Supplemental Materials: Appendices

Appendix 1: Search strategy A for MEDLINE, EMBASE, GLOBAL HEALTH, AMED and CAB

1. exp Food Hypersensitivity/
2. exp Milk Hypersensitivity/
3. exp Egg Hypersensitivity/
4. exp Peanut Hypersensitivity/
5. exp Tree nut Hypersensitivity/
6. exp Nut Hypersensitivity/
7. ((food or Oral Allergy Syndrome or milk or egg or peanut or arachis hypogaea or tree nut or hazelnut or brazil nut or walnut or chestnut or pistachio or almond or legumes or wheat or soy or fish or seafood or shellfish or shrimp or lobster or crab or crawfish or kiwi or apple or peach or apricot or cherry or pear or plum or tomato or green pea or potato or carrot or parsley or celery or additives) adj3 (allerg* or hypersensitivit*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. exp Desensitization, Immunologic/
10. exp Immunotherapy/
11. Desensitis?ation.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
12. Immunotherapy.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
13. Oral Immunotherapy.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
14. Oral desensiti?ation.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
15. Specific oral tolerance induction.mp.
16. Oral tolerance induction.mp.
17. Sublingual Immunotherapy.mp.
18. Specific Immunotherapy.mp.
19. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. exp Intervention Studies/
21. Intervention Studies.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
22. Analytical stud*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
23. Experimental stud*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
24. Etiology.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
25. exp Clinical Trial/
26. Trial.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
27. Clinical Trial.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

28. exp Controlled Clinical Trial/
29. Controlled Clinical Trial.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
30. Uncontrolled Trial.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
31. Randomi?ed Controlled Trial.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
32. Quasi-randomi?ed trial.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
33. Non-randomi?ed trial.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
34. exp Placebos/
35. Placebos.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
36. exp Random Allocation/
37. Random Allocation.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
38. exp Double-Blind Method/
39. Double-Blind Method.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
40. Double-Blind design.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
41. exp Single-Blind Method/
42. Single-Blind Method.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
43. Single-Blind design.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
44. Triple-Blind Method.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
45. Random*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
46. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45

47. 8 and 19 and 46

Search strategy B for The Cochrane Library, LILACS, TRIP, CINAHL, ISI Web of Science and BIOSIS

(Food hypersensitivity OR food allergy OR Oral Allergy Syndrome OR milk allergy OR egg allergy OR nut allergy OR peanut allergy OR arachis hypogaea allergy OR tree nut allergy OR hazelnut allergy OR legumes allergy OR wheat allergy OR soy allergy OR fish allergy OR seafood allergy OR shellfish allergy OR kiwi allergy OR apple allergy OR peach allergy OR additives hypersensitivity OR additives allergy)
AND
(Immunologic, desensiti*, OR immunotherapy OR oral immunotherapy OR sublingual immunotherapy OR oral desensiti* OR Specific Oral Tolerance Induction OR Oral Tolerance Induction)
AND

(Analytical stud* OR intervention stud* OR experimental stud* OR trial OR clinical trial* OR controlled clinical trial OR uncontrolled trial OR randomi* controlled trial OR quasi randomi* OR non randomi* OR random allocation OR single blind method OR double blind method OR triple blind method OR random*)

Appendix 2: List of experts contacted

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Appendix 3: Detailed characteristics of included studies

Study	Patients characteristics/ diagnosis criteria	Design	Foods	Type of immunotherapy		Clinical outcomes					Immunologic outcomes			
				H1	H2	OD	OT	RR	Adverse events/ medication use					
									SRs	LRs	SPT	TIgE/ SpIgE	IgG/ IgG4	Other
Burks, 2012	55 children aged 5 to 11 years (median 7); HE OIT - 40; placebo=15; inclusion criteria: clinical history of egg allergy (development of allergic symptoms within minutes to 2 hours after ingesting egg); serum egg-specific IgE antibody level > 5 kU/l (≥ 6 years), or > 12 kU/l (5 year old)	Randomised double-blind placebo-controlled trial	HE	Initial dose-escalation (clinical research setting), build-up, and maintenance phases double blind placebo controlled until 5g egg white challenge at 10 months. Open label thereafter Placebo then discontinued, OIT group on maintenance until 22 months Children who successfully passed the 10g challenge at 22 months discontinued oral immunotherapy and avoided all egg consumption until 10g (+whole cooked egg) food challenge at 24 months, to test for sustained unresponsiveness. Children who passed this challenge at 24 months were placed on a diet with ad libitum egg consumption and were evaluated for continuation of sustained unresponsiveness at 30 months and 36 months.		After 10 months of therapy, none of the children who received placebo and 55% of those who received oral immunotherapy passed the oral food challenge and were considered to be desensitized; After 22 months, 75% of children in the oral-immunotherapy group were desensitized. In the oral-immunotherapy group, 28% (11 of 40 children) passed the oral food challenge at 24 months and were considered to have sustained unresponsiveness. At 30 months and 36 months, all children who had passed the oral food challenge at 24 months were consuming egg.				Adverse events, 25.0% of 11,860 doses of oral immunotherapy with egg and 3.9% of 4018 doses of placebo. Respiratory & skin 3.2% of 4018 placebo doses, 12.2% of 11860 OIT doses Oral or pharyngeal 78% of OIT doses 20% of placebo (p<0.001) In the oral-immunotherapy group, 78% of children had oral or pharyngeal adverse events, as compared with 20% of those in the placebo group (P<0.001). After 10 months, the rate of symptoms in the oral-immunotherapy group decreased to 8.3% of 15,815 doses (data not shown)	SPT wheal sizes decreased significantly more from baseline to Month 22 among OIT subjects Vs placebo group (p=0.02) When positive skin tests were measured with end-point titration, egg OIT subjects had a median 1-log decrease, whereas placebo recipients had no change (p=0.009).	The median reduction in egg-specific IgE levels from baseline to Month 22 (-5.9 [range: -94.6, 16.6] kUA/L) for egg OIT was not significantly greater (p=0.06) than that for placebo (-1.9 range [-23.5, 37.1] kUA/L).	The median change from baseline to Month 22 in egg-specific IgG4 levels in the egg OIT group (median: 48.5 [range: -0.1, 162.1] kUA/L, p<0.001) was significantly higher than that for placebo.	Basophil activation decreased more during therapy in the egg OIT group compared with the placebo group and these differences were statistically significant (0.01 ug/mL stimulus, p=0.002; 0.1 ug/mL stimulus , p=0.001).
Caminiti, 2009	13 children of both sexes (8 boys) aged 5-10 yrs (mean age 8yrs);oral	Randomised double-blind placebo-controlled design for 6	CM		The desensitization schedule started with one drop of whole CM diluted 1:25 every week,		Full tolerance (200 ml of milk) was achieved in		1 child in the double-blind group with 4 ml of CM had urticaria, rhinitis, throat pruritis, vomiting, and circulatory collapse; he was	1 in the double-blind group and 2 patients in the open study	Baseline data - SPT for the confirmation of diagnosis	Baseline data - Specific IgE was measured for the		

