Assessing the risk of outcome reporting bias in systematic reviews

Kerry Dwan (kdwan@liv.ac.uk)

Jamie Kirkham (jjk@liv.ac.uk)

Definition: Outcome Reporting Bias

Definition: Selection of a subset of the original recorded outcomes, on the basis of the results, for inclusion in publication

Non-ignorable missing data problem

Types of selective reporting

- Outcomes
- Subgroups
- Adjusted versus unadjusted results
- Prognostic or risk factors
- Handling of continuous data
- PP rather than ITT
- Handling of missing data

*Selective reporting of analyses

*Dwan et al. 2014; PLoS Medicine

Types of selective outcome reporting

- **Selective reporting of the set of study outcomes**
  - Not all analysed outcomes are reported

- **Selective reporting of a specific outcome**
  - Hutton and Williamson (2000)
  - Selection from multiple time points
  - Subscales
  - Endpoint score versus change from baseline
  - Continuous versus binary (choice of cut-offs)
  - Different measures of same outcome, e.g. pain

- **Incomplete reporting of a specific outcome**
  - e.g. "Not significant" or "p>0.05"

Selective reporting of the set of study outcomes

- Not all analysed outcomes in a trial are reported

- Trial in your review does not report review outcome of interest

- Potentially a missing data problem if measured and analysed but not reported – similar impact to publication bias i.e. non-publication of whole studies

Empirical Evidence of ORB

PLOS | ONE

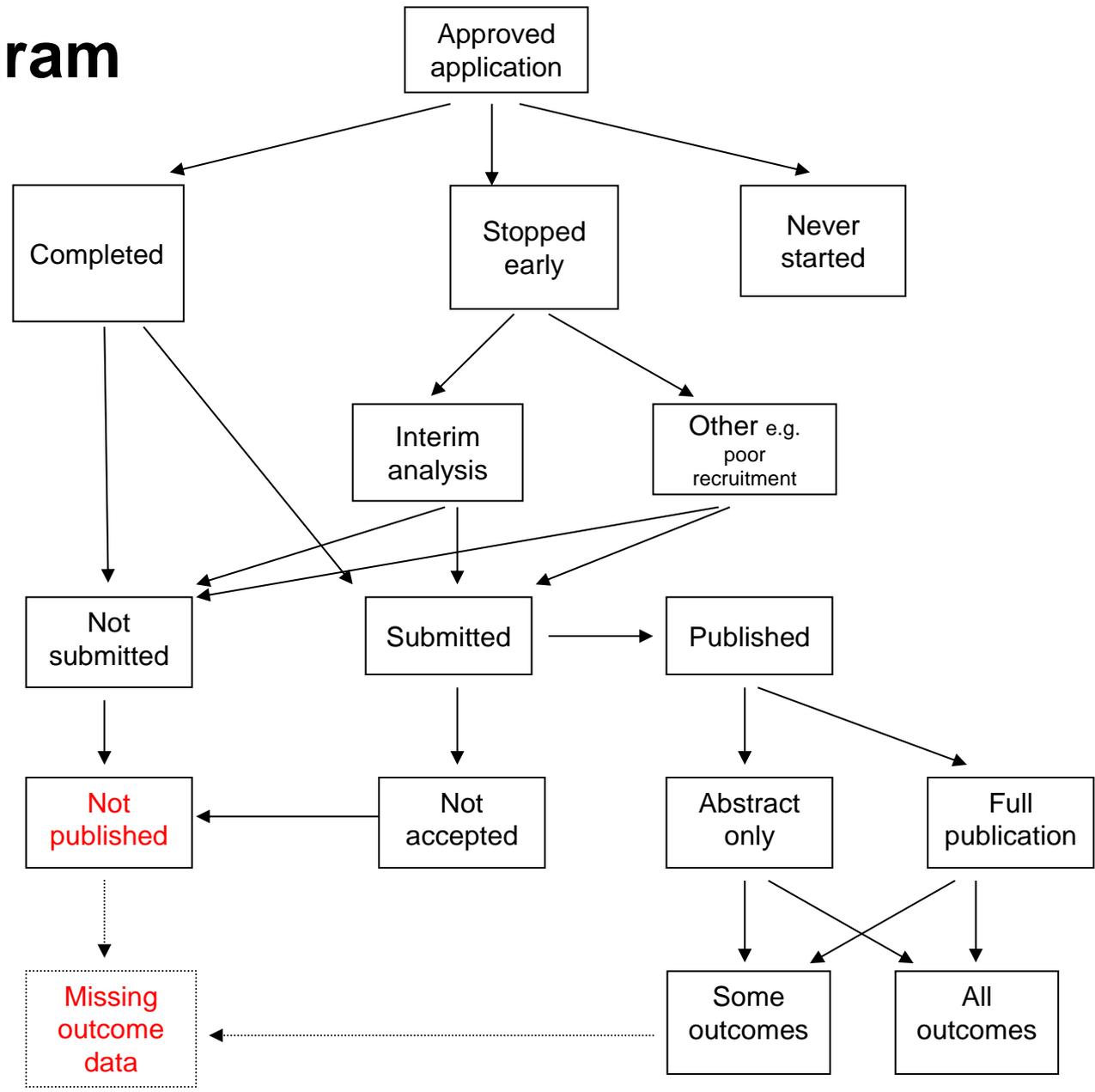## Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias — An Updated Review

