### **Meta-analysis and Forest plots**

Chris Cates 2017



## Learning Objectives

- 1. Understand why we need Meta-analyses
- 2. Describe the difference between a Systematic Review and a Meta-analysis
- 3. Interpret the results of a Meta-analysis as shown in a Forest plot
- Appreciate how to use Relative Risks and Control Group Event Rates to compare risks and benefits of treatment

## Clinical Scenario (from last week)

- A pregnant mother comes into A&E with an asthma exacerbation
- There is a debate between the Obstetric and the Respiratory teams
- She is not responding well to oral steroids and nebulised salbutamol
- "Should we add magnesium solution to the nebuliser when delivering nebulised salbutamol?"

## A difference of opinion

- The Obstetrician has read a Cochrane review showing how well nebulised magnesium works in acute asthma in pregnancy
- The Respiratory physician is not impressed with the evidence for nebulised magnesium in acute asthma adults

## Where to go next?

- The A& E Consultant rings you up
- Could you have a look at the evidence and help formulate a policy for the department?

## Assessing the impact of treatment

- Patients
- Intervention
- Comparison
- Outcomes
- Study Design

## Defining the Question

- In pregnant mothers with asthma, who have not had a good response to nebulised salbutamol and oral corticosteroids
- Does the addition of magnesium to the nebulised salbutamol
- Compared to continuing nebulised salbutamol
- Have and impact on
  - The risk of Hospitalisation
  - Improvement in Lung Function

## Steps in the process

- 1. Define an answerable question
- 2. Search for suitable evidence
- 3. Assess the quality of the evidence
- 4. Describe the results
- 5. Interpret the findings
- 6. Decide if practice needs to be changed

## How can Cochrane Reviews help?

- Cochrane Systematic Reviews use transparent processes that are published in advance as protocols
- They aim to IDENTIFY, ASSESS, SYTHESIZE and APPLY the results of Controlled Clinical Trials addressing a defined question

Hospital Librarian finds a Cochrane review on acute asthma in pregnancy

 You have had a chance to read the Badawy paper on nebulised magnesium in pregnant mothers with acute asthma from this review

### 2. What were the findings in this trial?

Badawy MSH, Hassanin IMA. The value of magnesium sulfate nebulization in treatment of acute bronchial asthma during pregnancy. Egyptian Journal of Chest Diseases and Tuberculosis 2014;**63**(2):285-89 doi: 10.1016/j.ejcdt.2013.12.011 http://www.sciencedirect.com/science/article/pii/S0422763813003129

#### Post Rx % predicted FEV1in Badawy trial



What does this Forest plot show? How many patients in each group? Mean % predicted FEV1 from each group? Mean difference in % predicted FEV1? Which treatment looks better? How much better? How sure are you? (Direction, Size and Uncertainty)

#### Post Rx % predicted FEV1in Badawy trial



## This is a pretty impressive treatment effect

### P value and its limitations

- P < 0.0001 means what?
- If the null hypothesis is true ......
- Then this result (or one more extreme) can be expected less than once in 10,000 due to the play of chance.
- How likely is it that the null is true?

### 95% Confidence Interval

- Is where we are 95% sure that the true population treatment effect lies
- This is the "precision" of the estimate of the treatment effect
- Narrow confidence intervals give a more precise estimate

#### Post Rx % predicted FEV1in Badawy trial



What does this Forest plot show? How many patients in each group? Mean % predicted FEV1 from each group? Mean difference in % predicted FEV1? Which treatment looks better? How much better? How sure are you? (Direction, Size and Uncertainty)

## What about the other trials?

- Don't just rely on the results of a single trial
- How does this trial compare to the other trials?
- Knightly R, Milan SJ, Hughes R, Knopp-Sihota JA, Rowe BH, Normansell R, Powell C. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD003898. DOI: 10.1002/14651858.CD003898.pub6