Study	Patients characteristics/ diagnosis criteria	Design	Foods	Type of immunotherapy		Clinical outcomes					Immunologic outcomes			
				H1	H2	OD	OT	RR	Adverse events/ medication use		SPT	TIgE/ SpIgE	IgG/ IgG4	Other
									SRs	LRs				
	desensitization – 10; placebo – 3;only 6 patients were randomised to double-blind desensitization with milk or soy formula as placebo; the diagnosis of CMA was based on clinical history, SPT, SpIgE, DBPCFC	patients only 7 patients underwent the protocol in open fashion			then doubled weekly until the 18th week to achieve an intake of 200 ml in ≈ 4 months; all doses were administered at the clinic under medical supervision		7 children; in 2 children failed, because of severe reactions; 1patient achieved a partial tolerance (64 ml of milk)		treated with i.m. epinephrine;antihistamines;i.v. corticosteroids and gradually recovered; the desensitisation stopped; 1 patient in the open study group with 4 ml of CM had rhinitis, cough, asthma, generalised urticaria, and laryngeal edema; he received i.m. epinephrine and corticosteroids; oral antihistamines; inhaled salbutamol and promptly recovered. 1 patient achieved a partial tolerance because with the dose of 64 ml she developed urticaria, angioedema, cough; i.m. antihistamines and corticosteroids were introduced	group had throat pruritis, gritty eyes, watery eyes, abdominal pain, transient erythema (face and hands); no medication has been taken		confirmation of diagnosis		
Enrique, 2005; Enrique, 2008 – follow-up study	23 adults (aged 18 to 60, mean age 29.4); active group=12; placebo=11; the diagnosis of hazelnut allergy on the basis of clinical history, SPT, SpIgE, DBPCFC	Randomised double-blind, placebo-controlled study	Hazelnut	After the build-up phase, all patients followed the same daily maintenance schedule consisting of 5 drops of the maximum concentration performed at home (1157 doses); total doses administered 1466	A biologically standardized hazelnut extract, graded in 5 strengths (F0, F1, F2, F3, FA) in glycerosaline solution was used; maximum dose of 25 drops from the most concentrated vial in 4 days; all doses of build-up phase were administrated in a hospital setting (309 doses) and was completed in 4 days (rush schedule); doses were administered at 15 minute intervals		Mean hazelnut quantity provoking objective symptoms increased from 2029 g to 11.56 g (P=0.02; active group) versus 3.49 g to 4.14 g (placebo; NS); almost 50% of patients who underwent active treatment reached the highest dose (20 g), but only 9% in the placebo		SRs 0.2% (3 reactions/1466 doses); they occurred during build-up phase and only antihistamines were used; 1 facial urticaria occurred in the placebo group and 2 reactions in 1 patient of the active group – skin pruritis and delayed urticaria; LRs: immediate oral itching were observed in 7.4% (109 reactions/1466 doses); during build-up phase 4 patients in the active group abdominal pain several hours after the ingestion on 1 occasion each	all LRs during maintenance phase were also oral itching, and all were in the same patient	All patients underwent SPT before and after treatment; Also, each patient was skin prick tested with a raw hazelnut extract to determine the in vivo reactivity of the extract; a concentration of 2.69 mg/ml hazelnut extract was calculated to cause a wheal size equal to that obtained with histamine; for this raw hazelnut extract, 1 mg corresponded to 1.84 mg of the allergen Cor a 8 and 2.88	SpIgE – non significant changes before and after treatment in both groups	IgG4 levels were measured before and after treatment – no statistical significance was found between the studied groups; in the active group, an increase in mean Ig4 levels from 7.34 allergen units (AU)/mL to 9.84 AU/mL (P<0.05) was observed	An increase in IL-10 levels after SLIT was only in the active group, rising from 1.62 pg/ml to 2.24 pg/ml (P<0.05); no differences were observed between the placebo and active groups

