Reporting of harms outcomes: A comparison of journal publications with unpublished clinical study reports of orlistat trials

Alex Hodkinson^{1*}, Carrol Gamble¹, Catrin Tudur Smith¹

¹MRC North West Hub for Trials Methodology Research, Department of Biostatistics, University of Liverpool, Liverpool.

E-mail address: ahoddy@liverpool.ac.uk (A.Hodkinson).

Supplementary Figure S1: Forest plots for all adverse event MedDRA preferred terms reported in CSR and journal publications.

These meta-analysis results are based on a subset of the eligible trials of orlistat and are presented for the purpose of methodological comparison rather than definitive clinical results

Gastrointestinal disorders

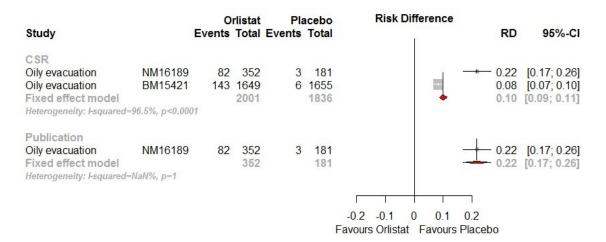
		1000	rlistat	7000	cebo		Risk Di	fference	•		
Study		Events	Total	Events	Total			T		RD	95%-CI
CSR											
Fatty/oil stool	NM16189	177	352	15	181				++	- 0.42	[0.35; 0.49]
Fatty/oil stool	M37013	77	174	18	169					0.34	[0.25; 0.42]
Fatty/oil stool	M37002	83	144	18	84				-+	- 0.36	[0.24; 0.48]
Fatty/oil stool	M37047	80	267	8	269			-		0.27	[0.21; 0.33]
Fatty/oil stool	BM15421	716	1649	85	1655				100	0.38	[0.36; 0.41]
Fixed effect model			2586		2358				•	0.37	[0.35; 0.39]
Heterogeneity: I-square	d=73.2%, p=0.0048	8									*
Publication									î		
Fatty/oil stool	NM16189	177	352	15	181				+	-0.42	[0.35; 0.49]
Fatty/oil stool	M37013	77	174	18	169					0.34	[0.25; 0.42]
Fixed effect model			526		350				-	0.38	[0.33; 0.44]
Heterogeneity: I-square	d=56.4%, p=0.1299	9									
							1	1 1			
						-0.4	-0.2	0 02	0.4		
						and the state of t	Orlistat	Favou	s Place	bo	

^{*}Corresponding author

		0	rlistat	Pla	cebo	Risk Difference		
Study		Events	Total	Events	Total	1	RD	95%-CI
CSR						No.		
Increased defecation	NM16189	48	352	16	181	 * 	0.05	[-0.01; 0.10]
Increased defecation	M37013	68	174	19	169		0.28	[0.19; 0.37]
Increased defecation	M37002	61	144	18	84	-	0.21	[0.09; 0.33]
Increased defecation	M37047	31	267	12	269	+	0.07	[0.03; 0.12]
Increased defecation	BM15421	362		279	1655		0.05	[0.02; 0.08]
Fixed effect model			2586		2358	•	0.08	[0.05; 0.10]
Heterogeneity: I-squared=86.7%,	p<0.0001							
Publication								
Increased defecation	NM16189	48	352	16	181	 • 	0.05	[-0.01; 0.10]
Increased defecation	M37013	68	174	19	169		0.28	[0.19; 0.37]
Fixed effect model			526		350	-	0.14	[0.10; 0.19]
Heterogeneity: I-squared=95.3%,	p<0.0001							
						-0.3 -0.2 -0.1 0 0.1 0.2 0.3		
						Favours Orlistat Favours Placel	00	

