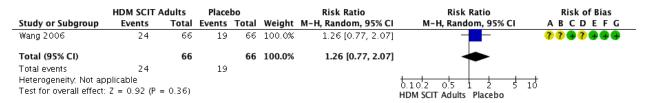
- 1. Should HDM SCIT versus no HDM SCIT be used for treatment in adult patients with asthma?
 - 1.1. FOREST PLOTS

1.1.1. Critical outcomes

Asthma exacerbations – assessed as number of patients required a 1.1.1.1. course oral prednisolone



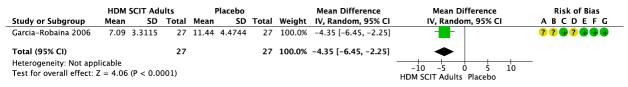
Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

1.1.1.2. Asthma control

We found no evidence

Steroid sparing effect (inhaled steroids) assessed as number of weeks 1.1.1.3. without using inhaled steroids



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias
- Safety (systemic reactions) assessed as number of patients with at least 1.1.1.4. one reaction

	HDM SCIT		Place			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	ABCDEFG
Alvarez 2002	0	12	0	11		Not estimable		777797
Ameal 2005	5	29	3	26	44.3%	1.49 [0.40, 5.65]	- 	779999
Basomba 2002	7	25	1	24	19.2%	6.72 [0.89, 50.61]	-	?? ? • ? • • ?
Bousquet 1985	4	20	0	10	9.8%	4.71 [0.28, 79.82]	- •	- ?? ? ? ? ? ?
Garcia-Robaina 2006	0	27	0	27		Not estimable		779999
Machiels 1990	0	0	0	0		Not estimable		?? ? • ? • • ?
Maestrelli 2004	2	31	0	41	8.7%	6.56 [0.33, 131.99]	-	— •?•••
Mungan 1999	1	10	0	11	8.2%	3.27 [0.15, 72.23]	-	- ?? \varTheta ? 🖷 ?
Olsen 1997	0	21	0	10		Not estimable		9992992
Pichler 1997	5	16	0	14	9.9%	9.71 [0.58, 161.31]	+	- ??
Total (95% CI)		191		174	100.0%	3.26 [1.34, 7.89]	•	
Total events	24		4					
Heterogeneity: Tau ² =	0.00 ; $Chi^2 = 2$.81. df :	= 5 (P =	0.731; [2 = 0%		1000 010	
Test for overall effect: 2			*	- 0			0.005 0.1 1 10	200
restroi overan entett.	2.02 (0.005,					HDM SCIT Adults Placebo	

- Risk of bias legend (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
 (D) Blinding of outcome assessment (detection bias)
 (E) Incomplete outcome data (attrition bias)
 (F) Selective reporting (reporting bias)
 (G) Other bias

1.1.2. <u>Important but no critical outcomes</u>

1.1.2.1. Symptom score

	HDM SCIT Adults				Placebo Std. Mean Difference			Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
Ameal 2005	-0.78	0.93	29	1.35	1.47	26	11.4%	-1.73 [-2.35, -1.10]		?? • ? • •
Armentia-Medina 1995	1.62	0.55	22	2.7	0.42	13	10.7%	-2.08 [-2.94, -1.22]		$\bullet \bullet \bullet ? \bullet ?$
Basomba 2002	0.33	0.27	24	0.09	0.3	25	11.5%	0.83 [0.24, 1.41]		?? • ? • ?
Costa 1996	0.9	0.7	11	1.5	0.8	11	10.6%	-0.77 [-1.64, 0.10]		4 ? ? ? 4 8 4
Garcia-Robaina 2006	11.63	2.4521	27	25.12	3.2357	27	10.0%	-4.63 [-5.68, -3.58]		$?? \oplus ? \oplus \oplus$
Machiels 1990	3.66	3.13	24	5.07	2.63	11	11.1%	-0.46 [-1.18, 0.26]		?? ?
Pichler 1997	3.5	1.75	16	7	11.25	14	11.1%	-0.44 [-1.17, 0.29]		?? ? • ? • •
Tabar 1999	2.1	10.31	44	6.38	11.13	19	11.6%	-0.40 [-0.94, 0.14]		???? ?
Wang 2006	0.178	0.26	64	0.397	0.69	65	12.0%	-0.42 [-0.77, -0.07]	*	?? ? ? ? .
Total (95% CI)			261			211	100.0%	-1.07 [-1.83, -0.30]	•	
Heterogeneity: $Tau^2 = 1$.	25; Chi²	= 104.60	0, $df = 8$	B (P < 0	.00001);	$1^2 = 92$	%		- , , ,	_
Test for overall effect: Z	= 2.72 (F	= 0.007	'n						HDM SCIT Adults Placebo	

