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Common statistical issues in Cochrane reviews; statistical contribution to CRGs

Cochrane methods training event 2016
Statistical methods training for statisticians supporting CRGs

Kerry Dwan
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Trusted evidence.
Informed decisions.
Better health.

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Outline

- Screening
- Common statistical issues
- Statistical contribution to CRGs
  - Refereeing and feedback
  - Training/ help/ advice
  - Forum

Screening process

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Item No.	Item name	Standard	Met?	Comment
	Implementation of protocol methods			
C27	***Searching trials registers***	Search trials registers and repositories of results, where relevant to the topic through ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) portal and other sources as appropriate.		
C37	***Rerunning s***			
C40	***Excluding s without use data***			
C68	***Comparing subgroups***			

Item No.	Item name	Standard	Met?	Comment
C76	***Assessing the quality of the body of evidence***	Use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome, and to draw conclusions about the quality of evidence within the text of the review.		
R97	***'Summary of findings' table***	Present a 'Summary of Findings' table according to recommendations described in Chapter 11 of the Cochrane Handbook (version 5 or later). Specifically: include results for one clearly defined population group (with few exceptions); indicate the intervention and the comparison intervention; include seven or fewer patient-important outcomes; describe the outcomes (e.g. scale, scores, follow-up);		
C73	***Interpreting results***			
C78	***Formulating implications for practice***			
R101	***Implications for practice***			

Item No.	Item name	Standard	Met?	Comment
	Completeness of reporting in the abstract & Internal consistency			
R11	***Abstract, Main results: bias assessment***	Provide a comment on the findings of the bias assessment.		
R12	***Abstract, Main results: findings***	Report findings for all primary outcomes, irrespective of the strength and direction of the result, and of the availability of data.		
R13	***Abstract, Main results: adverse effects***	Ensure that any findings related to adverse effects are reported. If adverse effects data were sought, but availability of data was limited, this should be reported.		
R18	***Consistency of summary versions of the review***	Ensure that reporting of objectives, important outcomes, results, caveats and conclusions is consistent across the text, the abstract, the plain language summary and the 'Summary of findings' table (if included).		
R86	***Consistency of results***	Ensure that all statistical results presented in the main review text are consistent between the text and the 'Data and analysis' tables.		

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Implementation of protocol methods

Searching trials registers	Search trials registers and repositories of results, where relevant to the topic through ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) portal and other sources as appropriate.
Rerunning searches	Rerun or update searches for all relevant databases within 12 months before publication of the review or review update, and screen the results for potentially eligible studies.
Excluding studies without useable data	Include studies in the review irrespective of whether measured outcome data are reported in a 'usable' way.
Comparing subgroups	If subgroup analyses are to be compared, and there are judged to be sufficient studies to do this meaningfully, use a formal statistical test to compare them.
Changes from the protocol	Explain and justify any changes from the protocol (including any post hoc decisions about eligibility criteria or the addition of subgroup analyses).

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Implementation of protocol methods

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Excluding studies without useable data


RESEARCH METHODS
& REPORTING

The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews

Jamie J Kirkham,[1] Kerry M Dwan,[1] Douglas G Altman,[2] Carrol Gamble,[1] Susanna Dodd,[1] Rebecca Smyth,[3] Paula R Williamson[1]

23% (167/712) of trials were excluded from reviews as the review primary outcome was not reported