Study	Patients characteristics/ diagnosis criteria	Design	Foods	Type of immunotherapy		Clinical outcomes					Immunologic outcomes			
				H1	H2	OD	OT	RR	Adverse events/ medication use					
									SRs	LRs	SPT	TIgE/ SpIgE	IgG/ IgG4	Other
											mg of the allergen Cor a 1			
Fernandez-Rivas, 2009; Garcia, 2010 – follow-up study	18-65 y.o. randomised to active [(n=33) (a Pru p 3 quantified peach extract)] or placebo [(n=16) (similar solution without peach allergen)] in 2:1 proportion during 6 months; the tolerance (DBPCFC), immunological changes (SPT, SpIgE, IgG4) and clinical efficacy (nature, severity and causal relation with the treatment of every adverse events) were evaluated; the diagnosis of peach allergy on the basis of clinical history, SPT, SpIgE, DBPCFC	Randomised double-blind, placebo-controlled trial	Peach	Home maintenance (6 months) Monday, Wednesday and Friday 1 dose 10.0 µg of Pru p 3 peach extract; patients visited the clinics once a month	Rush build-up phase (hospital): 1st day – 3 doses (0.22 µg) of Pru p 3; 2-nd day – 3 doses (1.12 µg); 3rd day – 3 doses (5.60 µg); 4th day – 3 doses (28.0 µg); 5th day – 1 dose (50 µg); sublingual-swallow technique comprised four vials containing 0.4, 2, 10 and 50 µg/ml of Pru p 3 or placebo; diary cards for recording any adverse event		Tolerance was assessed with a careful recording of adverse events. The main efficacy outcome was the change in the response to a DBPCFC with peach; after 6 months of SLIT in the active group the dose of Pru p 3 needed to induce LR or SR were 9 (3^2) and 3 (3^1) times higher respectively; inter group differences at T6 for SR were almost significant (Log Rank test, P=0.06)		SRs 16 occasions [(14 in the build-up phase (skin reactions in 6 patients, 1 rhinoconjunctivitis, 7 gastric complaints)]; 1 rhinoconjunctivitis during the hospital maintenance week, 1 gastrointestinal complaints during the home maintenance; all SRs were mild and subsided either spontaneously or with oral antihistamines, antacids and/or omeprazol; Placebo group: 3 SRs 1 in the build-up phase (cutaneous itching), and 2 in the first maintenance week (1 angioedema and 1 diarrhea)	Total 1480 adverse events(no serious; 1344 in the active group, and 12 in the placebo group p<0.0001) Active group: LRs 98.8% (n=1328); mostly during build-up phase and the first maintenance week (P=0.014); 94.9% (n=1260) located on the oropharynx, others gastric complaints	SPTs were performed before (T0), after 1 month if treatment (T1), and at the end of the trial (T6); after treatment the patients had a significant decrease in SPT (5.3 times) compared to controls	Serum samples of SpIgE were collected at T0; T1, and T6; SpIgE showed a significant increase both in the active (P<0.001) and placebo (P=0.025) groups, although the increase remained only significant at T6 in the former (active 4.23, P<0.001; placebo 4.04, P=0.079, T-test); no significant inter-group differences were observed (P=0.456); none of the patients with negative IgE to rPru p 3 at T0 converted to positive at T1 or T6	IgG4 was collected at T0; T1; T6; IgG4 to nPru p3 showed a different evolution between groups (P=0.022) with a significant increase in the active arm (P=0.007) not observed in the placebo one (P=0.185)	
Fleischer, 2013	40 subjects aged 12 to 37 years old (median 15); male 68%; were enrolled in a randomized, double-blind, placebo controlled study;	Randomized double-blind, placebo-controlled multicentre trial	Peanut	Dosing started at 0.000165 mg of peanut protein or placebo escalation through 660 ug occurred every 2 weeks, 660ug attained at 12 weeks. 3 doses attempted at a minimal interval of 30 minutes. If subjects failed 3-		The primary end point was the percentage of desensitized subjects measured with 5-g peanut powder OFC performed 44 weeks after initiation of therapy (Week 44 Unblinding OFC); subjects			Only 1 out of 127 adverse events required epinephrine and oral antihistamine	Only 127 (1.1%) of 11,854 total doses required treatment during the first phase: 125 (1.1%), oral antihistamine only; 1 (0.01%), albuterol only	No significant difference between SLIT and placebo	Sp IgE Week 44 peanut sp IgE 35.8 (3.3 to 75.0) in SLIT vs 20.1 (4.1 to 80.3) in placebo (NS). Increase between baseline and wk 44 in SLIT	Sp IgG4 Week 44 sp IgG4 0.7 (0.4 to 2.3) SLIT vs 0.5 (0.2 to 0.7) placebo (NS). Increase between baseline and wk 44 in SLIT.	Basophil activation % CD63+ values were significantly lower for Peanut SLIT subjects compared with Placebo subjects for the 10-2 mg/mL crude peanut

Study	Patients characteristics/ diagnosis criteria	Design	Foods	Type of immunotherapy		Clinical outcomes					Immunologic outcomes			
				H1	H2	OD	OT	RR	Adverse events/ medication use		SPT	TIgE/ SpIgE	IgG/ IgG4	Other
									SRs	LRs				
	inclusion criteria: Clinical history or physician's diagnosis of peanut allergy, positive peanut SPT response (wheal diameter >3mm) or detectable peanut-specific IgE (PN-IgE; >0.35 kilounits of antibody per liter [kUA/L]), positive baseline DBPCFC to peanut (defined as objective allergic symptoms at a cumulative dose of <2 g of peanut powder).			dose escalations after 3 consecutive biweekly attempts, 1- or 2-dose biweekly escalations were allowed subsequently. After each observed dose, subjects continued the same daily dose at home for 2 weeks. After 660 ug was achieved, single dose increases occurred, followed by 2 weeks of maintenance therapy of 1,386ug/d; Phase 1 subjects took a minimum dose of 165ug and a maximum maintenance dose of 1386 ug of peanut protein or placebo (420umL) at home on a daily basis for the maintenance period until the Week 44 Unblinding 5-g DBPCFC. After unblinding, subjects receiving active peanut SLIT continued on maintenance dosing with a 10-g OFC after approximately 1 year of maintenance therapy; Phase 2 Placebo subjects crossed over to active peanut SLIT and were escalated to		successfully consuming 5 g or at least 10-fold more peanut powder than the baseline OFC threshold were considered responders 70% (14) SLIT responders 15% placebo responders p<0.001; The median successfully consumed dose (SCD) at Week 44 was significantly higher than the baseline OFC for Peanut SLIT subjects (371 vs 21 mg, respectively; P 5.01) but not for Placebo subjects (146 vs 71 mg, respectively; P =.14). However, the median SCD after 44 weeks of therapy was not significantly different between treatment groups (P=0.16). All Week 44 responders still being followed were Week 68 responders. The median SCD increased to 996 mg, and this was significantly higher than at Week 44 (P =.05) and baseline (P =.009)								stimulant (P =008) and the 10-3 mg/mL crude peanut stimulant (P =.049) indicating a weak effect on basophil activation.