	MgS	50, + SAB	A		SABA			Mean Difference	Mean Difference
Study or Subgroup	Mean	<sup>™</sup> SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% CI
2.2.1 Adults									
Bessmertny 2002 (1)	63	21.9	37	68	21.9	37	24.3%	-5.00 [-14.98, 4.98]	
Hughes 2003 (2)	51.2	17.2788	28	41.3	18.7087	24	25.0%	9.90 [0.05, 19.75]	
Sarhan 2016 (3)	51.2	9.8	10	49.6	10.3	10	31.2%	1.60 [-7.21, 10.41]	
Subtotal (95% CI)			75			71	80.5%	2.18 [-3.30, 7.67]	
Heterogeneity: Chi <sup>2</sup> = 4	.37, df =	2 (P = 0.1	1); I² = !	54%					
Test for overall effect: Z	.= 0.78 (I	P = 0.44)							
<b>2.2.2 Children</b> Mahajan 2004 (4) <b>Subtotal (95% Cl)</b> Heterogeneity: Not app Test for overall effect: Z	75.4 Iicable (= 1.43 (I	26 P = 0.15)	31 <b>31</b>	67.3	18	31 <b>31</b>	19.5% <b>19.5</b> %	8.10 [-3.03, 19.23] <b>8.10 [-3.03, 19.23]</b>	
Total (95% CI)			106			102	100.0%	3.34 [-1.58, 8,26]	
Heterogeneity: Chi <sup>2</sup> = 5	24 df=	3(P = 0.1)	6): I <b>2</b> = 7	43%		102	1001070		-+++
Test for overall effect: Z	(= 1.33 (	P = 0.18)	-// ·						-20 -10 0 10 20
Test for subgroup diffe	rences: (		'. df = 1	(P = 0.3)	35), I <b>²</b> = 0%	6			Favours SABA alone Favours Mg504 + SABA
Footnotes									
(1) 65 mins from basel	ine								
(2) At 90 min from base	eline (30	min after f	the thir	d admin	istration o	f the st	udy drug)		
(3) Final score (2-3 hou	urs post l	baseline)							

(4) 20 mins from baseline

This Forest plot shows a **meta-analysis** of the trials in the Cochrane review reporting change in lung function with nebulised Magnesium Sulphate added to salbutamol

	MgS	50, + SAB	A		SABA			Mean Difference	Mean Difference
Study or Subgroup	Mean	<sup>™</sup> SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
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<u>Footnotes</u>									
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(3) Final score (2-3 hou	urs post l	baseline)							
(4) 20 mins from base	ine								

#### A Meta-analysis calculates the **weighted average** and its 95% CI from the trials (shown as the diamond)

	Mgs	SO, + SAB	A		SABA			Mean Difference	Mean Difference
Study or Subgroup	Mean	⊐ SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
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Subtotal (95% CI)	10.4	20	31	07.5		31	19.5%	8.10 [-3.03, 19.23]	
Heterogeneity: Not app	licable							. , .	
Test for overall effect: Z	(= 1.43	P = 0.15)							
		,							
Total (95% CI)			106			102	<b>100.0</b> %	3.34 [-1.58, 8.26]	
Heterogeneity: Chi <sup>2</sup> = 5	5.24, df =	3 (P = 0.1)	6); I <b>²</b> = -	43%					-20 -10 0 10 20
Test for overall effect: Z	Z= 1.33 (	P = 0.18)							Favours SABA alone Favours MdSO4 + SABA
Test for subgroup diffe	rences: (	Chi² = 0.87	', df = 1	(P = 0.3	35), I² = 0%	6			
<u>Footnotes</u>									
(1) 65 mins from base	line								
(2) At 90 min from base	eline (30	min after f	the thir	d admin	istration o	f the st	udy drug)		
(3) Final score (2-3 ho	urs post	baseline)							
(4) 20 mins from base	line								

- The "weight" of each trial is proportional to its precision.
- Large trials give precise treatment estimates (narrow confidence intervals) and carry more weight