ORBIT

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Comparing subgroups

PLOS ONE

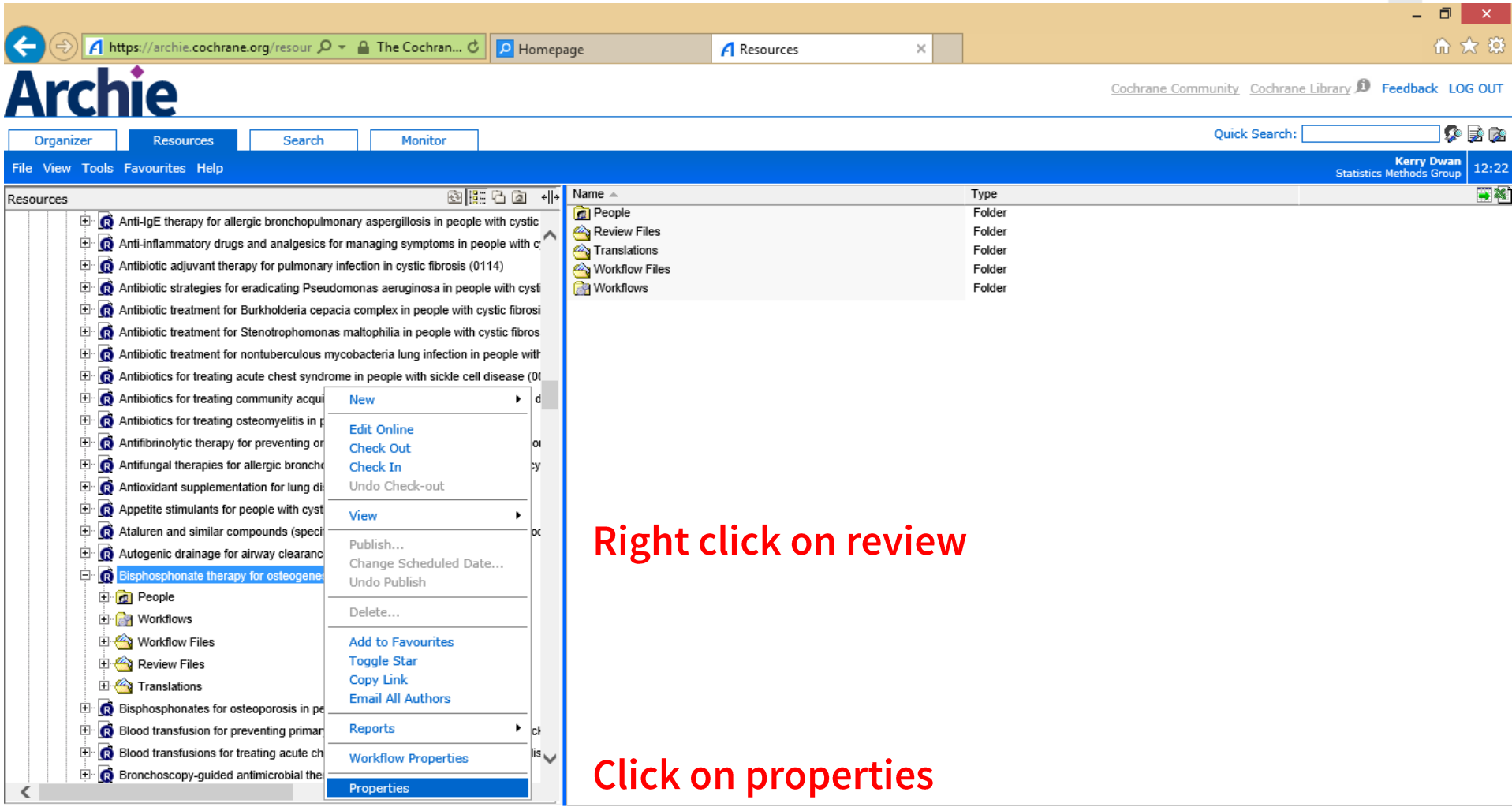
RESEARCH ARTICLE

Exploring Treatment by Covariate Interactions Using Subgroup Analysis and Meta-Regression in Cochrane Reviews: A Review of Recent Practice

Sarah Donegan[1]*, Lisa Williams[1], Sofia Dias[2☯], Catrin Tudur-Smith[1], Nicky Welton[2☯]

- 46% (24/52) reviews had a discrepancy between analysis planned and applied
- No reasons why covariates were chosen, post hoc covariates not identified
- Only 1 review reported whether an interaction was detected

Changes from protocol



Right click on review

Click on properties

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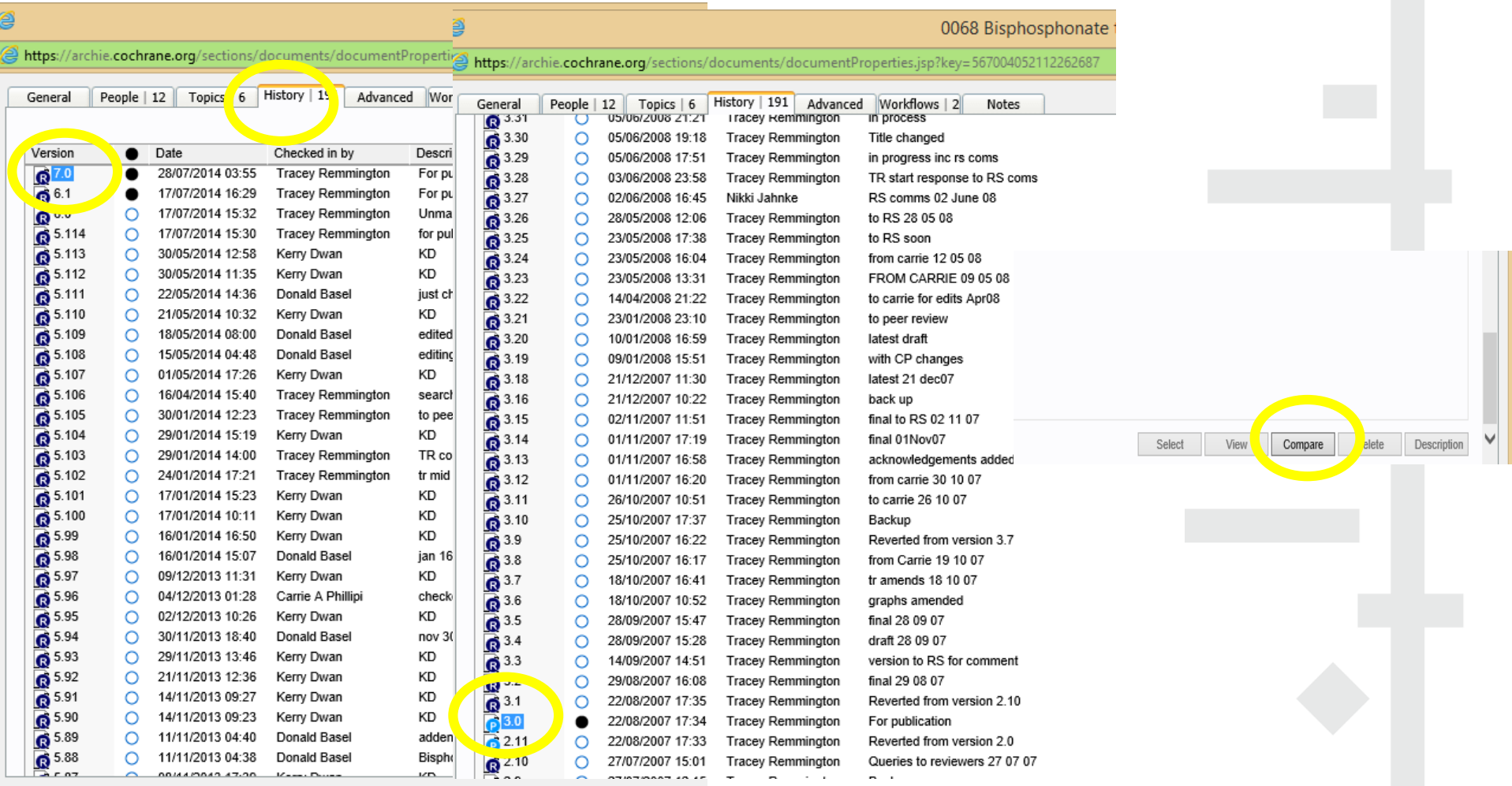

Go to History. Highlight protocol and review versions that you wish to compare by clicking and pressing Ctrl. Scroll down and click compare