Kerry Dwan*, Carrol Gamble, Paula R. Williamson, Jamie J. Kirkham, for the Reporting Bias Group[¶]

Department of Biostatistics, University of Liverpool, Liverpool, England

- Statistically significant outcomes more likely to be fully reported: OR 2.2 to 4.7 (Dwan et al, 2013)

Trial Flow Diagram

Approved application

Completed

Stopped early

Never started

Interim analysis

Other e.g. poor recruitment

Not submitted

Submitted

Published

Publication Bias ⇦ Not published

Not accepted

Abstract only

Full publication
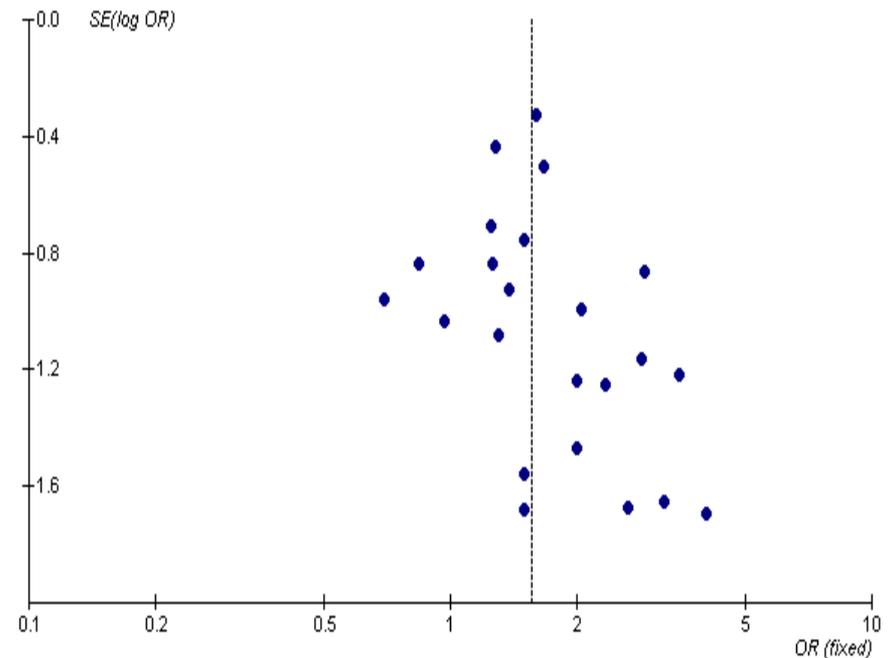
ORB ⇦ Missing outcome data

Some outcomes

All outcomes

Impact of ORB
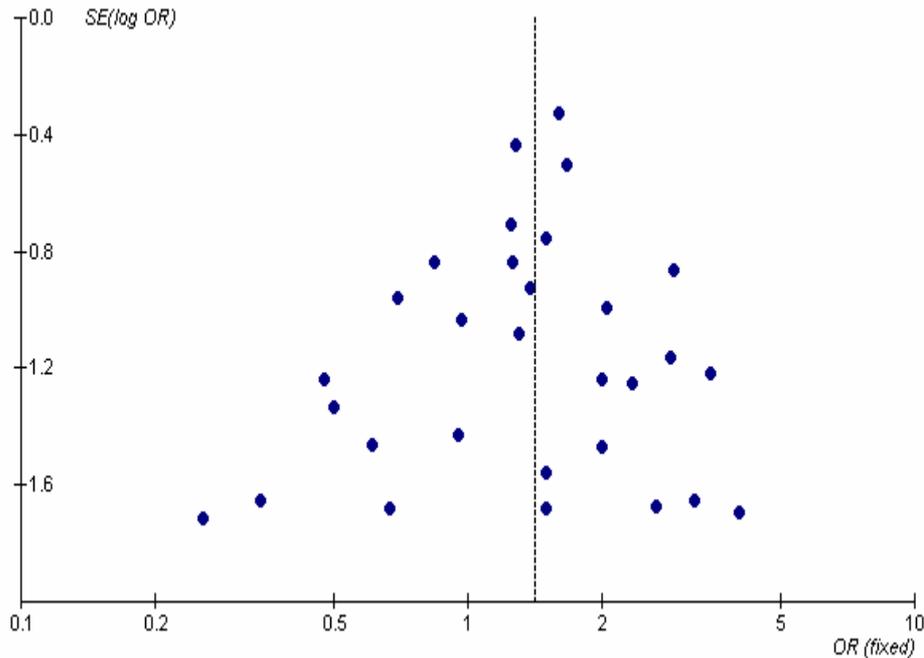
OR 1.41 (1.04,1.91)