	Mgs	SO, + SAB	BA		SABA			Mean Difference	Mean Difference	
Study or Subgroup	Mean	⊐ SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% CI	
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Hotorogonoitr: Chiž – A	11 df -	2/D = 0.11	CV: 12	100		102	100.070	5.54 [-1.50, 0.20]		
Test for everall effect: 7	1.24, ur = 7 = 1.007	3 (F = 0.1) D = 0.10\	0), I= 4	4370					-20 -10 Ó 10 20	0
Test for subgroup diffe	. — 1.33 ( roncoc: (	r — 0.10) ∩hi≅ — 0.97	7 df - 1	$(\mathbf{P} = 0.2)$	26) 17-09	4			Favours SABA alone Favours MgSO4 + SAB	A
Footpotee	iences. (	0.07	, ui – i	() = 0.,	55),1 = 07	0				
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(3) Final score (2-3 ho	urs nost	haseline)	are unit		ion anon o	i ino at	aay arag)			
(4) 20 mins from base	line	20001110)								

#### Can you describe the average treatment effect from these trials? Direction – Size – Uncertainty

	50 <sub>4</sub> + SAB	A		SABA			Mean Difference	Mean Difference Risk of Bias		
Study or Subgroup	Mean	ິ SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl	ABCDEF
2.2.1 Adults										
Bessmertny 2002 (1)	63	21.9	37	68	21.9	37	24.3%	-5.00 [-14.98, 4.98]		
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Listene new site ObiZ - C	0.4	2 (0 - 0 4)	100	1000		102	100.0%	5.54 [-1.56, 6.20]		
Heterogeneity: Chir = 5	0.24, di = (= 4, 22, 4	3 (P = 0.1) D = 0.40)	b); i= -	43%					-20 -10 0 10 20	
Test for overall effect. Z	.= 1.33 (	P = 0.18) Dhiz = 0.07	df_1	(D = 0 )	25) IZ - 00	,			Favours SABA alone Favours MgSO4 + 3	SABA
Test for subgroup diller	rences. (	∠nr= 0.87	, ui = 1	(P = 0	35), IF = 09	0			Disk of hiss langed	
Footnotes									Risk of plas legend	- hi)
(1) 65 mins from basel (2) At 00 min from base	line line (20	min offerd	la a thir	d a drain	istration a	fthe et	udu drug)		(A) Random sequence generation (selection (P) Allesstien senses ment (selection bios)	n pias)
(2) AL 90 MIN FOR DASE (2) Final energy (2, 2 hou	ure poet	min alter i bogolino)	ine inin	u aumin	Istration o	n the st	uay arug)		(B) Allocation concealment (selection bias)	norformanes bian)
(3) Final score (2-3 not (4) 20 mine from based	urs post i line	baseline)							(C) Binding of participants and personner ( (D) Blinding of outcome assessment (doto	vien bioe)
(4) zu mins irom basel	ine								(D) Binning of outcome assessment (detect	uon pias)
									(E) Incomplete outcome data (attition bias)	
									(F) Selective reporting (reporting blas)	

## What do the risks of bias in these trials indicate?

	Mgs	SO, + SAE	BA		SABA			Mean Difference	Mean Difference	
Study or Subgroup	Mean	⊂ SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl	
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Footnotes			1	Ų	,,,	-				
(1) 65 mins from base	line									
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(3) Final score (2-3 hou	urs post	baseline)					,			
(4) 20 mins from base	line	,								