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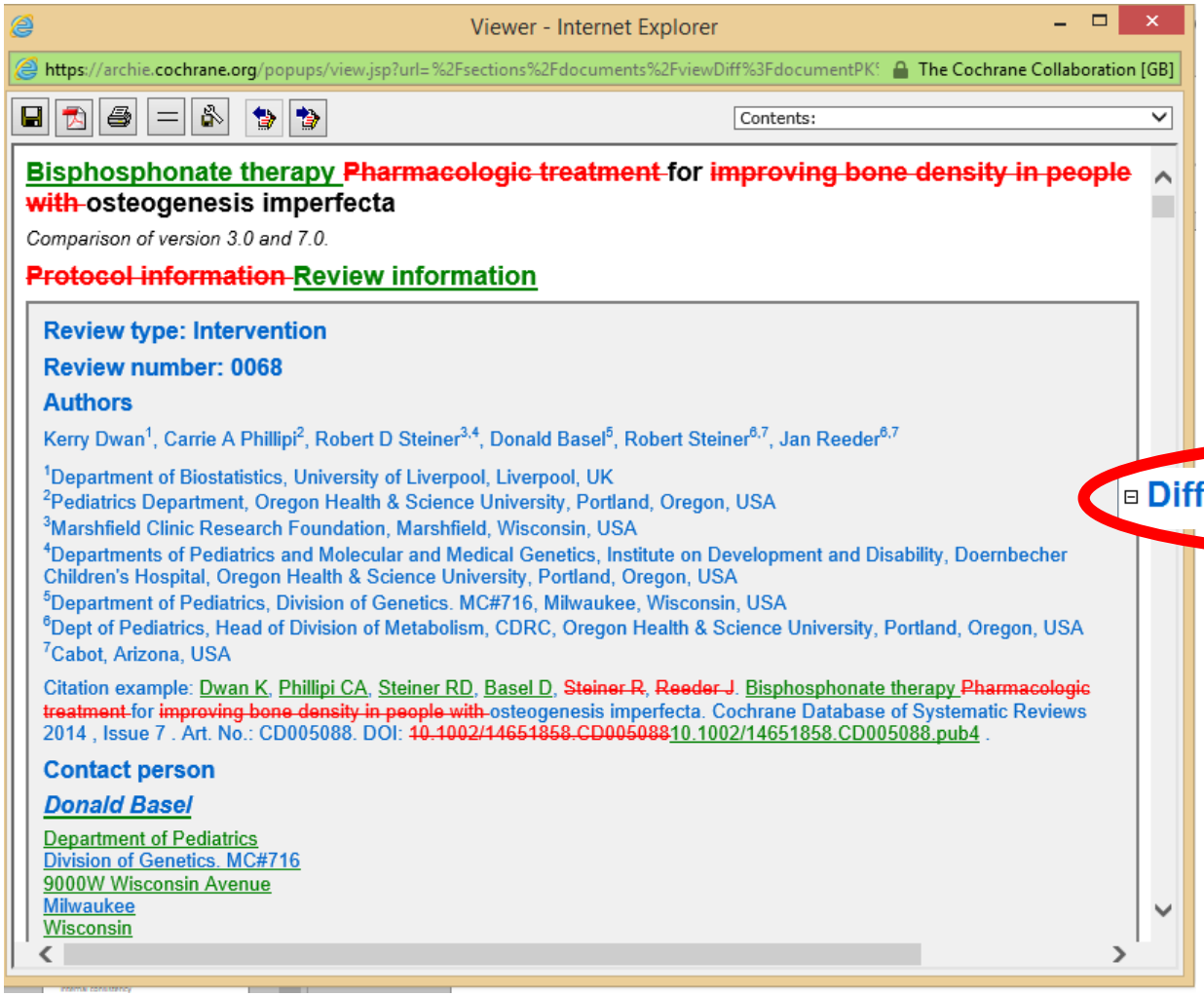

Differences between protocol and review

Interpretation

'Summary of findings' table	Present a 'Summary of Findings' table according to recommendations described in Chapter 11 of the Cochrane Handbook (version 5 or later). Specifically: include results for one clearly defined population group (with few exceptions); indicate the intervention and the comparison intervention; include seven or fewer patient-important outcomes; describe the outcomes (e.g. scale, scores, follow-up); indicate the number of participants and studies for each outcome; present at least one baseline risk for each dichotomous outcome (e.g. study population or median/medium risk) and baseline scores for continuous outcomes (if appropriate); summarize the intervention effect (if appropriate); and include a measure of the quality of the body of evidence for each outcome.
Assessing the quality of the body of evidence	Use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome, and to draw conclusions about the quality of evidence within the text of the review.
Formulating implications for practice	Base conclusions only on findings from the synthesis (quantitative or narrative) of studies included in the review.
Implications for practice	Provide a general interpretation of the evidence so that it can inform healthcare or policy decisions. Avoid making recommendations for practice.

Completeness of reporting in the abstract and internal consistency

Abstract, Main results: bias assessment	Provide a comment on the findings of the bias assessment.
Abstract, Main results: findings	Report findings for all primary outcomes, irrespective of the strength and direction of the result, and of the availability of data.
Abstract, Main results: adverse effects	Ensure that any findings related to adverse effects are reported. If adverse effects data were sought, but availability of data was limited, this should be reported.
Consistency of summary versions of the review	Ensure that reporting of objectives, important outcomes, results, caveats and conclusions is consistent across the text, the abstract, the plain language summary and the 'Summary of findings' table (if included).
Consistency of results	Ensure that all statistical results presented in the main review text are consistent between the text and the 'Data and analysis' tables.

Common statistical issues

Design

Comparison of protocol to review

- Outcomes – too many? Changes?