OR 1.55 (1.13,2.14)

Empirical Evidence

Study	Study level
	Are studies with statistically significant or positive results, more likely to be published than those finding no difference between the study group?
Easterbrook, 1991	OR 2.32, 95% CI; 1.25, 4.28.
Dickersin, 1992	OR 2.54, 95% CI; 1.63, 3.94
Dickersin, 1993	OR 12.30, 95% CI; 2.54, 60
Stern, 1997	HR 2.32, 95% CI; 1.47, 3.66, p=0.0003
Cooper, 1997	p<0.0001 (submission only)
Wormald, 1997	RR 4, 95% CI; 0.6, 32, p=0.10
Ioannidis, 1998	*
Pich, 2003	*
Cronin, 2004	OR 0.53, 95% CI; 0.25, 1.1 p=0.1
Decullier, 2005	OR 4.59, 95% CI; 2.21, 9.54
Decullier, 2006	OR 1.58, 95% CI; 0.37, 6.71

Empirical Evidence

Study	Outcome level				
	Primary outcome stated in protocol is the same as in the publication	Primary outcome stated in protocol is downgraded to secondary in the publication	Primary outcome stated in the protocol is omitted from the publication	Non primary outcome in the protocol is changed to primary in the publication	New primary outcome that was not stated in the protocol is included in the publication
Hahn, 2002	27% (4/15)	*	17% (1/6)	*	17% (1/6)
Chan, 2004a	67% (32/ 48)	23% (11/48)	13% (6/48)	9% (4/45)	18% (8/45)
Chan, 2004b	47% (36/76)	34% (26/76)	26% (20/76)	19% (12/63)	17% (11/63)
Ghersi, 2006	74% (143/194)	*	16% (31/194)	*	10% (20/194)
Von Elm, 2008	*	*	26% (24/92)	*	11% (11/101)
Smyth, 2010	90% (19/21)	5% (1/21)	5% (1/21)	5% (1/21)	5% (1/21)

Assessment within review

- Exclusion criteria should not include 'did not report outcome data of interest'

- Number of eligible trials > number included in MA/ fully reported in the text

- Orbit matrix generator:

   http://ctrc.liv.ac.uk/orbit/

Interventions for Burkitt's lymphoma in children

http://ctrc.liv.ac.uk/orbit/

Trial ID (author, date of publication)	Review primary outcome Overall survival	Review Outcomes				
		Event-free survival	Overall remission rate	Relapse rate	Toxicity and adverse events	Quality of life
Anderson 1983	✗	✗	✗	✗	✗	✗
Brecher 1997	✓	✓	✓	✗	✓	✗
Cairo 2003a	✗	O	✗	✗	✗	✗
Magrath 1973	✗	✗	✗	✓	✗	✗
Magrath 1976	✓	✗	✗	✓	✗	✗
Neequaye 1990	✓	✗	✗	✓	✗	✗
Olweny 1976	✓	✗	✓	✓	✗	✗
Olweny 1977	✓	✗	✗	✓	✓	✗
Patte 1991	✓	✓	O	✗	✓	✗
Sullivan 1991	✗	✓	✗	✗	✗	✗
Ziegler 1971	✗	✗	✗	✓	✗	✗
Ziegler 1971	✓	✗	✗	✓	✗	✗

ORBIT classification system

- **Clear that the outcome was measured and analysed**

Classification	Description	Level of reporting	Risk of bias
A	States outcome analysed but only reported that result not significant (typically stating p-value >0.05)	Partial	High Risk
B	States outcome analysed but only reported that result significant (typically stating p-value <0.05).	Partial	No Risk
C	States outcome analysed but insufficient data presented to be included in meta-analysis or to be considered to be fully tabulated.	Partial	Low Risk
D	States outcome analysed but no results reported.	None	High Risk

ORBIT classification system

- **Clear that the outcome was measured but not necessarily analysed**

Classification	Description	Level of reporting	Risk of bias
E	Clear that outcome was measured but not necessarily analysed. Judgment says likely to have been analysed but not reported because of non-significant results	None	High Risk
F	Clear that outcome was measured but not necessarily analysed. Judgment says unlikely to have been analysed but not reported because of non-significant results	None	Low Risk

Examples

   E : **Outcome – Overall mortality:** Trial reports on cause-specific mortality only.