- Risk of bias legend

 (A) Random sequence generation (selection bias)

 (B) Allocation concealment (selection bias)

 (C) Blinding of participants and personnel (performance bias)

 (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
 (G) Other bias

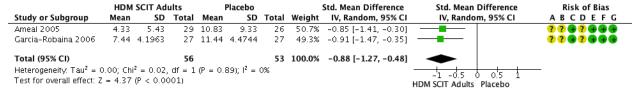
1.1.2.2. Medication score

HDM SCIT Adults		P	Placebo			Std. Mean Difference	Std. Mean Difference	Risk of Bias		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
Ameal 2005	-2.88	1.46	29	-0.89	1.57	26	10.6%	-1.30 [-1.88, -0.71]	-	?????
Basomba 2002	0.8	1.26	24	-0.2	1.63	25	10.6%	0.67 [0.10, 1.25]	-	?? ? • ? • • ?
Costa 1996	1	0.9	11	2.7	1.5	11	9.6%	-1.32 [-2.26, -0.38]		4????
Ferrer 2003	1.8	1.86	22	1.76	2.04	11	10.2%	0.02 [-0.70, 0.74]	+	? \varTheta ? ? 😛 😛 ?
Garcia-Robaina 2006	10.47	1.97	27	22.09	1.66	27	8.2%	-6.29 [-7.63, -4.94]		?? ? ? ? .
Machiels 1990	92.72	7.87	24	111.44	9.18	11	9.7%	-2.21 [-3.11, -1.31]		779797
Maestrelli 2004	0.5	20	41	5.2	13.34	31	10.8%	-0.27 [-0.73, 0.20]	+	9 ? 9 9 9 9
Paranos 1997	1	0.58	7	2.43	1.13	7	8.6%	-1.49 [-2.72, -0.26]		? ? ? ? ?
Tabar 1999	0.6	3.67	44	4.09	6.93	19	10.6%	-0.71 [-1.26, -0.16]	+	7777997
Wang 2006	0.184	0.32	64	0.292	0.81	65	11.0%	-0.17 [-0.52, 0.17]	†	?? ? ? ? .
Total (95% CI)			293			233	100.0%	-1.17 [-1.91, -0.43]	•	
Heterogeneity: Tau ² =	1.26; Chi ²	= 120	.18, df	= 9 (P <	0.0000	1); $ ^2 =$	93%		-10 -5 1 5	10
Test for overall effect: 2	2 = 3.11	P = 0.0	002)						HDM SCIT Adults Placebo	10

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

1.1.2.3. Quality of Life



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

1.1.2.4. Lung function: Small airways assessed as percentage or absolute improvement of MEF 25, MEF 50, MEF 75

We found no evidence

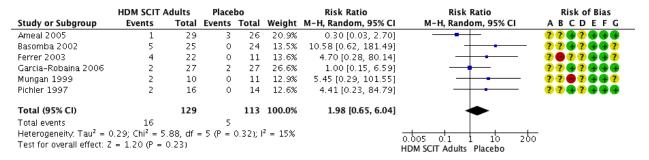
1.1.2.5. Lung function: Allergen specific bronchial provocation tests (ABPT) assess as PD20 FEV1 to allergen challenge

	HDM SCIT Adults		F	Placebo			Std. Mean Difference	Std. Mean Difference	Risk of Bias	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
Ameal 2005	8.6	7.83	29	5.02	7.24	26	36.1%	0.47 [-0.07, 1.00]	-	779799
Bousquet 1985	432	171	20	95	98.8	10	27.8%	2.16 [1.20, 3.12]	-	??? ??
Garcia-Robaina 2006	279.37	527.5	27	118.45	250.06	27	36.1%	0.38 [-0.15, 0.92]	<u>*</u>	?? ? • ? • •
Total (95% CI)			76			63	100.0%	0.91 [0.03, 1.78]	•	
Heterogeneity: Tau ² = 1				2 (P = 0.9)	004); l² =	82%			-4-5 6 3 4	_
Test for overall effect: 2	Z = 2.03 (1	P = 0.04	ł)						HDM SCIT Adults Placebo	

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
 (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Safety (local reactions) 1.1.2.6.