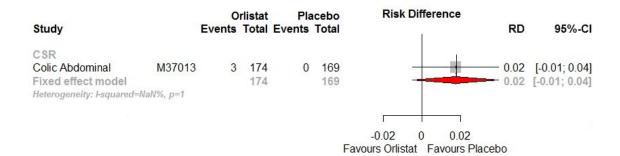
Study		_	rlistat Total	Pla Events	acebo Total	Risk Difference	RD	95%-CI
CSR Liquid stools Liquid stools Liquid stools Fixed effect model Heterogeneity: I-squared	M37013 M37047 BM15421		174 267 1640 2081	8 36 279	169 269 1637 2075		0.05 - 0.06 0.05 0.05	[-0.01; 0.12] [0.02; 0.08]
Publication Liquid stools Fixed effect model Heterogeneity: I-squared	M37013 d=NaN%, p=1	17	174 174	8	169 169		0.05 0.05	[0.00; 0.10] [0.00; 0.10]
						-0.1 -0.05 0 0.05 0.1 Favours Orlistat Favours Placet	00	

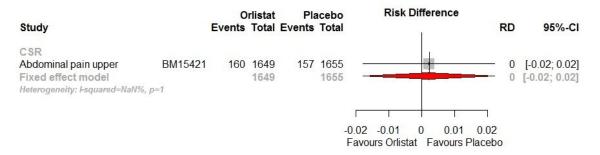
Study		CONTRACTOR CONTRACTOR	rlistat Total	Pla Events	acebo Total		Risk Di	ffere	nce	RD	95%-CI
Oily spotting Oily spotting Oily spotting Oily spotting Oily spotting Fixed effect model Heterogeneity: I-square	NM16189 M37002 M37047 BM15421 d=96.2%, p<0	102 83 51 109	144 267	7 18 35 2	181 84 269 1655 2189			+		0.25 0.36 0.06 0.06 0.10	[0.20; 0.31] [0.24; 0.48] [0.00; 0.12] [0.05; 0.08] [0.08; 0.11]
Publication Oily spotting Fixed effect model Heterogeneity: I-square	NM16189 d=NaN%, p=1	102	352 352	7	181 181				±	0.25 0.25	[0.20; 0.31] [0.20; 0.31]
						-0.4 Favour	-0.2 rs Orlistat	0 Fav	0.2 0.4 ours Placeb	00	



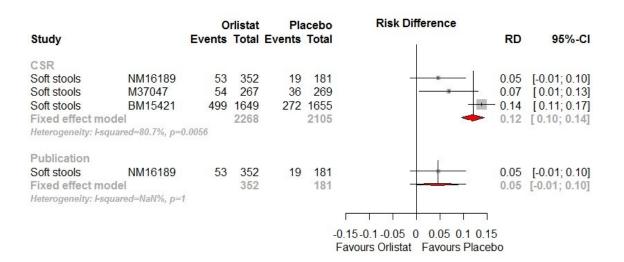
Study		2012	rlistat Total	Pla Events	cebo Total	Risk Diffe	7.35533	RD	95%-CI
Flatus with discharge Fixed effect model Heterogeneity: I-squared=75.69	NM16189 M37013 M37047 BM15421	70 13 30 188	352 174 267 1649 2442	5 3 5 16	181 169 269 1655 2274		0 0	.17 .06 .09 .10	[0.12; 0.22] [0.01; 0.10] [0.05; 0.13] [0.09; 0.12] [0.09; 0.12]
Publication Flatus with discharge Flatus with discharge Fixed effect model Heterogeneity: I-squared=92.19	NM16189 M37013	70 13	352 174 526	5 3	181 169 350		 0	.17 .06 .12	[0.12; 0.22] [0.01; 0.10] [0.09; 0.16]
						-0.2 -0.1 0 Favours Orlistat	0.1 0.2 avours Placebo		