Study or Subgroup	Proportion	SE	Weight	Proportion IV, Random, 95% CI
Silagy 2002 (2002)	0.47	0.07	23.3%	0.47 [0.33, 0.61]
Parmelli 2007 (2005-2006)	0.47	0.05	25.5%	0.47 [0.37, 0.57]
Kirkham 2010b (2006-2007)	0.22	0.02	27.9%	0.22 [0.18, 0.26]
Dwan 2013a (2006-2009)	0.39	0.07	23.3%	0.39 [0.25, 0.53]
Total (95% CI)			**100.0%**	**0.38 [0.23, 0.54]**

Heterogeneity: Tau² = 0.02; Chi² = 33.23, df = 3 (P < 0.00001); I² = 91%
Test for overall effect: Z = 4.78 (P < 0.00001)

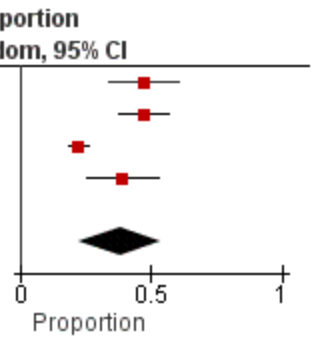

Figure 3. Random-effects meta-analysis of proportion of systematic reviews with any discrepancy in at least one outcome from protocol to published systematic review.

Handbook recommendations

- **Summary of Findings**

7 main outcomes (essential for decision making, patient important)

- **Primary**

No more than 3 (one benefit, one harm)

- **Secondary**

Limited number

Subgroups

- Handbook section 9.6
- Adequate number of studies, 10?
- Specify small number of characteristics in advance with rationale
- Confounding

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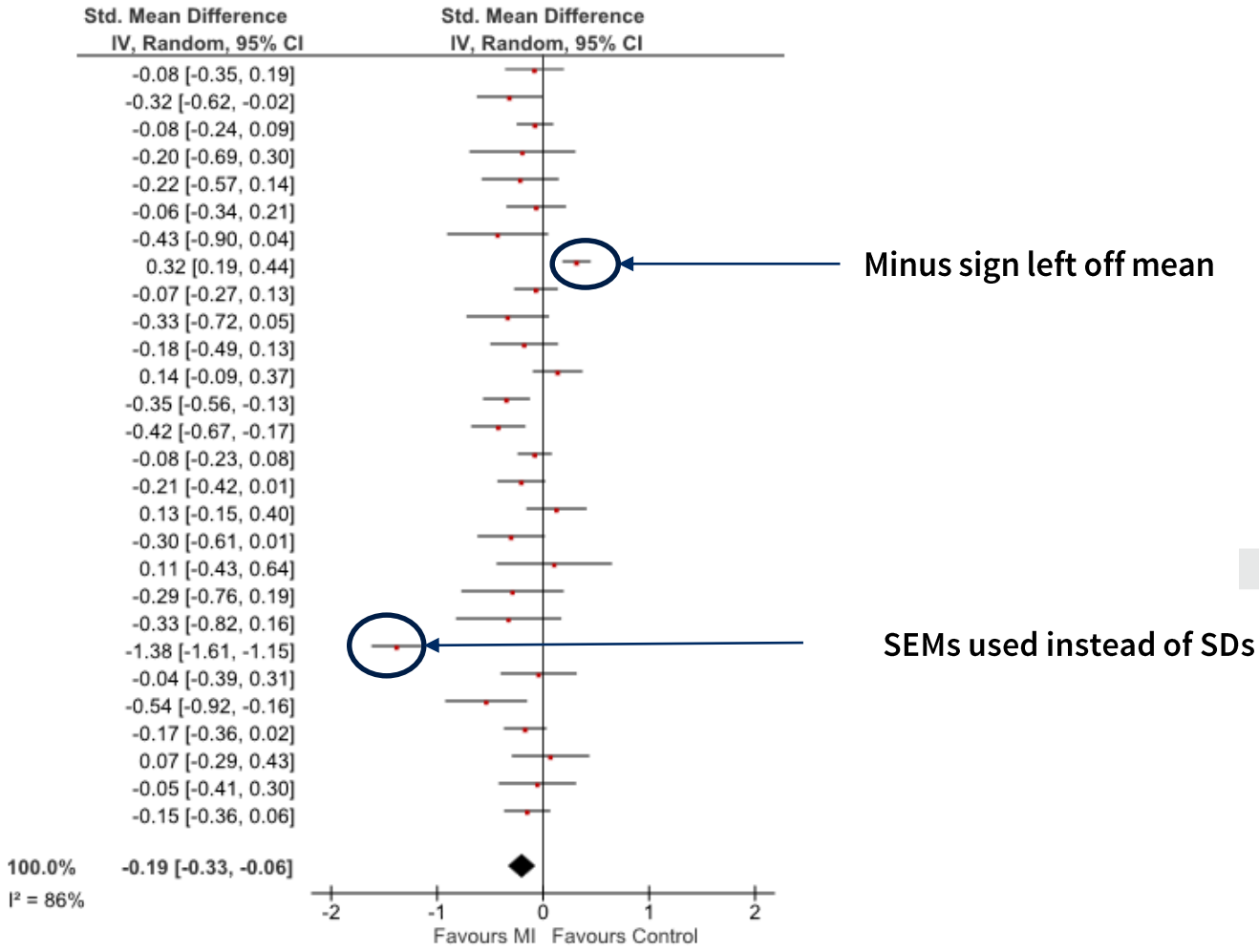
Data basics

- Numbers don’t add up
- Data entry errors/ transposition errors
- Graphs and text don’t match
- Differences between objectives, outcomes, plots



Minus sign left off mean

SEMs used instead of SDs

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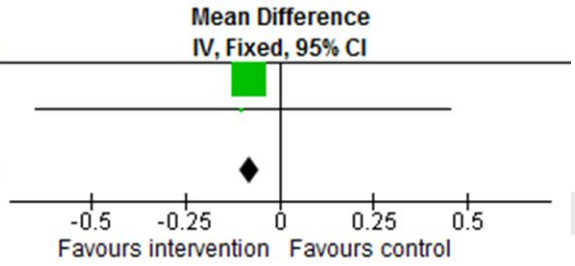
Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Study 1	0.6	0.001	33	0.68	0.07	34	99.8%	-0.08 [-0.10, -0.06]
Study 2	0.8	0.73	31	0.9	1.58	40	0.2%	-0.10 [-0.65, 0.45]
Total (95% CI)			**64**			**74**	**100.0%**	**-0.08 [-0.10, -0.06]**