Study	Patients characteristics/ diagnosis criteria	Design	Foods	Type of immunotherapy		Clinical outcomes					Immunologic outcomes			
				H1	H2	OD	OT	RR	Adverse events/ medication use					
									SRs	LRs	SPT	TIgE/ SpIgE	IgG/ IgG4	Other
				a maximum maintenance dose of 3696mg (1120mL).A5-g Crossover OFC was performed after 44 weeks of SLIT therapy										
Kim, 2011	18 children aged between 1 and 11 years were enrolled in a double-blind, placebo controlled study (active=11; placebo=7). The diagnosis based on a physician-documented clinical history, a CAP-FEIA peanut-specific IgE level of 7 kU/L or greater; SPTs to peanut were not required for enrolment	Randomised double-blind placebo-controlled design for 18 subjects who underwent 6 months of dose escalation and 6 months of maintenance dosing followed by a DBPCFC	Peanut		All observed dosing was performed in the hospital. The active group received dilutions of crude peanut extract (1:20 wt/vol) dissolved in 0.2% phenol and 50% to 55% glycerinated saline (max peanut concentration 5000 µg/ml. The placebo group received a glycerinated saline solution + phenol with caramel coloring (doses 1 to 8 pumps (50 µL per pump). The first day the starting dose was 0.25 µg of peanut protein (1 pump of 1:1000 dilution). Subjects then returned for 13 biweekly observed dose-escalation visits. After each observed dose escalation, subjects continued the same dose daily at home for 2 weeks. When the maintenance dose reached 2000-µg of peanut protein (8 pumps of 1:1 stock dilution) , subjects continued daily maintenance dosing at home for approximately 6 months	In active group the 12 mo DBPCFC subjects had a significant increase in reaction threshold after safely ingesting a median cumulative dose of 1710mg of peanut protein (a 20-fold greater amount of peanut protein and approximately equivalent to 6-7 peanuts). In control group the subjects only safely ingested a median cumulative dose of 85 mg (<1 peanut) and this level of desensitization is significant			One (0.02%) subject had mild wheezing which required albuterol Skin symptoms 0.6% active, 6.5% control	Reactions were reported with 11.5% of peanut doses and 8.6% of placebo doses. In active group most of the symptoms were transient oropharyngeal itching (9.3%), whereas skin itching was most common for those receiving placebo (6.5%). Of the 4182 active peanut doses, 11 (0.26%) home doses required antihistamines, no epinephrine required for whole study.	Titrated SPT were performed at baseline; 4 months; 8 months, and the day of the DBPCFC; SPT responses after 12 months of SLIT were significantly smaller in the active group compare to placebo (P=0.020) Active SPT 4mm range 0-11 vs. control 11.5mm range 3.5-2.1	Serum for SpIgE was obtained at baseline; 4 months; 8 months, and the day of the DBPCFC; Specific IgE levels in the active group saw statistically significant rise compare to placebo over the initial 4 months (P=0.002) and then over the remaining 8 months decreased (P=0.003)	Serum for IgG4 was obtained at baseline; 4 months; 8 months, and the day of the DBPCFC; IgG4 levels in the active group increased significantly during 12 months compare to placebo (P=0.014)	Whole blood for basophil activation was obtained at baseline and the day of the DBPCFC; There was decreased basophil responsiveness after stimulation with peanut in the active group (P=0.009). IL-5 levels decreased after 12 months (P=0.015). IL-13 levels in the active treatment group decreased after 12 months. However, this level was not significant compared with that in the placebo group (P=0.06) No difference in IL-10, IFN-γ, Treg
Lacono, 2013	20 children aged between 5 and 11 years pld (median 7 years 7	Randomised, not blinded clinical trial	Raw HE	SOIT done at home and in day hospital with raw hens egg emulsion; initial			No child could tolerate 40ml of egg in a single			All children in SOTI group had side effects 53 events, none required	SOTI vs control at 6 months SPT 5 (4–13) vs 10	SOTI vs control at 6 months Sp IgE 8.7 (3.3–17) vs		