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

1.2. EVIDENCE PROFILE

Author(s): Juan J. Yepes-Nuñez
Date: October 2018
Question: HDM SCIT compared to no HDM SCIT for treatment in adults patients with asthma
Setting: Outpatients

			Certainty a	ssessment			Nº of p	atients	Effec	t		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HDM SCIT	no HDM SCIT	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Asthma exa	cerbations - asse	essed as number of	f patients required a	course of oral pred	Inisolone (follow up	: 1 year)						
1	randomised trials	not serious ^a	not serious	not serious	very serious ^b	none	24/66 (36.4%)	19/66 (28.8%)	RR 1.26 (0.77 to 2.07)	75 more per 1,000 (from 66 fewer to 308 more)	ФФСС	CRITICAL
Asthma con	trol - not reporte	d										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Corticostero	id use (oral stero	oids) - not reported										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Corticostero	id use (inhaled s	teroids) - assessed	as the number of w	veeks without using	inhaled steroids (fo	ollow up: 1 year)						
1	randomised trials	not serious ^a	not serious	serious ^c	serious ^d	none	27	27	-	MD 4.35 lower (6.45 lower to 2.25 lower)	\bigoplus_{LOW}	CRITICAL
Systemic ad	lverse events – a	assessed as numbe	er of patients with at	least one reaction	(follow up: from 1 ye	ear to 3 years)						
10	randomised trials	not serious ^{e,f}	not serious	not serious ^g	serious ^d	none	24/191 (12.6%)	4/174 (2.3%)	RR 3.26 (1.34 to 7.89)	52 more per 1,000 (from 8 more to 158 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Symptom so	cores (follow up:	from 1 year to 2 year	ars)			!						
9	randomised trials	not serious ^{h,i}	serious ^j	not serious ^g	serious ^d	none	261	211	-	SMD 1.07 lower (1.83 lower to 0.3 lower)	ФФСС	IMPORTANT
Medication	scores (follow up	: from 1 year to 3 y	ears)									

			Certainty a	ssessment			Nº of p	atients	Effec	t			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HDM SCIT	no HDM SCIT	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance	
10	randomised trials	not serious ^k	serious ¹	not serious 9	serious ^d	none	293	233	-	SMD 1.17 lower (1.91 lower to 0.43 lower)	⊕⊕⊖⊖ Low	IMPORTANT	
Asthma Qol	Asthma QoL (follow up: 1 year)												
2	randomised trials	not serious ^m	not serious	not serious 9	very serious ^d	none	56	53	-	SMD 0.88 lower (1.27 lower to 0.48 lower)	⊕⊕⊖⊖ Low	IMPORTANT	
Lung function	Lung function: Small airways assessed as percentage or absolute improvement of MEF 25, MEF 50, MEF 75 - not reported												
-	-	-	-	-	-	-	-	-	-	-	-		
Lung function	on: Allergen spec	ific bronchial provo	cation tests (ABPT)	assess as PD20 FI	EV1 to allergen cha	illenge (follow up: from 1 year)							
3	randomised trials	not serious ^m	serious ⁿ	not serious ^g	very serious ^b	none	76	63	-	SMD 0.91 higher (0.03 higher to 1.78 higher)	⊕⊖⊖⊖ VERY LOW	IMPORTANT	
Local adver	se events (follow	up: from 1 year to	1.5 years)		-				·				
6	randomised trials	not serious °	not serious	not serious ^g	very serious ^b	none	16/129 (12.4%)	5/113 (4.4%)	RR 1.98 (0.65 to 6.04)	43 more per 1,000 (from 15 fewer to 223 more)	ФФСО	IMPORTANT	

CI: Confidence interval; RR: Risk ratio; SMD: Standardised mean difference; MD: Mean difference

Explanations

- a. Allocation concealment and random sequence generation were unclear in the studies included.
- b. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, and no optimal information size criterion met.
- c. Serious indirectness. The study used a surrogate outcome to assess HDM SCIT efficacy.
- d. No optimal information size criterion met.
- e. Nine out of ten studies did not provide information about allocation concealment.
- f. Two out of ten studies were rated as risk of bias. One study due to lack of random sequence generation, and another one due to lack of blinding of participants.
- q. Patients across studies received different HDM SCIT extracts. Allergen extracts are different between each AIT company and batch.
- h. Eight out of nine studies did not provide information about allocation concealment.
- i. One out of nine studies were rated as risk of bias due to selective reporting.
- j. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.0001; I-square 92%)
- k. Four out of ten studies were rated as risk of bias. Two studies due to lack of allocation concealment, one study due to lack of random sequence generation, another one due to lack of blinding of participants, and one study due to selective reporting.

- I. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.0001; I-square 93%)
- m. Allocation concealment, random sequence generation, and blinding of outcome assessment were unclear in the studies included.
- n. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.004; I-square 82%)
- o. One out of six studies were rated as high risk of bias due to lack of allocation concealment. Another study was also rated as high risk of bias due to lack of blinding.