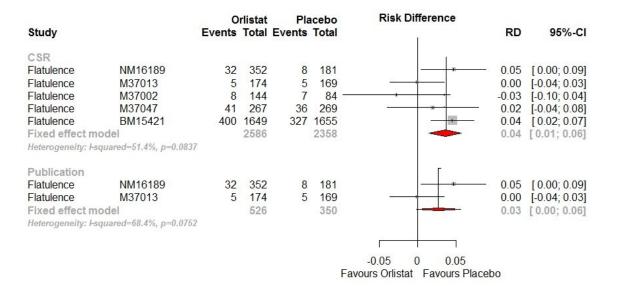
Study		CONTRACTOR STATE	rlistat Total	Pla Events	Total	Risk Difference	RD	95%-CI
CSR Abdominal pain Abdominal pain Abdominal pain Abdominal pain Abdominal pain Abdominal pain Fixed effect model Heterogeneity: I-squared	NM16189 M37013 M37002 M37047 BM15421	77 10 20 18 235	352 174 144 267 1649 2586	20 6 11 11 188	181 169 84 269 1655 2358		- 0.11 0.02 0.01 0.03 0.03 0.04	[-0.08; 0.10] [-0.01; 0.06] [0.01; 0.05]
Publication Abdominal pain Abdominal pain Fixed effect model Heterogeneity: I-squared	NM16189 M37013 -71.5%, p=0.0613	77 13	352 174 526	20 6	181 169 350	-0.15-0.1-0.05 0 0.05 0.1 0.15	- 0.11 0.04 0.08	[0.05; 0.17] [-0.01; 0.09] [0.04; 0.12]

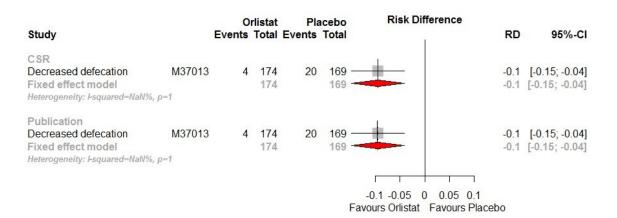


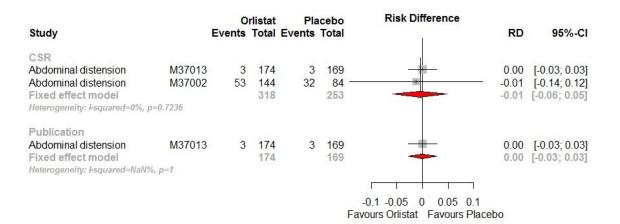


Study		2000	rlistat Total	Pla Events	cebo Total	Risk Difference	RD	95%-CI
CSR Solid stools Fixed effect mo Heterogeneity: I-squ	16/51/C/51/C/5/	11	174 174	9	169 169	-	0.01 0.01	[-0.04; 0.06] [-0.04; 0.06]
Publication Solid stools Fixed effect mo Heterogeneity: I-squ	000000000000000000000000000000000000000	11	174 174	9	169 169	-	0.01	[-0.04; 0.06] [-0.04; 0.06]
					F	-0.04-0.02 0 0.02 0.04 avours Orlistat Favours Pla		