Study	Patients characteristics/ diagnosis criteria	Design	Foods	Type of immunotherapy		Clinical outcomes					Immunologic outcomes			
				H1	H2	OD	OT	RR	Adverse events/ medication use		SPT	TIgE/ SpIgE	IgG/ IgG4	Other
									SRs	LRs				
	months); male 50%; were enrolled in a randomised controlled trial. Inclusion criteria: i) ≥t 1 anaphylactic reaction after accidental egg exposure within 12 months of pre-enrolment; (ii) previous SPT/IgE positive for egg (iii) a positive DBPCFC at ≤0.9 ml of raw egg emulsion.			day escalation phase 0.015 ml emulsion increased to 40 ml over 6 months			dose 9/10 (90%) of SOTI achieved partial tolerance (10-40ml) none of control subjects achieved tolerance p<0.00001; The median maximal tolerated dose was 20 ml (range: 5–30 ml) in SOTI children and 0.45 (range: 0.225–1.8) in controls			adrenaline, in control group 5 events SOTI vs control 23/53 vs 0/5 skin/respiratory, 21/53 vs 5/5 oral/GI; The children in the SOTI group had a relative risk of 4.96 (95% CI = 3.30–7.45) of incurring an adverse event, but there were no significant differences in the severity of reactions	(5.5–15) p=0.007	13.5 (10.5–5.4) p <0.001		
Longo, 2008	60 children randomised in 2 groups: A – SOTI (n=30, mean age 7.9yrs); B-milk –free diet (n=30, mean age 8.1 yrs); followed for 1 year; all children with severe CMP-induced systemic reactions; the diagnosis of CMA on the basis of clinical history, SPT, SpIgE, DBPCFC	Randomised trial	CM	After discharging from hospital children followed a slow increasing phase (increasing by 1 ml every second day) personalized for each subject, on the basis of the frequency and severity of side effects and confidence of parents; when home dosing reached 150 ml of whole milk in a single dose, the patients were asked to eat other dairy products; SOTI was considered to have failed if the child did not reach at least 5 ml of undiluted milk in a single dose after 1 year or if participants were stopped for	SOTI had 2 phases: the first – rush phase took place in the hospital for 10 days and were dosed daily (first day: 6 doses of diluted milk at 1-hour intervals; second, third, and fourth day: 4 doses of diluted milk at 2-hour intervals; and then 3 daily doses at 2-hour intervals, increasing the concentration of the solution each day to reach whole milk); all children were given antihistamine daily (oxatomide), 1 mg/kg per day)		Maximum tolerance: the number of children could tolerate 150 ml of CM or more in a single dose; partial tolerance: the number of children able to drink at least 5 ml but less than 150 ml in a single dose; after 1 year, 11 (36%) of children in group A had become completely tolerant, 16 (54%) could take limited amounts of milk (5-150 ml), and 3		The rush phase: i.m. epinephrine 4 times in 4 children, nebulized epinephrine in 18 children and more than once in 7 children because of recurring respiratory symptoms. Slow (home) dosing: 2 children required treatment in the emergency department (oral steroids, antihistamine, and i.m. epinephrine (1 case).	In group B 6 (20%) children had mild reactions (accidental exposure)	SPT was performed at baseline but was not considered as end-point at the one year follow-up	SpIgE was measured at baseline; at 6 and 12 months; SpIgE measured at 6 and 12 months showed a significant decrease after SOTI in 15 of 30 patients (graphical description); cutoff point of 100 kUA/L		

Study	Patients characteristics/ diagnosis criteria	Design	Foods	Type of immunotherapy		Clinical outcomes					Immunologic outcomes			
				H1	H2	OD	OT	RR	Adverse events/ medication use		SPT	TIgE/ SpIgE	IgG/ IgG4	Other
									SRs	LRs				
				adverse effects			(10%) were not able to complete the study because of adverse effects							
Martorell, 2011	60 children aged 24-36 months with IgE-mediated allergy to CMPs were enrolled in this trial; 30 (treatment group0 and 30 children (control group) were kept on a milk-free diet and followed up for 1 year; the diagnosis of CM allergy on the basis of clinical history, SPT, SpIgE, DBPCFC	Randomized, controlled, parallel-group, multicentre trial	CM		Day 1 in hospital: doses hourly; milk (dilution) 1/100 dose (ml): 1,2,3,4,8 Dilution 1/10: dose 1.6 ml Day 2 hospital: milk dilution 1/10: 1.6ml Doses hourly: 3.2; 6;12 ml and pure milk 2.5 ml; Dose maintained at home, with elevation once a week in hospital Total 16 weeks; At the end of the study, OD was offered to the CG patients who had not achieved tolerance		After 1-year follow-up period, 90% of the children in active group had become completely tolerant vs 23% in CG			24 patients in AG (80%) [14 moderate (47%) and 10 mild (33%) reaction]. The most common manifestations were urticaria-angioedema, followed by cough	SPT decreased significantly after the treatment in the active group compared to controls ($p<0.0001$)	SpIgE decreased after the treatment in the active group significantly (AG 11.5 ± 13.84, median 7 versus 33.75 ± 34.17 kU/L)		
Meglio, 2013	20 children with median age 8.4 years; active group=10; control=10 with HE allergy were enrolled in this open trial. The diagnosis of HE allergy on the basis of SPT, SpIgE, DBPCFC and convincing history	Randomized, controlled open trial	HE	Initial day escalation phase: Started from 1 drop (mixed raw egg white and yolk) diluted 1:100 with water, corresponding to 0.27 mg of HE proteins; Build-up phase: The HE doses were doubled every 8 days until day 80. Maintenance phase: Subsequently, the HE doses were doubled every 16 days to achieve a total daily intake of 25 ml in 6 months		8/10 children (80%) in the active group achieved the daily intake of 25 ml over a 6-month period. 1 child (10%) could tolerate up to 2 ml/day while another child (10%) failed the desensitisation				1 child had urticarial and pruritus around 3 ml of raw he and the treatment was stopped	SPT no differences; no between group comparisons	SpIgE tests were determined with REAST (Reverse Enzyme Allergo Sorbent Test) and ISAC (Immuno Solid-phase Allergen Chip) methods; no comparisons between groups;	No comparisons between groups	
Morisset, 2007a;	CMA: 57 children aged	Randomised trial	CM Egg	OD protocol from 1 ml whole		A SBPCFC to milk was			Unable to differentiate systemic and local reactions	Unable to differentiate	SPT was performed at	SpIgE was measured at		

