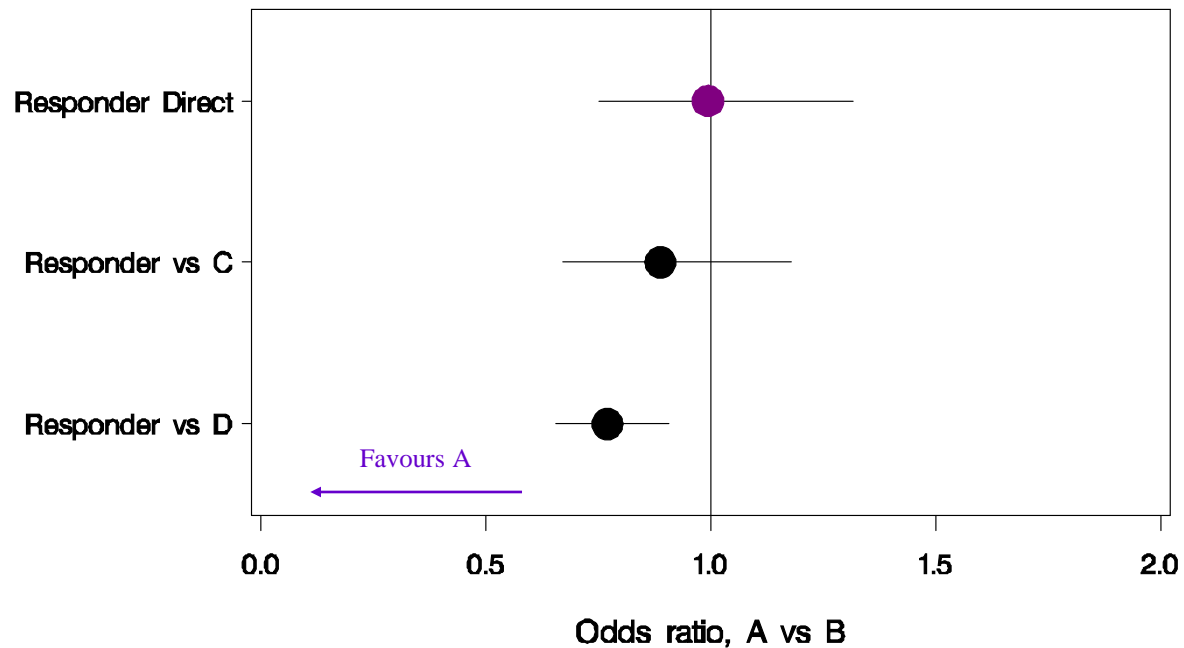
T_{BC} = effect for B vs C

T_{AB} = effect for A vs B

$$SE(T_{AB}) = \sqrt{((SE(T_{AC}))^2 + (SE(T_{BC}))^2)}$$

Indirect Comparison Results

Forest plot for indirect comparisons, responder analysis
Purple symbols represent the direct comparison in head to head trials



If the confidence limits span one then the difference is not statistically significant
A value < 1 suggests the response rate for A/comparator $<$ the response rate for B/comparator
This favours A

Where are we?

- Goal was to show A better than B
- $OR < 1$ in favour of A
- Direct estimate essentially no difference
- Indirect both favour A

What else can we do?

- Use all information in one model
- Obtain a combined result
- Develop idea with one meta-analysis
- One indirect comparison
- A global model
 - Includes all studies (direct and indirect)

A Modelling Approach to a Meta-Analysis

- Example, Meta-analysis of B vs D
- Fit a logistic model (PROC GENMOD)

$$\log(OR) = a + b_T.tmt + b_S.Study$$

- Use SAS
- Compare result with previous results

Model Results (B vs D)

Contrast Estimate Results							
Label	Estimate	Standard Error	Alpha	Confidence Limits		Chi-Square	Pr > ChiSq
(B vs D)	0.3141	0.0569	0.05	0.2026	0.4256	30.48	<.0001
Exp(B vs D)	1.369	0.0779	0.05	1.2245	1.5305		

Previous Result			
Label	Estimate	Confidence Limits	
Fixed Effects OR	1.367	1.22	1.53
Random Effects OR	1.367	1.22	1.53

A Modelling Approach to an Indirect Comparison

- Indirect comparison, D as common
- Fit a logistic model (PROC GENMOD)

$$\log(OR) = a + b_T.tmt + b_S.Study$$

- Use SAS
- Compare result with previous results

Model Results for Indirect Comparison

Contrast Estimate Results							
Label	Estimate	Standard Error	Alpha	Confidence Limits		Chi-Square	Pr > ChiSq
indirect	-0.2623	0.083	0.05	-0.4249	-0.1	10	0.0016
Exp(indirect)	0.7693	0.0638	0.05	0.6538	0.9051		