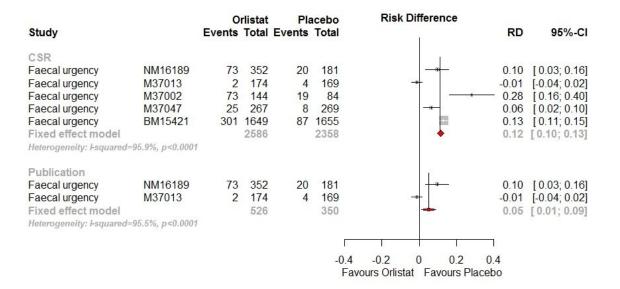


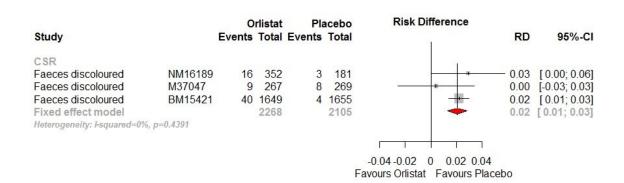


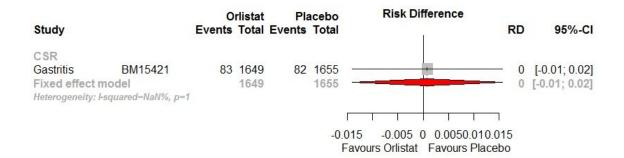


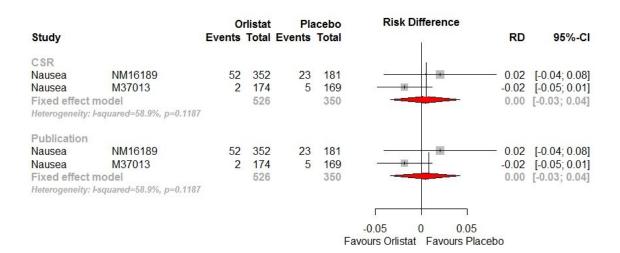


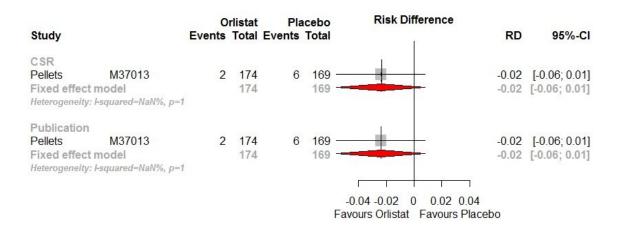
Study		2002 C.	rlistat Total	Pla Events	cebo Total		Risk Diff	erence	RD	95%-CI
CSR Faecal incontinence Faecal incontinence Faecal incontinence Fixed effect model Heterogeneity: I-squared=84	NM16189 M37047 BM15421	31 26 60	352 267 1649 2268	1 6 4	181 269 1655 2105				0.08 0.08 0.03 0.04	[0.05; 0.11] [0.04; 0.11] [0.02; 0.04] [0.04; 0.05]
Publication Faecal incontinence Fixed effect model Heterogeneity: I-squared=Na	NM16189	31	352 352	1	181 181			\pm	0.08	[0.05; 0.11] [0.05; 0.11]
						-0.1 Favo	-0.05 0 urs Orlistat	0.05 (Favours Place	⊓).1 cebo	