## How do these results compare with the Badawy trial?

	MgS	50, + SAB	A		SABA			Mean Difference	Mean Difference
Study or Subgroup	Mean	ື SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
2.3.1 In Pregnancy									
Badawy 2014 Subtotal (95% CI)	56.31	8.25	30 30	32.68	7.15	30 30	21.9%	23.63 [19.72, 27.54]	
Jataraganaitr blat ar	nlianhla		50			50	21.370	23.03 [13.12, 21.34]	
Telefoyenelly, Not ap	7 – 44 0		00043						
restior overall ellect.	2 = 11.8	10 (P < 0.0	0001)						
2.3.2 Other adults									
Bessmertny 2002	63	21.9	37	68	21.9	37	19.5%	-5.00 [-14.98, 4.98]	
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Heterogeneity: Tau <sup>2</sup> =	: 27.99; (	Chi <sup>2</sup> = 4.37	', df = 2	: (P = 0.1	l 1); l² = 54	%			
Test for overall effect:	Z = 0.52	(P = 0.60)	)						
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Test for subgroup diff	ferences	Chi² = 25	5.45, df	= 2 (P <	0.00001),	l² = 92	.1%		Favours SABA alone Favours MgSO4 + SABA
Footnotes									

(1) Final score (2-3 hours post baseline)

## How similar are the results of all these trials?

	MgS	0, + SAB	BA		SABA			Mean Difference	Mean Difference
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<u>Footnotes</u>									
(1) Final score (2-3 h	ours pos	tbaseline	e)						

#### What is Heterogeneity between trial results?



#### $I^2$ =(91%) represents the proportion of the total variability that comes from differences between the trials



#### Should these trial results be combined in a metaanalysis?

	Mgs	50, + SAB	A		SABA			Mean Difference	Mean Difference
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Test for overall effect:	Z = 0.52	(P = 0.60)	)						
2.3.3 Children									
Mahajan 2004	75.4	26	31	67.3	18	31	18.9%	8.10 [-3.03, 19.23]	
Subtotal (95% CI)			31			31	<b>18.9</b> %	8.10 [-3.03, 19.23]	
Heterogeneity: Not ap	oplicable								
Test for overall effect:	Z=1.43	(P = 0.15)	)						
Total (95% CI)			136			132	100.0%	8.00 [-4.18, 20.18]	
Heteregeneity. Tau -	- 171.98,	CHIT = 45.	31, ui-	- 4 (F -	<del>8.88891);</del>	<u>P</u> = 91°	%		
Test for overall effect:	Z = 1.29	(P = 0.20)	)						Eavours SABA alone Eavours MdSO4 + SABA
Test for subgroup dif	ferences	: Chi² = 25	i.45, df	= 2 (P <	0.00001)	, <b>I</b> ² = 92	.1%		
Footnotes							_		

(1) Final score (2-3 hours post baseline)

#### • What are possible reasons for the heterogeneity?

	MgS	O, + SAB	A		SABA			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	<sup>™</sup> SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	ABCDEF
2.3.1 In Pregnancy										
Badawy 2014 Subtotal (95% CI)	56.31	8.25	30 <b>30</b>	32.68	7.15	30 <b>30</b>	21.9% <b>21.9</b> %	23.63 [19.72, 27.54] 23.63 [19.72, 27.54]	<b>★</b>	•?••?•
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 11.8	6 (P < 0.0	0001)							
2.3.2 Other adults										
Bessmertny 2002	63	21.9	37	68	21.9	37	19.5%	-5.00 [-14.98, 4.98]		
Hughes 2003	51.2	17.2788	28	41.3	18.7087	24	19.6%	9.90 [0.05, 19.75]		• ? • • • •
Sarhan 2016 (1)	51.2	9.8	10	49.6	10.3	10	20.1%	1.60 [-7.21, 10.41]		???????
Subtotal (95% CI)			75			71	59.2%	2.18 [-5.96, 10.31]	<b>•</b>	
Heterogeneity: Tau² =	: 27.99; C	¦hi² = 4.37	', df = 2	(P = 0.	11); I² = 54	%				
Test for overall effect:	Z=0.52	(P = 0.60)	)							
2.3.3 Children										
Mahajan 2004	75.4	26	31	67.3	18	31	18.9%	8.10 [-3.03, 19.23]		
Subtotal (95% CI)			31			31	18.9%	8.10 [-3.03, 19.23]		
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z=1.43	(P = 0.15)	)							
			420			422	400.0%	0.001.4.40.20.401		
Total (95% CI)			130			152	100.0%	8.00 [-4.18, 20.18]		
Heterogeneity: Tau* =	171.98;	Chif = 45.	.31, df :	= 4 (P <	0.00001);	If = 919	%		-50 -25 0 25 50	† 
Test for overall effect:	Z=1.29	(P = 0.20)	)						Favours SABA alone Favours MgSO4 + SAB	A
l est for subgroup diff	erences:	Chif = 25	.45, df	= 2 (P «	< 0.00001),	F= 92	.1%			
<u>Footnotes</u>									<u>Risk of bias legend</u>	
(1) Final score (2-3 h	ours pos	t baseline	e)						(A) Random sequence generation (selection bi	as)
									(B) Allocation concealment (selection bias)	
									(C) Blinding of participants and personnel (perf	ormance bias)
									(D) Blinding of outcome assessment (detection	bias)
									(E) Incomplete outcome data (attrition bias)	