   F : **Ongoing study** – outcome being measured but no reason to suggest outcome analysed at current time

ORBIT classification system

- **Unclear whether the outcome was measured**

Classification	Description	Level of reporting	Risk of bias
G	Not mentioned but clinical judgment says likely to have been measured and analysed.	None	High Risk
H	Not mentioned but clinical judgment says unlikely to have been measured.	None	Low Risk

Examples
- G : Strong belief that the PO would have been measured, e.g. Overall survival/Mortality in trials in Cancer/Aids patients
- H : Follow-up appears to be too short to measure the PO, e.g. PO is live birth rate and the trial reports only on pre-birth outcomes

ORBIT classification system

- Clear the outcome was not measured

Classification	Description	Level of reporting	Risk of bias
I	Clear that outcome was not measured.	N/A	No Risk

Examples

I : **Outcome – Muscle Strength:** "No measurements of muscle strength were taken because the assessment of muscle strength with hemiparetic subjects is very difficult".

Assessment for individual study

- **Review trial report**
  - how likely to have been selectively not reported?
  - methods section, results section
  - incomplete reporting of outcomes
  - related outcomes reported
    (e.g. cause-specific and overall mortality)
  - battery of tests usually taken together
    (e.g. systolic and diastolic blood pressure)
  - knowledge of area suggests it is likely

- **Trial protocol – search PubMed and web (www.who.int/trialsearch)**
- **Trial registry**

- **Abstracts of presentations – mention outcomes not reported in trial report?**

Example Review: Human Albumin (2002, Issue 1)
Outcome: death for subgroup hypoalbuminaemia

- 18 (763 individuals) eligible, 16 (719 (94%)) included

- Pooled OR (95% CI): 1.51 (0.82, 2.77)

- Two trials with no data: no information in either report to indicate outcome recorded, however knowledge of clinical area suggests data would be collected routinely

- Classification G

- For one of the included studies, interim report (n=52) reported outcome (significant difference) whereas full report (n=94) did not.

- Original MA included preliminary data.

Reviews with no suspicion of ORB in review primary outcome	Reviews requiring further assessment of review primary outcome
126 (557 trials)	**157 (2005 trials)**

Trials fully reporting review primary outcome **557**	Trials fully reporting review primary outcome in review and trial report:	1040	Total trials partially/ not reporting on review primary outcome:	**788**
	Trials fully reporting review primary outcome in trial report only:	177	Could not assess trial reports (Non-English):	76
	Total trials reporting on the review primary outcome:	**1217**	Total trials for ORB assessment:	**712**
			Trials included in review:	*545*
			Trials excluded from review (NROD):	*167*

Total number of trials reporting on the review primary outcome

1774

ORBIT - what was assessed?

Sensitivity and Specificity

- **Was the review primary outcome measured?**

			Information from trialist		
			Primary outcome measured	Primary outcome not measured	
ORBIT assessment	Primary outcome measured	G-classification	4	7	11
		G-classification (no event)	19	0	19
		Total	**23**	**7**	**30**
	Primary outcome not measured	H-classification	2	23	25
			25	**30**	**55**

Sensitivity: 92% (23/25, 95% CI 81%, 100%)
Specificity: 77% (23/30, 95% CI 62%, 92%)

Sensitivity and Specificity

Did ORB occur?

			Information from trialist		
			Bias	No Bias	
ORBIT assessment	Primary outcome measured	Bias (E and G classification)	7	11	18
	Primary outcome not measured	No Bias (F and H classification)	1	43	44
			8	**54**	**62**

- **Sensitivity: 88% (7/8, 95% CI 65%, 100%)**
- **Specificity: 80% (43/54, 95% CI 69%, 90%)**

Results

Classification		Total n (%*)	
A :	Analysed p>0.05	30	(4)
B:	Analysed p<0.05	8	(1)
C:	Analysed but insufficient for MA	117	(16)
D:	Analysed but no results reported	0	(0)
E:	Measured but not necessarily analysed (High Risk)	122	(17)
F:	Measured but not necessarily analysed (Low Risk)	33	(5)
G:	Not mentioned – LIKELY measured	207	(29)
H:	Not mentioned – UNLIKELY measured	176	(25)
I:	Outcome NOT measured	19	(3)

* Calculated as a percentage of all trials with an ORB classification (712)

ORBIT: key messages

- ORB suspected in at least one trial in 34% of 283 Cochrane reviews (Kirkham, 2010)

- 42 significant meta-analyses
  - 8 (19%) would not have remained significant
  - 11 (26%) would have overestimated the treatment effect by > 20%

- Review primary outcome less likely to be prone to ORB than other outcomes
  - under-recognition of the problem

- Interviews with trialists: 29% trials displayed ORB (Smyth, 2010)

Group exercise

Melatonin review BMJ 2006

- Management of secondary sleep disorders
- Sleep onset latency: the time between lying down to sleep and beginning of sleep

- Nine studies identified
  - 3 studies did not report sleep onset latency
  - 6 studies included in meta-analysis
  - Mean difference -13.22 (95% CI: -27.33, 0.89, random effects model)