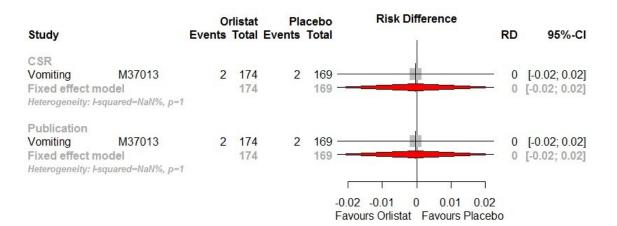


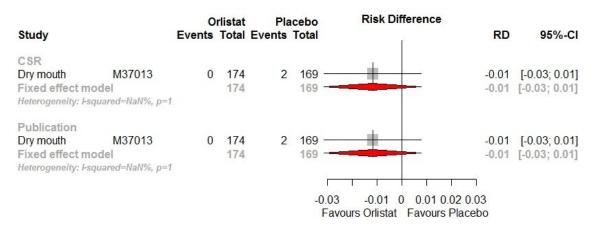


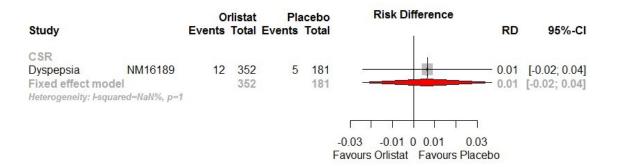


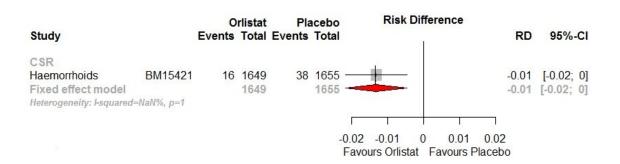










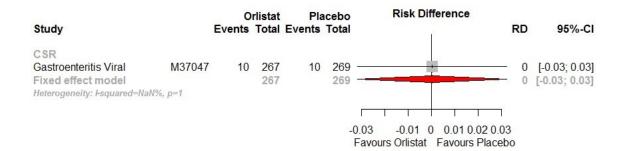


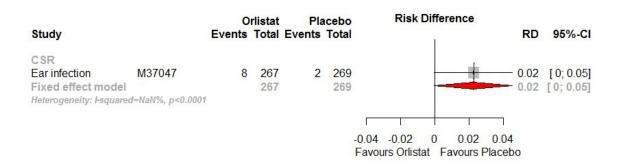
Infections and infestations

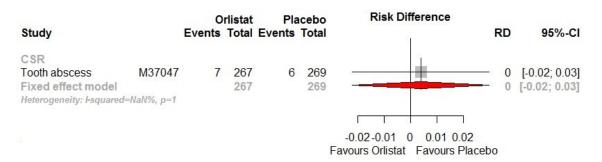
	0	rlistat	Pla	cebo	Risk Difference		
Study	Events	Total	Events	Total	Ĩ	RD	95%-CI
CSR							
Nasopharyngitis NM16189	99	352	46	181	- 1	0.03	[-0.05; 0.11]
Nasopharyngitis M37002	17	144	8	84	+	0.02	[-0.06; 0.10]
Nasopharyngitis M37047	48	267	43	269	- 1	0.02	[-0.04; 0.08]
Fixed effect model		763		534		0.02	[-0.02; 0.07]
Heterogeneity: I-squared=0%, p=0.9902							
Publication							
Nasopharyngitis NM16189	99	352	46	181	- +	0.03	[-0.05; 0.11]
Fixed effect model		352		181		0.03	[-0.05; 0.11]
Heterogeneity: I-squared=NaN%, p<0.000	1						
				100			
				D.	SI II	NI Access	
				-0.1	-0.05 0 0.05	0.1	
				Fav	ours Orlistat Favours Pla	acebo	

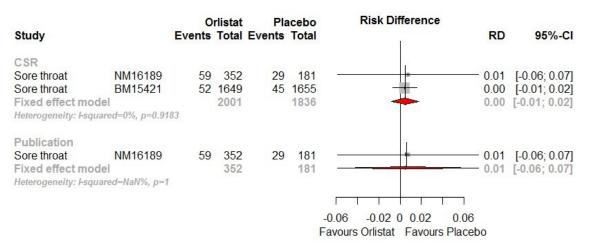
Study		Or Events	rlistat Total	200	cebo Total	Risk Difference	RD	95%-CI
CSR Upper respiratory tract infection Upper respiratory tract infection Fixed effect model Heterogeneity: Fsquared-62.7%, p=0.1014	NM16189 M37002	114 6	352 144 496	48 4	181 84 265	-	- 0.06 -0.01 0.04	[-0.02; 0.14] [-0.06; 0.05] [-0.02; 0.10]
Publication Upper respiratory tract infection Fixed effect model Heterogeneity: I-squared=NaN%, p<0.0001	NM16189	114	352 352	48	181 181		— 0.06 — 0.06	[-0.02; 0.14] [-0.02; 0.14]
					F	-0.1 -0.05 0 0.05 0.1 Favours Orlistat Favours Plac	ebo	

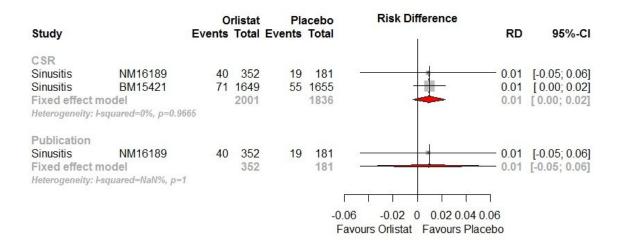
Study	200	rlistat Total	Pla Events	acebo Total		RD	95%-CI
CSR Influenza M37002 Influenza M37047 Influenza BM15421 Fixed effect model Heterogeneity: I-squared=0%, p=0.720		144 267 1649 2060	500000000000000000000000000000000000000	269	-	0.00 0.03 0.01 0.02	[-0.06; 0.07] [-0.02; 0.09] [-0.01; 0.04] [-0.01; 0.04]