(F) Selective reporting (reporting bias)

#### • What are possible reasons for the heterogeneity?

### **HOSPITAL ADMISSIONS**

#### Rate of asthma hospitalisations until term



### Can you describe the difference in admission rates until term in Badawy 2014? (Direction - Size - Uncertainty)

#### Rate of asthma hospitalisations until term



Can you describe the difference in admission rates until term in Badawy 2014? (Direction - Size - Uncertainty) What is the ratio of admissions on MgSO4 compared to SABA alone?

#### Rate of asthma hospitalisations until term



#### Magnesium = 30\*0.4 = 12 admissions SABA alone = 30\*3.2 = 96 admissions Ratio = 12/96 = 0.125 What is the ratio of admissions on MgSO4

compared to SABA alone?



This is a Meta-analysis of **admissions to hospital** for nebulised MgSO4 in addition to salbutamol and ipratropium It has been analysed as a dichotomous outcome using Risk Ratios

	MgSO4+SAB	A+ipra	Placebo+SABA	+ipra		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	ABCDEF
1.4.1 Adults								
Gallegos-Solórzano 2010	2	30	7	30	1.3%	0.29 [0.06, 1.26]	<	?
Goodacre 2013	254	332	278	358	49.9%	0.99 [0.91, 1.07]		
Hossein 2016	11	25	18	25	3.4%	0.61 [0.37, 1.01]	·	• ? • • ? ?
Subtotal (95% CI)		387		413	54.6%	0.95 [0.87, 1.03]		
Total events	267		303					
Heterogeneity: Chi <sup>2</sup> = 6.33, c	#f = 2 (P = 0.04)	; I² = 68%	6					
Test for overall effect: Z = 1.3	33 (P = 0.18)							
1 / 2 Childron								
Powell 2012	222	262	245	266	45.4%	0.06.00.02.1.011		
Subtotal (95% Cl)	202	252	245	256	45.4%	0.96 [0.92, 1.01]		
Total events	232	202	245	200				
Heterogeneity: Not applicab	le		240					
Test for overall effect: Z = 1.7	70 (P = 0.09)							
Total (95% CI)		639		669	<b>100.0</b> %	0.95 [0.91, 1.00]		
Total events	499		548					
Heterogeneity: Chi <sup>2</sup> = 6.30, c	#f = 3 (P = 0.10)	; I <sup>z</sup> = 52%	6					
Test for overall effect: Z = 1.9	32 (P = 0.06)						Favours MgSO . + SABA + ipratropium Favours placebo + SABA + ipratropiu	m
Test for subgroup difference	es: Chi² = 0.13,	df = 1 (P	= 0.72), I <b>²</b> = 0%					
<u>Risk of bias legend</u>								
(A) Random sequence gene	eration (selectio	on bias)						
(B) Allocation concealment (	(selection bias)							
(C) Blinding of participants a	and personnel (	performa	ance bias)					
(D) Blinding of outcome ass	essment (dete	ction bias	S)					
(E) Incomplete outcome data	a (attrition bias)							
(E) Selective reporting (report	rting bias)							

## The same meta-analysis showing Risks of Bias. Note that Badawy did not report this outcome so we have no information in pregnancy.