- Author's conclusions: Favoured melatonin but not significant

Sleep onset latency forest plot
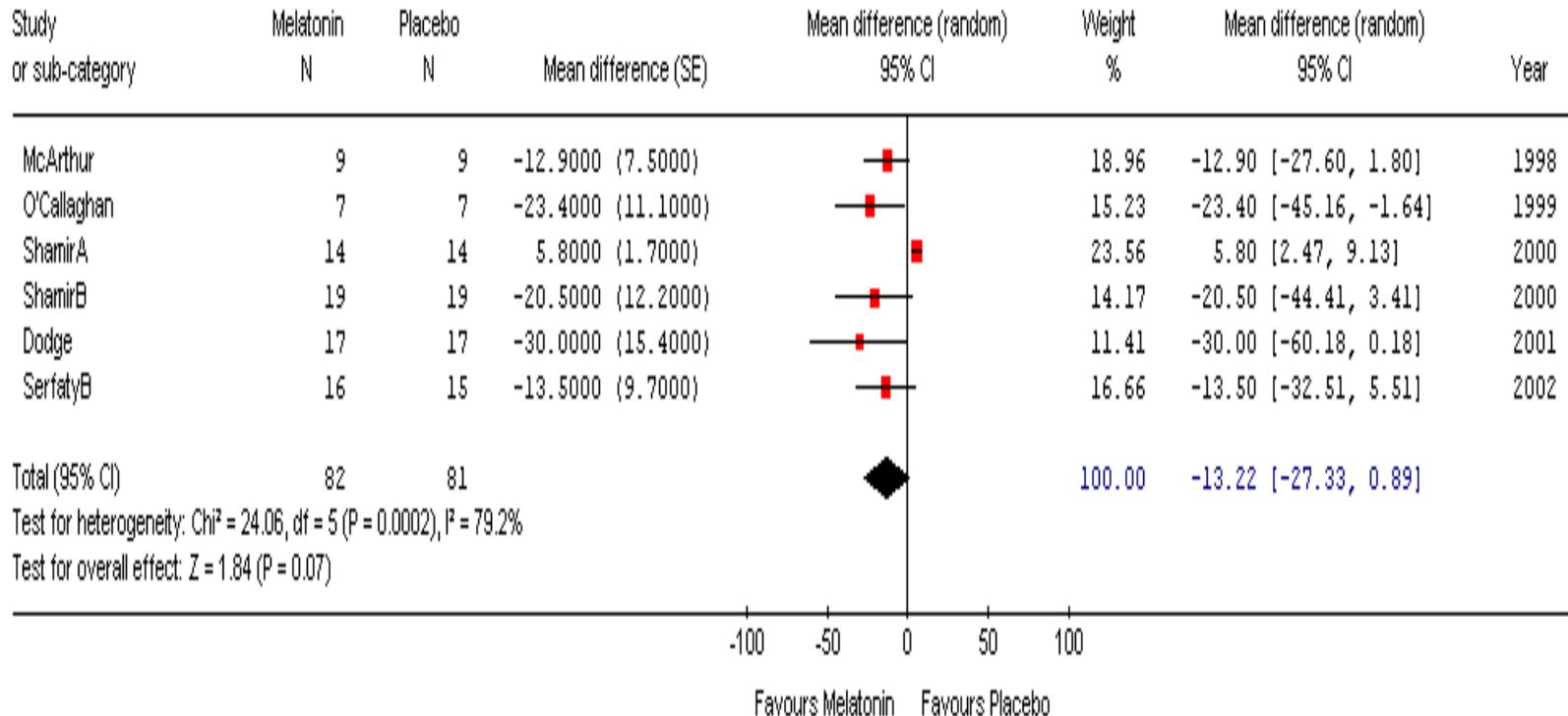
ORBIT classification system

Classification	Description	Level of reporting	Level of suspicion of ORB
	Clear that the outcome was measured and analysed		
A	States outcome analysed but only reported that result not significant (typically stating p-value >0.05).	Partial	High risk
B	States outcome analysed but only reported that result significant (typically stating p-value <0.05).	Partial	Low risk
C	States outcome analysed but insufficient data presented to be included in meta-analysis or to be considered to be fully tabulated.	Partial	Low risk
D	States outcome analysed but no results reported.	None	High risk
	Clear that the outcome was measured		
E	Clear that outcome was measured but not necessarily analysed. Judgment says likely to have been analysed but not reported because of non-significant results	None	High risk
F	Clear that outcome was measured but not necessarily analysed. Judgment says unlikely to have been analysed but not reported because of non-significant results	None	Low risk
	Unclear that the outcome was measured		
G	Not mentioned but clinical judgment says likely to have been measured and analysed.	None	High risk
H	Not mentioned but clinical judgment says unlikely to have been measured.	None	Low risk
	Clear that the outcome was NOT measured		
I	Clear that outcome was not measured.	N/A	No risk

Feedback

Melatonin review
Singer, 2003

- N=151

- Did not report sleep onset latency

- Paper stated: could not reliably determine sleep latency in a large multi centre trial and chose not to include as a primary outcome