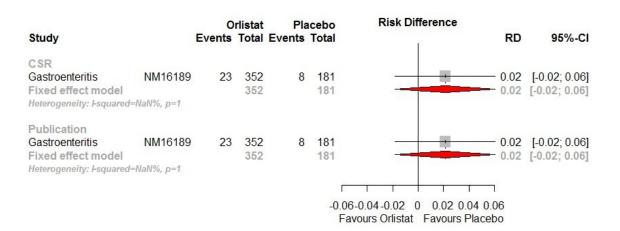


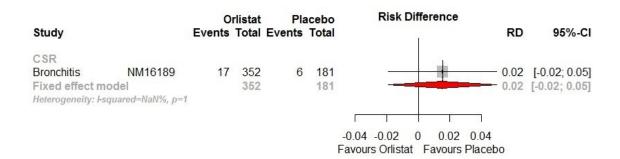


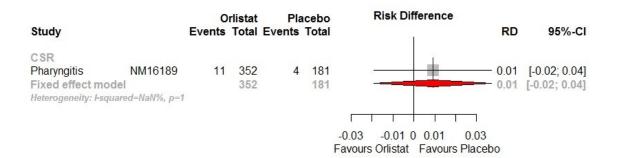


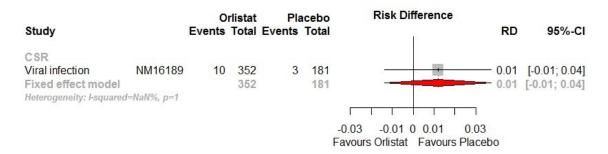


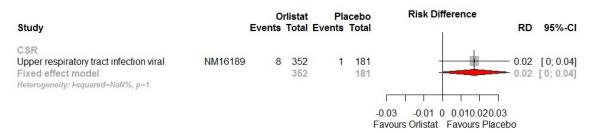


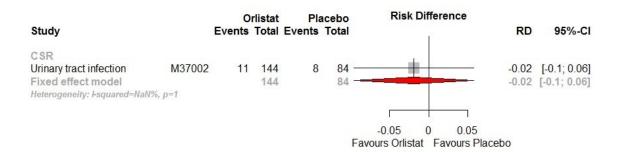










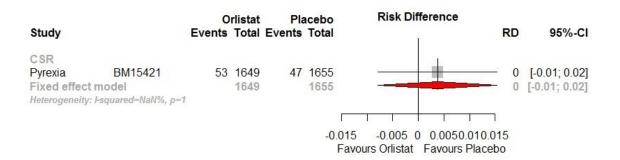


Metabolism and nutrition disorders

Study		Or Events	rlistat Total	1076	acebo Total	Risk Difference	RD	95%-CI
C SR Hypoglycaemia Fixed effect model	M37047	45	267 267	26	269 269		0.07	[0.01; 0.13] [0.01; 0.13]
Publication Hypoglycaemia Hypoglycaemia Fixed effect model	M37002 M37047	2 45	144 267 411	4 26	84 269 353		0.07	[-0.08; 0.02] [0.01; 0.13] [0.00; 0.09]
Heterogeneity: I-squared=	=90.1%, p=0.0015				F	-0.1 -0.05 0 0.05 0	(253)	

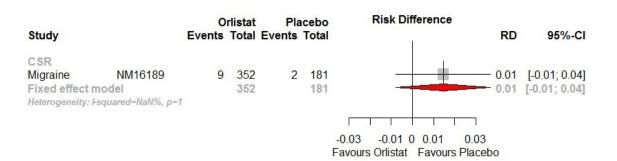
General disorders and administration site conditions

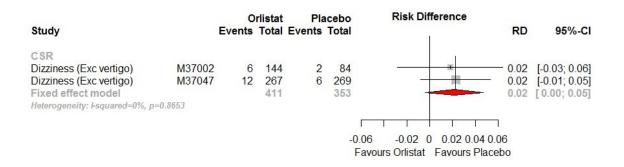
Study	E	200	rlistat Total E	70.00	cebo Total		Risk Di	fference	RD	95%-CI
CSR Influenza like illness Fixed effect model Heterogeneity: I-squared=Na	M37047	13	267 267	9	269 269		_	1		[-0.02; 0.05] [-0.02; 0.05]
						-0.04		0 0.02 0. Favours Pla	77.27	