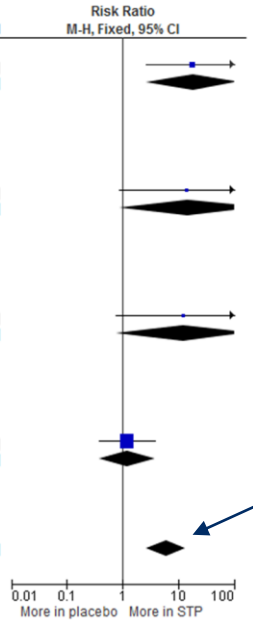
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 6.67 (P < 0.00001)



1.8 Adverse effects

Study or Subgroup	STP Events	STP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 Drowsiness						
Chiron 2000	19	21	1	20	16.7%	18.10 [2.67, 122.86]
Subtotal (95% CI)		**21**		**20**	**16.7%**	**18.10 [2.67, 122.86]**
Total events	19		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.96 (P = 0.003)						
1.8.2 Loss of appetite						
Chiron 2000	7	21	0	20	8.3%	14.32 [0.87, 235.36]
Subtotal (95% CI)		**21**		**20**	**8.3%**	**14.32 [0.87, 235.36]**
Total events	7		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
1.8.3 Loss of weight						
Chiron 2000	6	21	0	20	8.3%	12.41 [0.74, 206.86]
Subtotal (95% CI)		**21**		**20**	**8.3%**	**12.41 [0.74, 206.86]**
Total events	6		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						
1.8.4 Weight gain						
Chiron 2000	5	21	4	20	66.7%	1.19 [0.37, 3.81]
Subtotal (95% CI)		**21**		**20**	**66.7%**	**1.19 [0.37, 3.81]**
Total events	5		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
Total (95% CI)		**84**		**80**	**100.0%**	**6.04 [2.67, 13.65]**
Total events	37		5			

Heterogeneity: Chi² = 9.36, df = 3 (P = 0.02); I² = 68%
Test for overall effect: Z = 4.32 (P < 0.0001)
Test for subgroup differences: Chi² = 7.88, df = 3 (P = 0.05), I² = 61.9%



Higher proportions of participants were reported to experience side effects in the treatment group compared with placebo (100% vs 25%; RR 6.04, 95% CI 2.67 to 13.65).

Analysis

- Unit of analysis
  - Crossover trials, cluster trials
- Subgroups
  - Post hoc, wrong analysis, incorrect interpretation
- Heterogeneity problems
- SMDs and MDs
  - Used incorrectly, not often back transformed
- Random effects versus fixed effects
  - Inconsistently used

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Crossover trials

- Common in chronic and rare diseases
- Only 60% of Cystic Fibrosis and Genetic Disorder reviews describe an appropriate method for including cross-over data
- 51% use the methods described
- 30% of cross-over trials were included in analysis incorrectly, overestimating variability in analyses

Nolan et al. (submitted)

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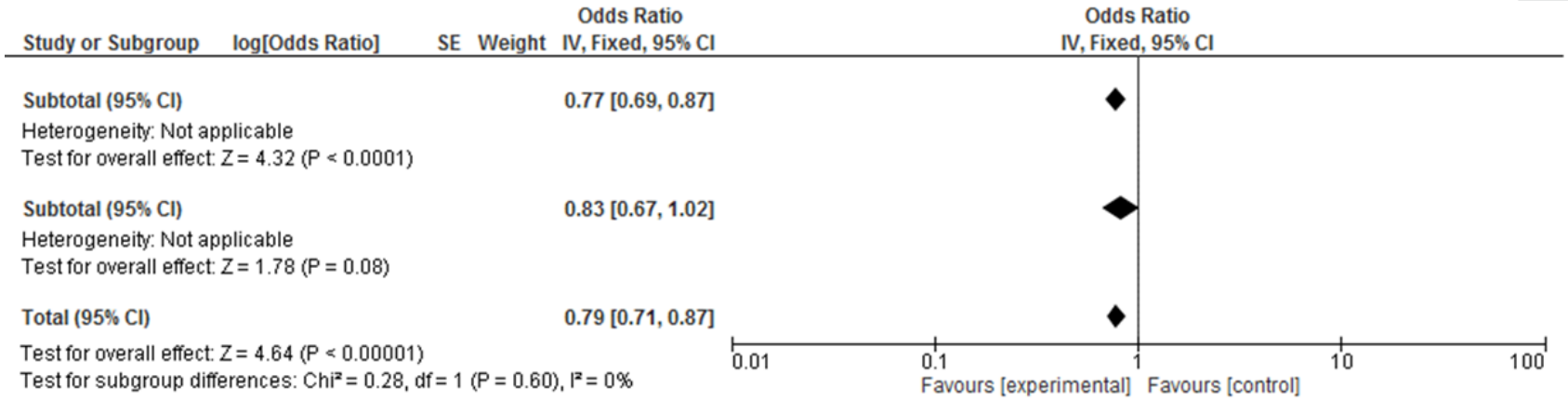
Cluster trials

- 56% (28/50) of reviews stated cluster trials were eligible for inclusion
- 24% (8/33) of reviews reported the method of cluster adjustment
- Only one review assessed all five cluster trial specific risk of bias criteria
- 33% (9/27) of reviews that presented unadjusted data provided a warning that confidence intervals may be artificially narrow
- 38% (13/34) of reviews excluded the unadjusted results from meta-analysis

Richardson et al, accepted PLoS ONE

Subgroups



Abstract:
Our review also suggests that (INTERVENTION) may have more beneficial effects in (SUBGROUP).

PLS
In the further analyses, there is evidence indicated that the effects of (INTERVENTION) in reducing (OUTCOME) rate may be different between (SUBGROUP 1) and (SUBGROUP 2), with more benefits observed in (SUBGROUP 1).