Previous Result			
Label	Estimate	Confidence Limits	
Indirect Vs D	0.7702	0.6546	0.9062

A Global Model to Use ALL Information

- Use ALL studies
 - (A vs B, A vs C, A vs D, B vs C, B vs D)
- Fit the logistic model (PROC GENMOD)

$$\log(OR) = a + b_T.tmt + b_S.Study$$

- Use SAS

All Studies Together

Model Results for (3) Direct Comparisons only

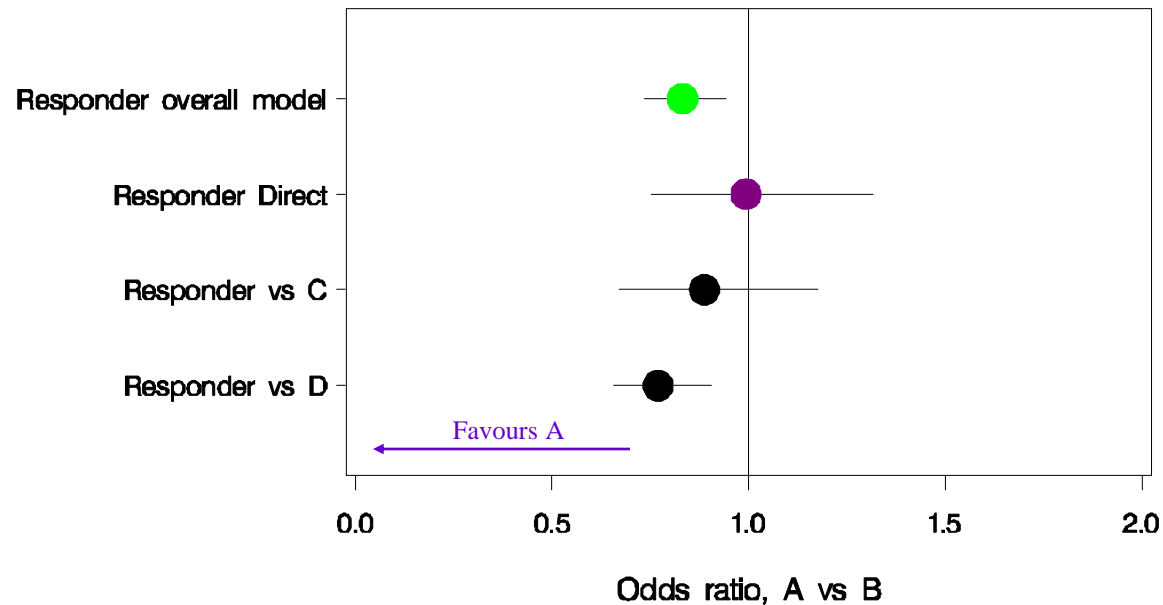
Label	Estimate	Standard Error	Alpha	Confidence Limits		ChiSq	Pr > ChiSq
A vs B direct	-0.0125	0.1428	0.05	-0.2924	0.2673	0.01	0.9301
Exp (A vs B direct)	0.9876	0.141	0.05	0.7465	1.3065		

Model Results using ALL Studies

Label	Estimate	Standard Error	Alpha	Confidence Limits		ChiSq	Pr > ChiSq
overall A vs B	-0.1833	0.0642	0.05	-0.3092	-0.0574	8.14	0.0043
Exp (overall A vs B)	0.8325	0.0535	0.05	0.734	0.9443		

Presenting All Information Graphically

Forest plot for direct and indirect comparisons and overall model, responder analysis
Purple symbols represent the direct comparison in head to head trials
Green symbols represent the results from the overall model



If the confidence limits span one then the difference is not statistically significant
A value < 1 suggests the response rate for A/comparator $<$ the response rate for B/comparator
This favours A

Conclusion From the Analysis

- **Direct comparison on 3 trials essentially no difference (marginally in favour of A)**
- **Two series of indirect analysis both in favour of A**
- **All combined suggested A significantly better than B**

Issues

- Is this a fixed or random effects model?
- A fixed effects
- An improvement is to fit study as a random term
- Possible using SAS Proc Glimmix
- In this example the between study variance was very small in all analyses ($FE \approx RE$)

Issues/considerations

- **Comparability of studies**
 - Drug B vs C or D studies published
 - Drug A vs B internal study information
 - Drug A vs C or D internal/published
- **Can include study design factors (e.g length)**
- **Explore differences between few in-house direct studies and published used for indirect**

Conclusion

- A hypothetical scenario
- Three direct studies of A vs B
- Numerous for indirect analysis with D as common comparator
- Several with C as common comparator
- Using all information may improve estimate
- Apply with caution
- Explore differences between direct and overall result