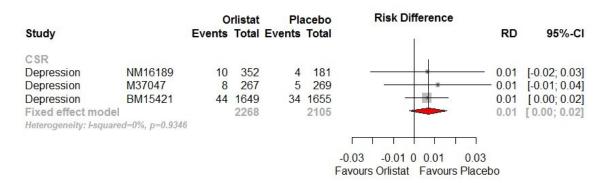
Nervous system disorders

Study		Orlistat s Total	Pla Events	acebo Total	Risk Difference	RD	95%-CI
CSR Headache NN Fixed effect model Heterogeneity: I-squared=	M16189 13	4 352 352	56	181 181	-	0.07 0.07	[-0.01; 0.16] [-0.01; 0.16]
Publication Headache NN Fixed effect model Heterogeneity: I-squared=	116189 13 NaN%, p=1	4 352 352	56	181 181 -0.15	5-0.1-0.05 0 0.05 0.1	0.07 0.07 0.15	[-0.01; 0.16] [-0.01; 0.16]



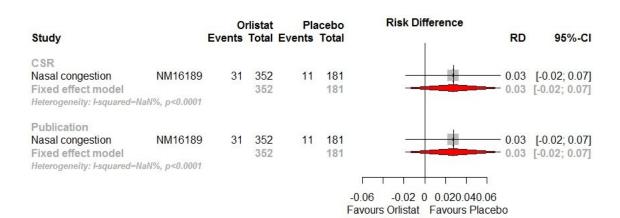


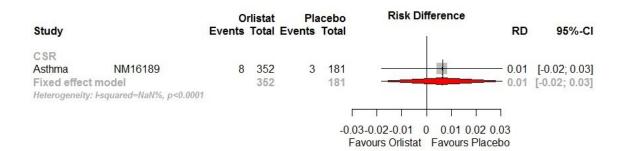
Psychiatric disorders

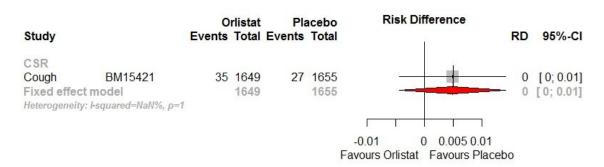


Respiratory, thoracic and medicinal disorders

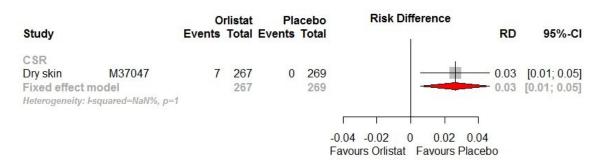
Study			rlistat Total	Pla Events	cebo Total	Risk Difference	RD	95%-CI
CSR Rhinitis seasonal Rhinitis seasonal Rhinitis seasonal Fixed effect model Heterogeneity: Fsquared=	NM16189 M37047 BM15421 0%, p=0.9572	21 7 41	352 267 1649 2268	9 5 22	181 269 1655 2105		- 0.01 0.01 0.01 0.01	[-0.03; 0.05] [-0.02; 0.03] [0.00; 0.02] [0.00; 0.02]
Publication Rhinitis seasonal Fixed effect model Heterogeneity: I-squared=	NM16189 NaN%, p=1	21	352 352	9	181 181		- 0.01 - 0.01	[-0.03; 0.05] [-0.03; 0.05]
					1	-0.04 -0.02 0 0.02 0.04 Favours Orlistat Favours Place		