- When contacted by us, they reiterated this was as per protocol

Serfaty, 2002

- N=25
- Did not report sleep onset latency
- Paper stated: carers recorded bed time and sleep onset time in a daily diary
- p>0.05 for all reported outcomes

- When contacted by us, results were supplied
- Analysis supplied indicated sleep onset latency was not statistically significant (p=0.23)
- Awaiting response regarding reason for lack of inclusion
- A different trial by the same researcher reported sleep onset latency (2003)

Van Wieringen, 2001

- N=81

- Did not report total sleep time or onset latency
- Paper stated in methods section: main outcome measures are sleep onset, sleep onset latency and sleep duration
- Paper stated in results section: No significant treatment interaction effect found for the polysomnography and diary parameters
- $p<0.05$ for lights off time, waking time and for melatonin secretion

- When contacted by us, IPD were supplied
- $p>0.05$ for sleep onset latency and total sleep time
- Reason for not reporting outcomes: "Melatonin advanced sleep onset, but did not influence sleep onset latency significantly and this was because patients were allowed to go to bed when they wanted. Later discovered they were important."

Reporting bias due to selective outcome reporting

Melatonin trials: as published/**all information**

Trial	Judgement	Text
Van Wieringen	High risk Low risk	Reported as P>0.05 IPD were supplied by authors
Serfaty	High risk(?) Low risk	Data were available but not analysed Results were supplied by authors
Singer	High risk(?) Low risk	Outcome not reliably determined Reiterated by the author as per protocol

"One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis"

"The study report fails to include results for a key outcome that would be expected to have been reported for such a study"

Solutions to ORB

Non-Statistical Solutions

- Obtain the missing outcome data

Statistical Solutions (sensitivity analyses)

- Bound for maximum bias (*Williamson and Gamble* 2007; 8:9)
- Multivariate meta-analysis (*Kirkham et al.* (2012); 31(20): 2179-2195)
- Explicit modelling techniques (*Copas et al.* 2014; 15(2): 370-383)
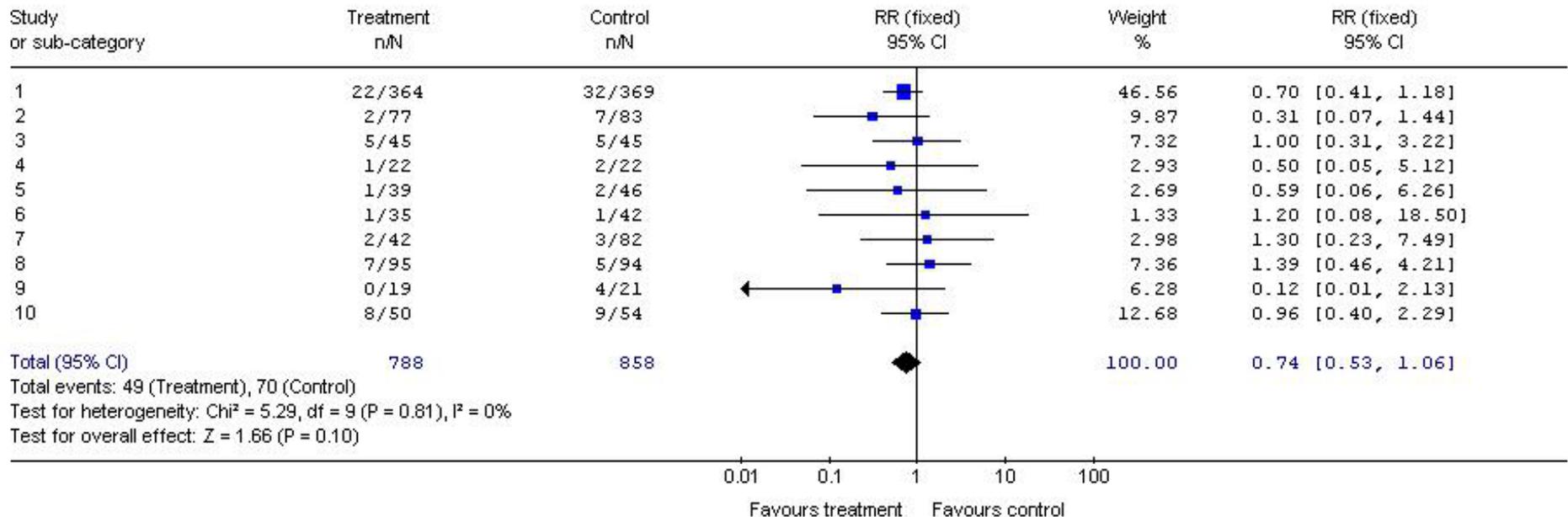- Other methods, e.g. regression approaches

Sensitivity analysis results

- Sleep onset latency

    - Original meta-analysis:
    MD -13.2 (-27.3, 0.89)