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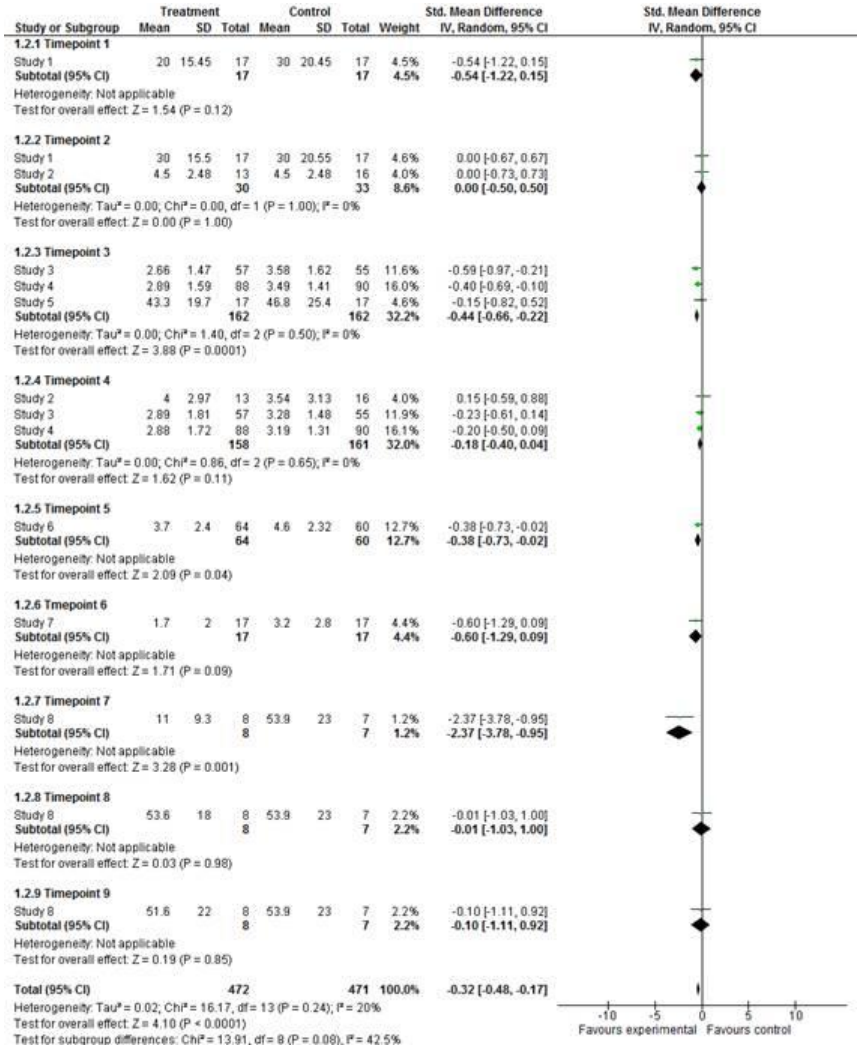
Subgrouped by timepoints



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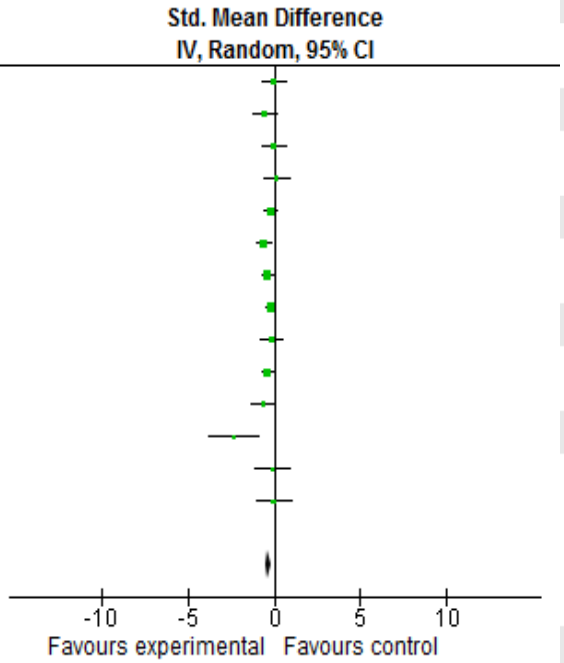
Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Study 1	30	15.5	17	30	20.55	17	4.6%	0.00 [-0.67, 0.67]
Study 1	20	15.45	17	30	20.45	17	4.5%	-0.54 [-1.22, 0.15]
Study 2	4.5	2.48	13	4.5	2.48	16	4.0%	0.00 [-0.73, 0.73]
Study 2	4	2.97	13	3.54	3.13	16	4.0%	0.15 [-0.59, 0.88]
Study 3	2.89	1.81	57	3.28	1.48	55	11.9%	-0.23 [-0.61, 0.14]
Study 3	2.66	1.47	57	3.58	1.62	55	11.6%	-0.59 [-0.97, -0.21]
Study 4	2.89	1.59	88	3.49	1.41	90	16.0%	-0.40 [-0.69, -0.10]
Study 4	2.88	1.72	88	3.19	1.31	90	16.1%	-0.20 [-0.50, 0.09]
Study 5	43.3	19.7	17	46.8	25.4	17	4.6%	-0.15 [-0.82, 0.52]
Study 6	3.7	2.4	64	4.6	2.32	60	12.7%	-0.38 [-0.73, -0.02]
Study 7	1.7	2	17	3.2	2.8	17	4.4%	-0.60 [-1.29, 0.09]
Study 8	11	9.3	8	53.9	23	7	1.2%	-2.37 [-3.78, -0.95]
Study 8	51.6	22	8	53.9	23	7	2.2%	-0.10 [-1.11, 0.92]
Study 8	53.6	18	8	53.9	23	7	2.2%	-0.01 [-1.03, 1.00]
Total (95% CI)			**472**			**471**	**100.0%**	**-0.32 [-0.48, -0.17]**