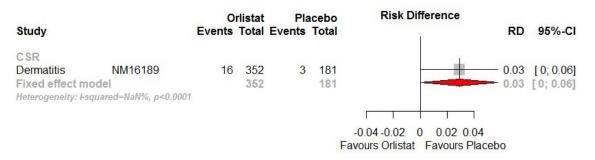


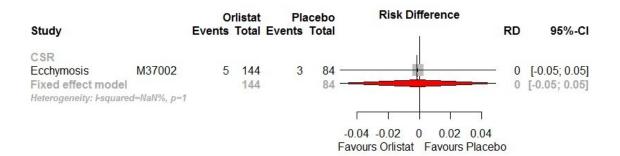




Skin & Subcutaneous tissue disorders

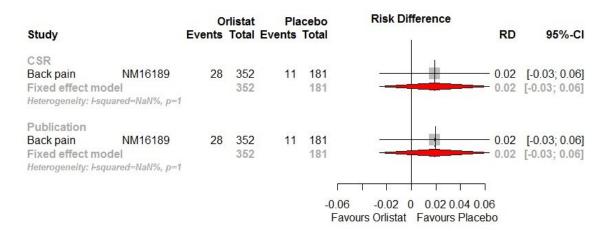




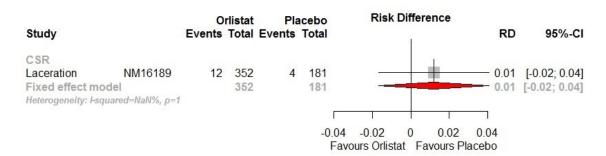


Injury and positioning

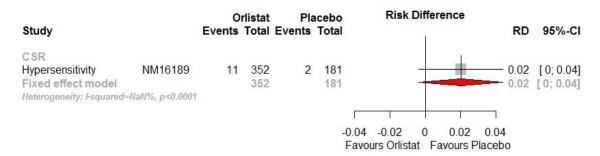
Study	0.000	rlistat Total	Pla Events	acebo Total	Risk Difference	RD	95%-CI
CSR Joint sprain Joint sprain Fixed effect model Heterogeneity: I-square	and a second	352 1649 2001	17 42	181 1655 1836		- 0.01 0.00 0.00	[-0.05; 0.06] [-0.01; 0.01] [-0.01; 0.01]
Publication Joint sprain Fixed effect model Heterogeneity: I-square	35	352 352	17	181 181		- 0.01 - 0.01	[-0.05; 0.06] [-0.05; 0.06]
				F	-0.04 -0.02 0 0.02 0.04 Favours Orlistat Favours Place	bo	



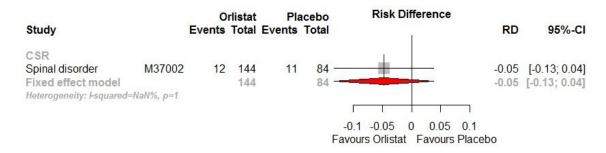
Study	377	rlistat Total	Pla Events	cebo Total	Risk Difference	RD	95%-CI
CSR Limb injury NM16189 Fixed effect model Heterogeneity: I-squared=NaN%, p-	18	352 352	5	181 181	-	0.02	[-0.01; 0.06] [-0.01; 0.06]
Publication Limb injury NM16189 Fixed effect model Heterogeneity: I-squared=NaN%, p	18	352 352	5	181 181	-0.04 -0.02 0 0.02 0.0 Fayours Orlistat Fayours Pla	A STATE OF THE STA	[-0.01; 0.06] [-0.01; 0.06]

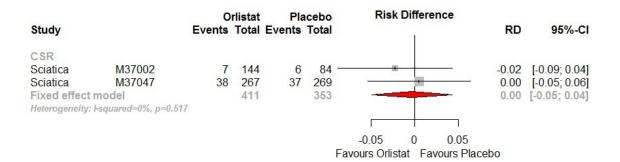


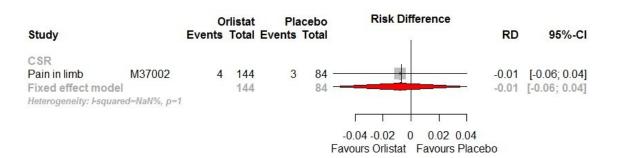
Immune system disorders



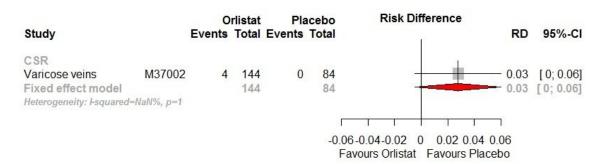
Musculoskeletal, connective tissue and bone disorders







Varicose veins



Supplementary Table S1: Search criteria used in both Cochrane central and MEDLINE.

Search set	CENTRAL	MEDLINE
1	(Orlistat or Xenical)	randomized controlled trial.pt.
2		controlled clinical trial.pt.
3		randomized.ab.
4		placebo.ab.
5		clinical trials as topic.sh.
6		randomly.ab.
7		trial.ti.
8		7 or 5 or 2 or 6 or 1 or 4 or 3
9		(orlistat or Xenical).tw.
10		8 and 9