    - Sensitivity analysis:
    MD -3.5 (-17.6, 10.6)

- Results far less favourable to melatonin

MVMA – a practical example (within-study correlations unknown)

- Two binary outcomes of interest: TF and mortality
- 15 eligible trials all reported TF: pooled RR
  - (95% CI) of 1.11 (1.02, 1.21) [favours combination]

Review: Example
Comparison: 01 Treatment versus control
Outcome: 01 Mortality

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
1	22/364	32/369		46.56	0.70 [0.41, 1.18]
2	2/77	7/83		9.87	0.31 [0.07, 1.44]
3	5/45	5/45		7.32	1.00 [0.31, 3.22]
4	1/22	2/22		2.93	0.50 [0.05, 5.12]
5	1/39	2/46		2.69	0.59 [0.06, 6.26]
6	1/35	1/42		1.33	1.20 [0.08, 18.50]
7	2/42	3/82		2.98	1.30 [0.23, 7.49]
8	7/95	5/94		7.36	1.39 [0.46, 4.21]
9	0/19	4/21		6.28	0.12 [0.01, 2.13]
10	8/50	9/54		12.68	0.96 [0.40, 2.29]
Total (95% CI)	788	858		100.00	0.74 [0.53, 1.06]

Total events: 49 (Treatment), 70 (Control)
Test for heterogeneity: Chi² = 5.29, df = 9 (P = 0.81), I² = 0%
Test for overall effect: Z = 1.66 (P = 0.10)

0.01   0.1   1   10   100
Favours treatment   Favours control

MVMA – a practical example

Review: Example
Comparison: 02 Treatment versus control
Outcome: 01 Treatment Failure

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
01 Both outcomes					
1	188/370	188/384		33.72	1.04 [0.90, 1.20]
2	48/77	59/83		10.38	0.88 [0.70, 1.09]
3	19/36	18/33		3.43	0.97 [0.62, 1.50]

?Some of the trials reporting only treatment failure did so because the results were statistically significant whereas the all-cause mortality results were not and were suppressed?

12	10/35	3/32		0.57	3.05 [0.92, 10.10]
13	67/77	50/69		9.64	1.20 [1.01, 1.42]
14	130/378	99/372		18.24	1.29 [1.04, 1.61]
15	14/35	12/36		2.16	1.20 [0.65, 2.22]
Subtotal (95% CI)	571	554		31.53	1.33 [1.15, 1.55]

Total events: 235 (Treatment), 169 (Control)
Test for heterogeneity: Chi² = 5.75, df = 4 (P = 0.22), I² = 30.5%
Test for overall effect: Z = 3.78 (P = 0.0002)

Total (95% CI)	1355	1406		100.00	1.11 [1.02, 1.21]

Total events: 603 (Treatment), 561 (Control)
Test for heterogeneity: Chi² = 17.00, df = 14 (P = 0.26), I² = 17.7%
Test for overall effect: Z = 2.50 (P = 0.01)

0.01   0.1   1   10   100

Favours treatment   Favours control

MVMA – a practical example (fixed effect meta-analysis)

Model		All-cause Mortality (b_1)				Treatment Failure (b_2)			
		Pooled Risk Ratio	Standard Error	P-value	95% Confidence Interval	Pooled Risk Ratio	Standard Error	P-value	95% Confidence Interval
UFMA	0	0.778	0.182	0.168	(0.545, 1.111)	1.095	0.040	0.024	(1.012, 1.184)
BFMA	0.021 (impute)	0.782	0.182	0.177	(0.548, 1.117)	1.095	0.040	0.024	(1.012, 1.184)
BFMA	0.2	0.818	0.180	0.264	(0.575, 1.164)	1.097	0.040	0.020	(1.015, 1.187)
BFMA	0.309 (impute)	0.841	0.178	0.330	(0.594, 1.191)	1.099	0.040	0.018	(1.016, 1.188)
BFMA	0.4	0.861	0.175	0.393	(0.611, 1.213)	1.099	0.040	0.017	(1.017, 1.189)
BFMA	0.6	0.909	0.165	0.561	(0.657, 1.256)	1.101	0.039	0.014	(1.020, 1.189)
BFMA	0.7	0.933	0.158	0.662	(0.685, 1.271)	1.101	0.038	0.012	(1.021, 1.188)
BFMA	0.8	0.959	0.147	0.775	(0.718, 1.280)	1.102	0.037	0.010	(1.024, 1.185)

Solutions Summary

- Trial level
(i) Education
(ii) Core outcome sets
(iii) Better reporting - CONSORT statement, submission of protocol with manuscript (Lancet, BMJ, PLoS Med) and EQUATOR (http://www.equator-network.org/)
(iv) Reporting of legitimate outcome changes (Evans, 2007)
(v) RECs (substantial protocol amendments)
(vi) Trial and protocol registration
(vii) FDA legislation – outcome results to be made available. Need for comprehensive worldwide adoption
(viii) Funders (Guidelines)

- Review level
(i) Risk of bias assessment in Cochrane reviews
(ii) Individual patient data repository (feasibility project)
(iii) Core outcome sets
(iv) Statistical methods

ORBIT: key messages

- **Systematic review primary outcome data**
    - missing in 25% eligible trials in Cochrane reviews
    - missing in at least one trial in 55% reviews
    - a wasted opportunity?