Study	Patients characteristics/ diagnosis criteria	Design	Foods	Type of immunotherapy		Clinical outcomes					Immunologic outcomes			
				H1	H2	OD	OT	RR	Adverse events/ medication use		SPT	TIgE/ SpIgE	IgG/ IgG4	Other
									SRs	LRs				
Morisset, 2007b	between 13 months and 6.5 years (mean 2.2 ± 1 yrs) were randomised to OD group (n=27) and A group (interrupted avoidance n=30) for 6 months; Egg allergy: OD group (n=49, mean age 3.5 yrs); A group (n=35, mean age 3.6 yrs); the diagnosis of CM and egg allergy on the basis of clinical history, SPT, SpIgE, SBPCFC			pasteurized milk day 1 to 20 ml day 1 (first week); second week – 50 ml/day; third week – 100 ml/day; fourth week 100 ml/day and introduction of cream desserts, yoghurts or cream cheese; fifth and sixth week – 250 ml/day and dairy products; seventh week and thereafter: routine amounts, not quantified. OD protocol with hard-boiled eggs: first week – 1 g of egg yolk once a day, every day; second week – 1 g of yolk and 1 g EW once a day, every day; third week – 2 g of yolk and 2 g of EW once a day, every other day; fourth week – 4 g of yolk and 4 g of EW once a day, every other day; second month: introduction of biscuits and crackers, etc; third month: introduction of flans, cream desserts		positive in 11.1% of those following OD vs. 40% after A ($p<0.025$). The size of SPT decreased after OD and increased after A (-3.4 mm vs. +0.84 mm, $p<0.002$) Egg allergy: After 6 months, in the OD group, the mean size of the SPT was significantly reduced compared to the A group.				systemic and local reactions	baseline and after 6 months; In both trials SPT was significantly lower in active group compared to controls ($p<0.05$)	baseline and after 6 months; SpIgE decreased in both groups. However, the decrease in IgE was greater in the "recovery" subgroup: 3.07 vs. 1.6 kU/l ($P<0.1$) and 8.21 vs. 6.7 kU/l in the "failure" subgroup (P ns)		
Pajno, 2010	30 children (active=15; control=15) aged between 4 and 10 y.o. were enrolled in the study. The diagnosis	Randomised single-blind controlled study	CM		Fresh CM or soy formula was administered at the clinic at weekly intervals at increasing doses of 0.1,0.3,1,3,10,30,and 100 ml with 30		In 10 patients in the active group achieved full tolerance to CM (200		In 3 patients systemic reactions occurred and then stopped OIT.	7 children had mild reactions – abdominal pain, throat pruritis, gritty eyes and they were transient (just in 1 case	SPT was performed only for the confirmation of diagnosis	SpIgE levels were measured at baseline; after 8 weeks, and at the end of the study; No	IgG4 was measured at baseline; after 8 weeks, and at the end of the study; At week 18 the levels of	

Study	Patients characteristics/ diagnosis criteria	Design	Foods	Type of immunotherapy		Clinical outcomes					Immunologic outcomes			
				H1	H2	OD	OT	RR	Adverse events/ medication use		SPT	TIgE/ SpIgE	IgG/ IgG4	Other
									SRs	LRs				
	of CM allergy based on clinical history, SPT, CAP-RAST assay and DBPCFC				minutes between doses. The initial dose started from 1 drop of whole milk diluted 1:25. The dose was doubled every week at the clinic until week 18 to achieve an intake of 200 mL in approximately 4.5 months		mL) and in 1 patient partial tolerance (100 mL) 10/13 tolerance, 10/15 on intention to treat			antihistamines were given)		significant difference in specific IgE levels between the active and control groups	IgG4 in the active group were significantly higher than in the control group (P<0.01) Mean (SD) difference 23.8 (5.3) vs. 4.3 (1.7)	
Patriarca, 1998	Cases (n=14) 4-14 yrs old, mean not given (median 5.5 p=0.486); 6/14 male (43%); one female entered three times Controls (n=10) aged 5-13 (median 7.5); 6/10 male (60%); the diagnosis of allergy on the basis of medical history of food allergy, SPT >3 mm, SpIgE, DBPCFC (all but one who had life threatening reaction)	Quasi RCT One subject entered into the intervention group on 3 occasions when desensitized to milk, egg, fish. Hence 24 subjects in trial from 22 individuals	CM 6 (43%) Egg 5 (36%) Fish 2 (14%) Apple 1 (7%)	Initial day escalation phase: CM 10 drops 10 ml; days 1-12, 4 drops increased to 12/day Egg 10 drops egg in 100 ml water; days 1-20 4 drops to 36 drops x 3 Fish 10 ml 6% fish extract in 90 ml water; days 1 to 24 4 drops to 108 drops Apple 1 ml apple mixed in 9 ml water; days 1 to 34 1 dropx2 to 6 drops x4 Build-up phase: Milk 13 to 104 drops 1 drop milk to 30 ml x4 Egg 21 to 90 1 drop to 30 mlx3 Fish 25 to 120 15 drops 6% extract to 200 g boiled fish/day Apple 35 to 109 1 drop apple mix to 1 apple a day Maintenance phase: Milk 100 ml 2-3x/week Egg 1 egg 2-3 x/week Fish 200 g boiled/week Apple 1 2x/week	12/14 (86%) successfully able to eat any foods without problems in follow-up 3-6 yrs; 2 failures due to attendance; in controls all DBPCFC at 6 months positive, also SPT, RAST still positive at 6 months (P<0.0001)				6/14 urticaria, 2 asthma, 1 angioedema, 2 abdominal pain, 4 none; all reactions were mild and easily controlled by antihistamines	SPT was performed at baseline and after treatment; No changes in SPT	Total and SpIgE were performed at baseline and after treatment; No changes in total IgE or SpIgE			
Salmivesi 2012	28 children aged 6-14	Randomized, double-blind,	CM	The amount of milk protein	The first dose (0.06 mg) and eight later	24 (86%) patients			In the active group wheezing in 5 (19.2%I, but no	Active group: subjective				