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1.3. SOF TABLE

Summary of findings:

HDM SCIT compared to no HDM SCIT for treatment in adults patients with asthma

Patient or population: adults patients with asthma Setting: Outpatients Intervention: HDM SCIT Comparison: no HDM SCIT

Outcomes	Anticipated absolute e	ffects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence	Comments
	Risk with no HDM SCIT	Risk with HDM SCIT	(95 % GI)	(Studies)	(GRADE)	
Asthma exacerbations - assessed as number of patients required a course of oral prednisolone (follow up: 1 year)	288 per 1,000	363 per 1,000 (222 to 596)	RR 1.26 (0.77 to 2.07)	132 (1 RCT)	LOM ap	
Asthma control - not reported	-		-	-	-	
Corticosteroid use (oral steroids) - not reported	-	see_comment	-	-	-	
Corticosteroid use (inhaled steroids) - assessed as the number of weeks without using inhaled steroids (follow up: 1 year)	The mean corticosteroid use (inhaled steroids) - assessed as the number of weeks without using inhaled steroids (follow up: 1 year) was 0	The mean corticosteroid use (inhaled steroids) - assessed as the number of weeks without using inhaled steroids (follow up: 1 year) in the intervention group was 4.35 lower (6.45 lower to 2.25 lower)	-	54 (1 RCT)	LOW a.c.d	
Systemic adverse events – assessed as number of patients with at least one reaction (follow up: from 1 year to 3 years)	23 per 1,000	75 per 1,000 (31 to 181)	RR 3.26 (1.34 to 7.89)	365 (10 RCTs)	⊕⊕⊕⊖ MODERATE d,e,f,g	

Summary of findings:

HDM SCIT compared to no HDM SCIT for treatment in adults patients with asthma

Patient or population: adults patients with asthma Setting: Outpatients

Setting: Outpatients Intervention: HDM SCIT Comparison: no HDM SCIT

Outcomes	Anticipated absolute e	ffects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence	Comments
	Risk with no HDM SCIT	Risk with HDM SCIT	(33% 01)	(Studies)	(GRADE)	
Symptom scores (follow up: from 1 year to 2 years)		-		472 (9 RCTs)	⊕⊕⊖⊖ LOW d.g.h.i.j	
Medication scores (follow up: from 1 year to 3 years)		-		526 (10 RCTs)	⊕⊕⊖⊖ LOW d.g.k.i	
Asthma QoL (follow up: 1 year)		-		109 (2 RCTs)	⊕⊕⊖⊖ LOW d,g,m	
Lung function: Small airways assessed as percentage or absolute improvement of MEF 25, MEF 50, MEF 75 - not reported - not reported	-			-	-	
Lung function: Allergen specific bronchial provocation tests (ABPT) assess as PD20 FEV1 to allergen challenge (follow up: from 1 year)		-	-	139 (3 RCTs)	⊕⊖⊖⊖ VERY LOW b,g,m,n	
Local adverse events (follow up: from 1 year to 1.5 years)	44 per 1,000	88 per 1,000 (29 to 267)	RR 1.98 (0.65 to 6.04)	242 (6 RCTs)	LOW b.g.o	

^{*}The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; SMD: Standardised mean difference; MD: Mean difference

Summary of findings:

HDM SCIT compared to no HDM SCIT for treatment in adults patients with asthma

Patient or population: adults patients with asthma

Setting: Outpatients Intervention: HDM SCIT Comparison: no HDM SCIT

Outcomes	Anticipated absolute ef	ffects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no HDM SCIT	Risk with HDM SCIT				

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

Explanations

- a. Allocation concealment and random sequence generation were unclear in the studies included.
- b. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, and no optimal information size criterion met.
- c. Serious indirectness. The study used a surrogate outcome to assess HDM SCIT efficacy.
- d. No optimal information size criterion met.
- e. Nine out of ten studies did not provide information about allocation concealment.
- f. Two out of ten studies were rated as risk of bias. One study due to lack of random sequence generation, and another one due to lack of blinding of participants.
- a. Patients across studies received different HDM SCIT extracts. Allergen extracts are different between each AIT company and batch.
- h. Eight out of nine studies did not provide information about allocation concealment.
- i. One out of nine studies was rated as risk of bias due to selective reporting.
- j. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.0001; I-square 92%)
- k. Four out of ten studies were rated as risk of bias. Two studies due to lack of allocation concealment, one study due to lack of random sequence generation, another one due to lack of blinding of participants, and one study due to selective reporting.
- I. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.0001; I-square 93%)
- m. Allocation concealment, random sequence generation, and blinding of outcome assessment were unclear in the studies included.
- n. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.004: I-square 82%)
- o. One out of six studies were rated as high risk of bias due to lack of allocation concealment. Another study was also rated as high risk of bias due to lack of blinding.