- **Interviews with trialists about outcomes in protocol but not trial report:**
    - outcomes not measured
    - outcomes measured but not analysed
    - general lack of clarity about importance and/or feasibility of data collection for outcomes chosen

Conclusions

- Awareness of ORB is limited but the problem must receive as much attention as between-study selection bias

- Reviewers must consider the amount of, and reasons for, data potentially missing from a meta-analysis

- To boost confidence in the review, we recommend the sensitivity of the conclusions to plausible biases should be investigated

- If robustness is lacking, present and interpret correctly both the original meta-analysis which assumes no selective reporting and the sensitivity analysis, including a description of the assumptions made regarding the nature of selection.

References – empirical evidence

1. Hahn S, Williamson PR and Hutton JL. Investigation of within-study selective reporting in clinical research: follow-up of applications submitted to an LREC. Journal of Evaluation in Clinical Practice 2002; **8.3** (August).
2. Dwan K, Altman DG, Clarke M, Gamble C, Higgins JPT, Sterne JAC, Williamson PR, Kirkham JJ. Evidence for the selective reporting of analyses and discrepancies in clinical trials: a systematic review of cohort studies of clinical trials. *PLoS Medicine* 2014; **11**(6):e1001666.
3. Chan A-W, Hrbjartsson A, Haahr M, Gtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: Comparison of protocols to publications. JAMA 2004; 291: 2457-2465.
4. Dundar Y, Dodd S, Williamson PR, Dickson R, Walley T. (2006) Case study of the comparison of data from conference abstracts and full-text articles in health technology assessment of rapidly evolving technologies- does it make a difference? International Journal of Technology Assessment in Health Care 22(3): 288-94.
5. Chan AW, Krleza-Jeric K, Schmid I, Altman DG. Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research. *CMAJ* 2004;171 (7): 735-740.
6. Chan AW and Altman DG. Identifying outcome reporting bias in randomised trials on Pubmed: review of publications and survey of authors. *BMJ* 2005; 330: 753-758.
7. Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan A-W, et al. (2013) Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias - An Updated Review. PLoS ONE 8(7):e66844.
8. Smyth RMD, Jacoby A, Altman DG, Gamble C, Kirkham JJ, Williamson PR (2011) Frequency and reasons for outcome reporting bias in clinical trials: interviews with trialists. BMJ, 6;342:c7153

References – methodological

1. Williamson PR and Gamble C. Application and investigation of a bound for outcome reporting bias. *Trials* 2007, **8:**9.
2. Williamson PR, Gamble C, Altman DG and JL Hutton. (2005) Outcome selection bias in meta-analysis. *Statistical Methods in Medical Research*, 14: 515-524.
3. Williamson PR and Gamble C. (2005) Identification and impact of outcome selection bias in meta-analysis. *Statistics in Medicine*, 24: 1547-1561.
4. Hutton JL and Williamson PR. Bias in meta-analysis due to outcome variable selection within studies. *Applied Statistics* 2000*;* **49**: 359-370.
5. Hahn S, Williamson PR, Hutton JL, Garner P and Flynn EV. Assessing the potential for bias in meta-analysis due to selective reporting of subgroup analyses within studies. *Statistics in Medicine* 2000*;* **19**: 3325-3336.
6. Evans S. When and how can endpoints be changed after initiation of a randomized clinical trial? *PLoS Clinical Trials* 2007; e18
7. Sinha I, Jones L, Smyth RL, Williamson PR. A Systematic Review of Studies That Aim to Determine Which Outcomes to Measure in Clinical Trials in Children. *PLoS Medicine* 2008;Vol. 5, No. 4, e96
8. Kirkham JJ, Dwan K, Dodd S, Altman DG, Smyth R, Jacoby A, Gamble C, Williamson PR. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ* 2010;340:c365
9. Dwan K, Gamble C, Kolamunnage-Dona R, Mohammed S, Powell C, Williamson PR. Assessing the potential for outcome reporting bias in a review: A tutorial. *Trials 2010,* **11:**52 doi:10.1186/1745-6215-11-52
10. Copas J, Dwan KM, Kirkham JJ, Williamson PR. A model-based correction for outcome reporting bias in meta-analysis. *Biostatistics* 2014; **15**(2): 370-383.
11. Kirkham JJ, Riley RD, Williamson PR. A multivariate meta-analysis solution for reducing the impact of outcome reporting bias in systematic reviews. *Statistics in Medicine* (2012); **31**(20): 2179-2195.