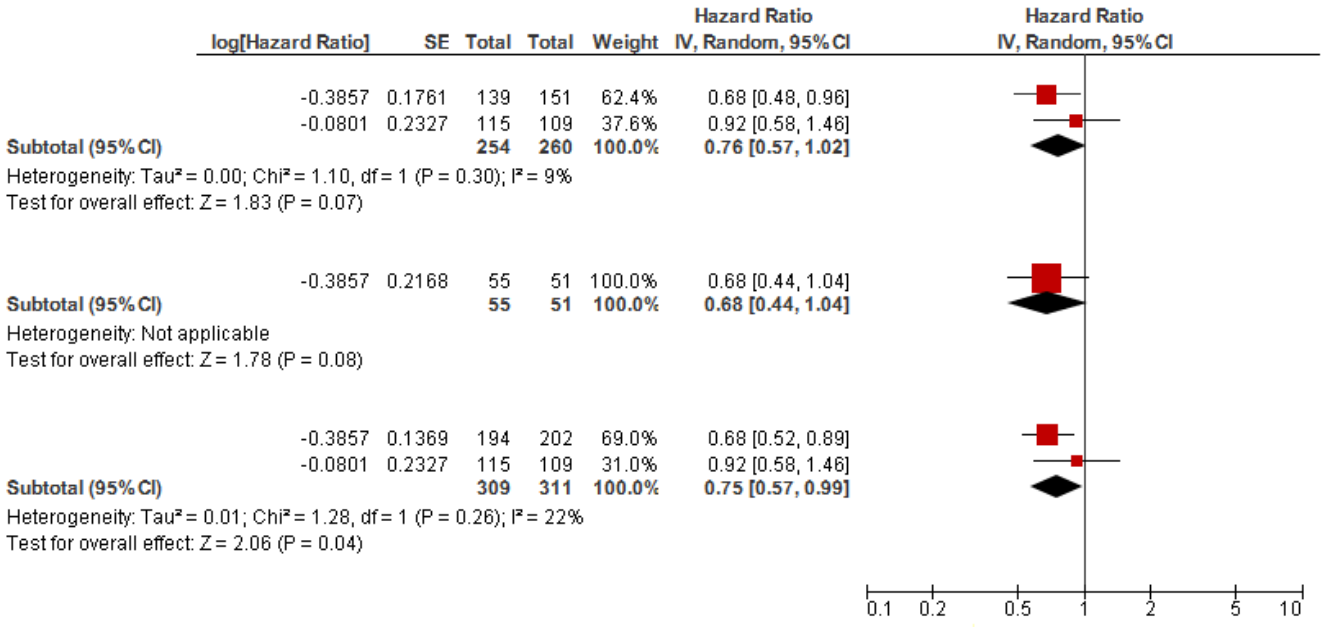
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 16.17$, df = 13 (P = 0.24); $I^2 = 20\%$

Test for overall effect: Z = 4.10 (P < 0.0001)



Studies included multiple times

We considered statistical heterogeneity between trials to be substantial if, following meta-analysis, I^2 was greater than 30% and either T^2 is greater than zero, or there was a low P-value (< 0.10) in the Chi^2 test for heterogeneity. If substantial heterogeneity was identified used the random-effects (RE) model instead of the fixed-effects (FE) model to pool data.



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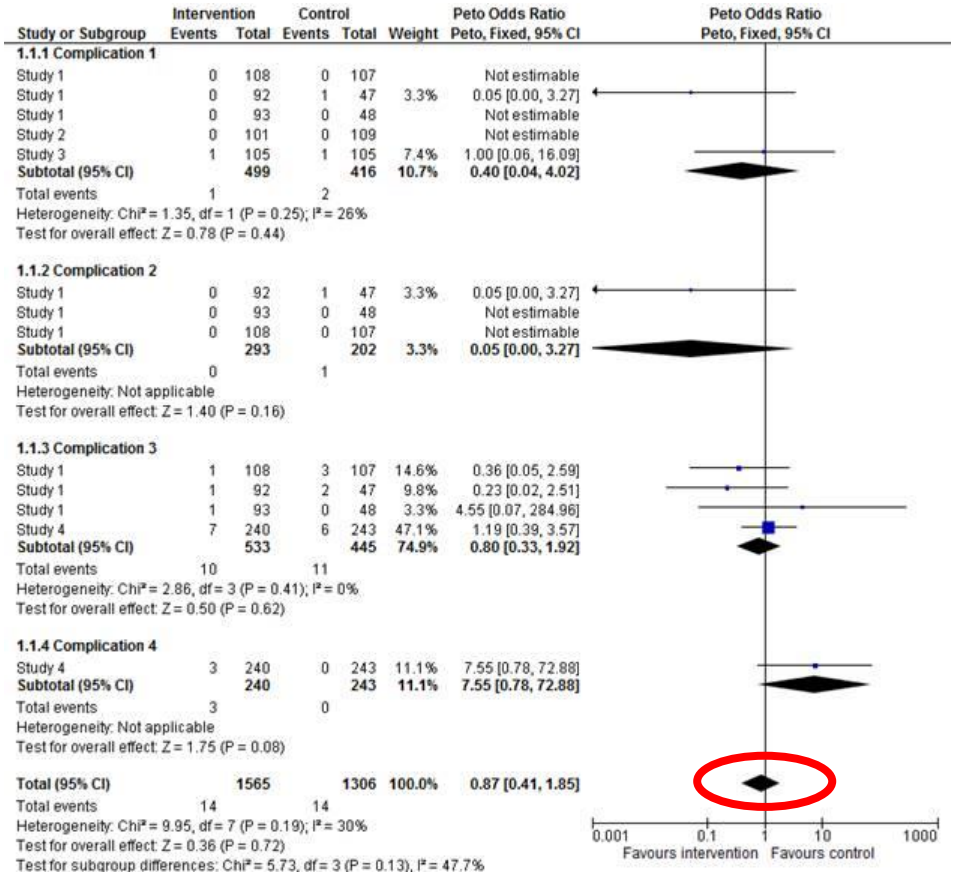
Risk of Bias

- Sequence generation
  - Often inconsistencies within reviews
- Allocation concealment
  - Often confused with blinding
- Blinding
- Incomplete outcome data
  - Often incompletely addressed
- Selective reporting
  - Often confused with incomplete outcome data
  - Reviewers do not know how to address this

Interpretation

- Confusion of risk and odds
- Conclusions don’t match results and SoF tables
- Spin
- Over interpretation of high risk of bias trials



Pooled effect was based on more participants than were recruited and was presented in the SoF table, abstract, PLS

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Errors we may not see

- Have any papers been missed?
- Have the right results been copied from the papers?
- Have the standard deviations been confused with standard errors?