Study	Patients characteristics/ diagnosis criteria	Design	Foods	Type of immunotherapy		Clinical outcomes					Immunologic outcomes			
				H1	H2	OD	OT	RR	Adverse events/ medication use		SPT	TIgE/ SpIgE	IgG/ IgG4	Other
									SRs	LRs				
	years (active=18; control=10) with CMA were enrolled in this trial; the diagnosis of CMA on the basis of clinical history, SPT, SpIgE, DBPCFC	placebo controlled study		increased daily, being doubled every week, from 0.06 to 6400 mg; The final dose of 6400 mg was given at home on day 162, and control visit was held within 2 weeks, all other dose increases were performed at home according to a prospective, daily schedule;	doses were given in the outpatient clinic; All 10 children in the control group successfully completed an open-lable OIT by an identical protocol	completed the protocol: 16/18 in active and 8/10 placebo; After OIT: 14 children tolerated 6400 mg, and other two 960 and 1920 mg			emergency rooms were needed. Follow-up 3.0-3.5 years later, one child had stopped using CM products because of severe eczema and severe asthma; one anaphylactic reaction took place when milk avoidance was restored	abdominal and oral symptoms; Control group: subjective abdominal and oral symptoms				
Skripak, 2008	20 children aged between 6 and 21 were divided into 2 groups: Active (n=13; male 8, mean age and SD 9.3 ± 3.3 from the pediatric clinics); Placebo group (n=7, male 4, mean age and SD 10.2 ± 3.3); the diagnosis of CMA on the basis of clinical history, SPT, SpIgE, DBPCFC	Randomised double-blind, placebo-controlled study	CM	Home dose was initiated at the highest dose tolerated on the dose escalation day after 7 to 14 days on a given dose, they returned to the hospital to receive a dose increase (table 1); once a dose of 500 mg (equivalent to 15 ml of milk) was achieved, they continued on that dose daily for 13 weeks, after which they underwent DBPCFC	The hospital-based dose-escalation started with 0.4 mg of milk protein; doubling doses were given every 30 minutes to a maximum of 50 mg (cumulative dose, 98.7 mg); participants had to tolerate a minimum dose of 12 mg (cumulative dose, 23.7 mg) to proceed with home dosing		The median milk threshold dose in both groups was 40 mg at the baseline DBPCFC, after OIT in the active group the median cumulative dose inducing a reaction was 5140 mg (range 2540-8140); all patients in the placebo group reacted at 40 mg (P=0.0003)		Among 2437 active OIT doses vs. 1193 placebo doses, there were 1107 (45.4%) vs. 134 (11.2%) total reactions; SRs (gastrointestinal, lower respiratory tract, and skin symptoms)were rare, occurring with a median frequency of 1% of active doses vs. none in the placebo group (P=0.01) Skin side effects 0.9% vs. 0.1% p=0.1 Respiratory 8.1% vs. 2.3% p=0.3	LRs (oral pruritis, abdominal pain) with a median frequency of 16% and 2% of active doses, respectively (P= 0.006 and 0.02)	SPTs were performed at baseline and after OIT (23 week). Not changes between groups	SpIgE was measured at baseline and after treatment (23 week); Total serum CM IgE levels did not change, on average,	IgG4 was measured at baseline and after treatment (23 week); Although there was no significant change in CM IgG4 levels in the placebo group, there was a median increase from baseline of 767% in the active group (P = 0.002, table III and fig 5)	
Staden, 2007	45 children (SOTI=25, control group=20) were included (29 boys, 16 girls, median age 2.5 years, range 0.6-12.9); the diagnosis of CMA or HE allergy on the basis of	Randomised clinical trial	CM hens' egg (HE)	SOTI was carried out at home with starting dose for CM 0.02 mg CM protein from 3.5% fresh pasteurized CM; HE – starting dose 0.006 mg lyophilized HE protein (induction phase);			At follow-up DBPCFC 9 of 25 children (36%) showed permanent tolerance in the SOTI group; 3 of 25 (12%) were tolerant		In 4 children in the SOTI group generalized urticaria, bronchial obstruction, or angioedema, which were treated with antihistamines and steroids; in the control group 1 child had severe reactions (vomiting, paleness, circulatory disorder) after accidental exposure; 2 children during follow-up DBPCFC had bronchial obstruction, generalized urticaria, and	21/25 (84%) mild symptoms	SPT data not available	Total and SpIgE levels were measured at baseline and after treatment; With respect to total IgE there was no significant alteration in values for either SOTI		

Study	Patients characteristics/ diagnosis criteria	Design	Foods	Type of immunotherapy		Clinical outcomes					Immunologic outcomes			
				H1	H2	OD	OT	RR	Adverse events/ medication use		SPT	TIgE/ SpIgE	IgG/ IgG4	Other
									SRs	LRs				
	clinical history, SPT, RAST, DBPCFC 47 recruited, 45 reported, 2 lost to follow up or failed to start			Doses were increased according to the individual tolerance to a maximum dose of 8250 mg CM protein (250 ml CM) or 2800 mg HE protein (around ½ HE); the maintenance phase followed with a minimum daily maintenance dose of 3300 mg CM protein (100 ml CM) and 1600 mg HE protein (around ¼ HE) plus deliberate intake for 67 days (table 1 and 2)			with regular intake and 4 of 25 (16%) were partial responders; in the control group, 7 of 20 children (35%) were tolerant 16/25 (64%) tolerant in active group, 7/20 (35%) in control group P=0.05		circulatory disorders and were equipped with an epinephrine self-administration-pen			or elimination group (data not shown) Sp IgE decreased significantly over time in children who developed their natural tolerance under elimination diet as expected ($P < 0.05$; fig 3B). Under intervention with SOTI, children in the responder group and partial responder groups (patterns I-III) showed a similar response ($P < 0.001$; fig 3A graphical description). There was no significant change in SpIgE in children who had to stop SOTI (pattern IV, non-responder) and the ones who were non-responders under elimination diet. Children in SOTI group who were responders had lower Sp IgE levels than the non-responders at the beginning		