#### How would you explain this effect at the meeting? (Direction, Size and Uncertainty)



What is the Risk Ratio? 0.95 What is the Relative Risk Reduction on MgSO<sub>4</sub>? 100% - 95% = 5% What is the Absolute Risk Reduction?



The risk of admission on SABA is 548/669 = 82% What is the Relative Risk Reduction? 5% What is the Absolute Risk Reduction? 5% of 82%, which is 4 Percentage Points



#### What is the uncertainty?

The Lower 95% CI for the Risk Ratio? 0.91 What is the Relative Risk Reduction on  $MgSO_4$ ? 100% - 91% = 9%



The risk of admission on SABA is 548/669 = 82% What is the Relative Risk Reduction? 9% What is the Absolute Risk Reduction? 9% of 82%, which is **7 Percentage Points** 

### Can we show this as a picture?

• Let's look at a "Cates plot"?



#### In the control group 82 people out of 100 had participants were admitted, compared to 78 (95% CI 74 to 82) out of 100 for the inhaled magnesium sulphate group.



In the control group 82 people out of 100 had participants with one or more hospitalisations, compared to 78 (95% CI 75 to 82) out of 100 for the inhaled magnesium sulphate group.



In the control group 82 people out of 100 had participants were admitted, compared to 75 out of 100 for the inhaled magnesium sulphate group.

Upper 95% CI: O percentage points Absolute Risk Reduction





## In the control group 82 people out of 100 had participants were admitted, compared to 82 out of 100 for the inhaled magnesium sulphate group.

### **Baseline characteristics**

Characteristics	Group (A)		Group (B)	
	No	%	No	%
Age Mean ± SD	$25.93 \pm 4.01$		$25.66 \pm 3.82$	
Education				
Illiterate	5	16.67	4	13.34
Lower than University	21	70	20	66.67
Parity				
Primigravida	8	26.66	10	33
Multigravida	22	73.34	20	67
Duration of pregnancy				
1st trimester	2	6.67	3	10
2nd trimester	19	63.34	18	60
3rd trimester	9	30	9	30

 Table 1
 The socio demographic and pregnancy duration in both groups.

### What is missing from this table?

You have seen the evidence!	
What did you make of the	
risks of Bias in Badawy?	

#### Risk of bias table #

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk 🔻	
Allocation concealment (selection bias)	Unclear risk 🔻	
Blinding of participants and personnel (performance bias)	Unclear risk 🔻	
Blinding of outcome assessment (detection bias)	Unclear risk 🔻	
Incomplete outcome data (attrition bias)	Unclear risk 💌	
Selective reporting (reporting bias)	Unclear risk 🔻	

#### □ Badawy 2014

Methods	You have seen the evidencel	
Participants		
Interventions	What did you make of the	
Outcomes	terrar ara you mane of me	
Notes	risks of Bias?	

#### Risk of bias table #

Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Unclear risk 💌		
Allocation concealment (selection bias)	Unclear risk 💌		
Blinding of participants and personner (performance bias)	low w	ould you summarise	
Blinding of outcome assessment (detection bias)	he ev	idence you have	
Incomplete outcome data (attrition S	een?		
Selective reporting (reporting bias)	Vhat	would your advice be	
+	o the	A&E consultant?	

### Take Home messages

- Don't just rely on the results of a single study
- 2. Look at the difference between the trials as well as the weighted average!
- 3. Think about bias as well as the play of chance (as the 95% CI only includes uncertainty around the latter)

# There is further reading on my website

## •www.nntonline.net

- Link to the article in Breathe on Understanding Systematic Reviews
- You can have a go at using Visual Rx
- There are short articles on Critical Appraisal
- Short articles on Statistics related to metaanalysis