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Ways of avoiding/fixing the problems

- Experienced reviewers
- Tuition
- Peer review
- Statistician as an author on every review?

Statistical contribution to CRGs

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Refereeing

- Protocols?
- Reviews
  - New, updates, all or a selection?

- Check every number?
- Read original papers?
- Do analyses for reviewers?

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- Numbers that stand out (perfect homogeneity, single outlying results, sample size does not match with precision relative to other studies)

- For non-standard RCT designs - evidence of how SEs were adjusted (check methods against plots).

- For primary outcomes select the biggest study or the one that has most weight and check the analysis results against the paper.

- For other outcomes pick a study entirely at random and check numbers used against what is available in published trial report or elsewhere. If authors have stated that they got unpublished data then move on to next study.

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Feedback

- Constructive feedback
- Do you see reviewers responses to comments and changes made?
- Final sign off by a statistician?

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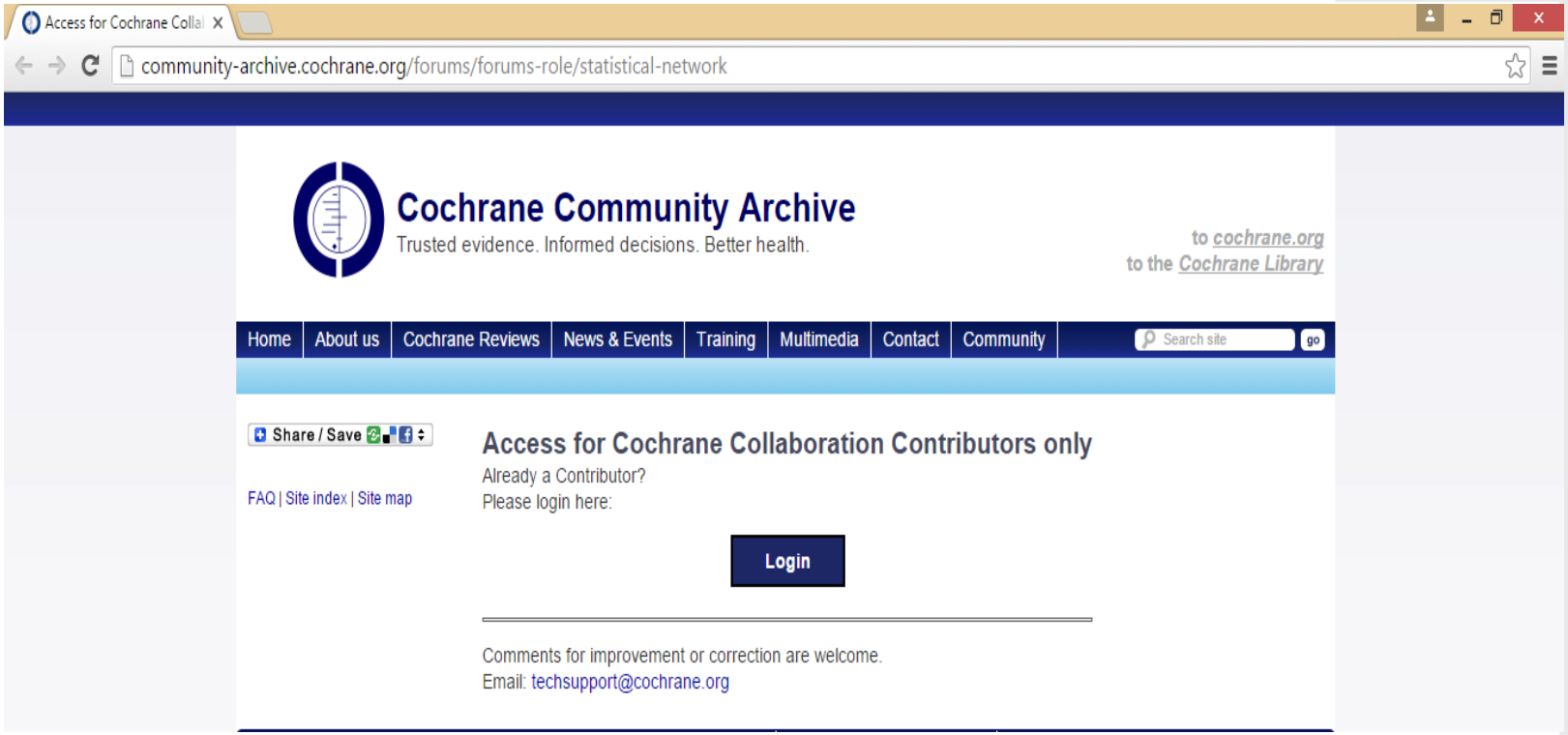
Forum



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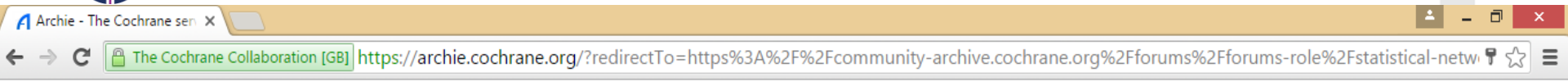

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Submitted by Kerry Dwan on 23 April 2015 - 2:13pm CEST Statistical Network

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Training/help/advice

- What training needs do you have?
- Should there be a mentoring process?
- Exemplar reviews?