Study	Patients characteristics/ diagnosis criteria	Design	Foods	Type of immunotherapy		Clinical outcomes					Immunologic outcomes			
				H1	H2	OD	OT	RR	Adverse events/ medication use					
									SRs	LRs	SPT	TIgE/ SpIgE	IgG/ IgG4	Other
												of the study (P <0.05).		
Varshney, 2011	28 children aged 1-16 years randomised in 2 groups: Active – [n=19, age (mo), median range 84 (38-126)]; Placebo – [n=9, age (mo), 69 (28-114)]; followed for 1 year. The diagnosis of peanut allergy on the basis of clinical history, SPT, SpIgE	RCT	Peanut	At home the dosing was resumed if children missed less than 3 daily doses, if from 3 to 5 doses were missing children returned for an observed dose	Initial day escalation phase: in clinical area; 0.1 mg peanut protein (as flour) or placebo; dose doubled every 30 minutes until 6 mg or symptoms; Build-up phase: in clinical area first day, dose from escalation phase day before; every 2 weeks dose increased by 50-100% until 75 mg/day tolerated, then 25-33% until maintenance dose of 4000 mg achieved within 44 weeks; Maintenance phase: 4000 mg/day, for 1 month then returned for DBPCFC at 48 weeks	16/19 active group reached maintenance dose, 9/9 in controls; Active group at DBPCFC all 16/16 ingested 5000 mg (approximately 20 peanuts); placebo median dose 280 mg (0-1900 mg) p<0.001			At DBPCFC 0/16 in active group required epinephrine, 3/9 in placebo group needed epinephrine	1/16 in active group were mild symptoms which required antihistamines	SPT were performed at enrolment and at the time of oral food challenge (12 months); SPT in active group decreased from 7 range (5.5-15) to 1.75 (0-10), p<0.001; No changes in placebo group 7(5.5-13) to 4 (0-12.5);	SpIgE was measured at enrolment and at the time of food challenge (12 months); SpIgE in active group had initial increases but did not show significant change from baseline during DBPCFC	IgG4 was measured at enrolment and at the time of food challenge (12 months); IgG4 was increased significantly after OIT compare to placebo (p<0.001)	Cytokine analysis was performed at baseline; at 9 months, and at the time of oral food challenge; IL-5, IL-13 declined in active group, no change in placebo group; also, no change in IL-10, IFN-γ in active or placebo; in active group increased ratio FoxP3 hi to Fox P3 intermediate CD4 CD25, not for tetanus toxoid; no changes in T-regs of controls
Mansouri, 2007	Intervention group n=20, 40% (8=female), 8 mo-18 yrs, mean age 56 mo; Control group n=13 (31% female) 4 mo-13 yrs, mean age 52 mo; the diagnosis of CMA on the basis of clinical history, SPT, RAST and DBPCFC	Quasi-RCT (no formal randomisation), control group no placebo, followed up	CM		Dose 0.06 mg increased to 6.4 g/day over 6 months; 1 drop of CM diluted in 25 drops of water 0.06 mg of CM; initial dose given for 7 days, doubled every 7 days for 70 days, then doubled every 16 days; if concurrent viral infection dose not doubled; 1,2,4 drops of non diluted CM given in hospital; Build-up phase: 1:25 diluted, 1-49 days 1-64 drops; 50-70 5-20 drops of CM; 70-180 2-200 ml CM; Maintenance phase:		18/20 (90%) able to tolerate 200 ml/day; avoidance group are still symptomatic after CM (reassessed, DBPCFC, SPT, IgE)			80% mild reactions during desensitisation (nausea, abdominal pain, throat itching, eczema, dyspnoea) responded to antihistamine; 10% children wheezed, slower increase in dose was employed	SPT were performed at baseline and after treatment	Total and SpIgE were measured at baseline and after treatment; IgE reduced after desensitisation (P=0.004); SpIgE reduced after desensitisation (P=0.001)		

Study	Patients characteristics/ diagnosis criteria	Design	Foods	Type of immunotherapy		Clinical outcomes					Immunologic outcomes			
				H1	H2	OD	OT	RR	Adverse events/ medication use					
									SRs	LRs	SPT	TIgE/ SpIgE	IgG/ IgG4	Other
					200 ml undiluted milk a day									
Patriarca, 2003	59 cases aged 3-55 yrs; 32 children (54%) <16 yrs (mean age not given); 25/59 male (42%) Controls n=16 aged 5-29 no further information; the diagnosis of allergy on the basis of clinical history, SPT, RAST, DBPCFC	Quasi-RCT, not randomised, controls refused desensitization	Milk 29 (44%) Egg 15 (23%) Albumin 3 (4.5%) Fish 11 (17%) Orange 2 (3%) Apple 1 (1.5%) Corn 1 (1.5%) Beans 1 (1.5%) Peanut 1 (1.5%) Lettuce 1 (1.5%) Peach 1 (1.5%)	Milk 10 drops in 100ml water 1-18 1-18drops/day Egg 10drops in 100ml 1-33 1drop to 36drops x3 Fish 25g cod in 50ml water Days 0.000033mg-160g days 1 to 165 Build-up phase: Milk 19-136 1drop milk to 120ml Egg pure egg day 34 to 139 1drop to 50ml (1 egg) Maintenance phase: Milk 120ml (1 glass) 2-3x/wk Egg 1 egg 2-3x/wk Fish 160g boiled cod, 2-3x/wk Other foods 2-3x/wk 136 days milk; 139 days egg; 165 days fish	Desensitization success rate 45 out of 54 (83%) (ITT 68%)				During the protocol, 51.1% of patients experienced reactions (urticaria, angioedema, or abdominal pain) which were controlled by antihistamines or sodium cromolyn; in 9 patients (16.7%) treatment was stopped due to the occurrence of skin reactions or gastrointestinal symptoms (diarrhea, vomiting and abdominal pain) not controlled by antihistamines or sodium cromolyn		SPT were performed at baseline and after treatment	SpIgE was measured at baseline; after 6, 12 and 18 months; During the oral desensitisation a significant decrease in Sp IgE after 6 (P<0.01); 12 (P < 0.01) and 18 months (P < 0.01; fig 1; graphical description)	IgG4 was measured at baseline; after 6, 12 and 18 months; A significant increase in IgG4 after 6 (P<0.01), 12 (P<0.01) and 18 months (P<0.01) fig 1 graphical description)	
Patriarca, 2007	42 cases (18 girls; 24 boys; aged 3-16 yrs); 14/42 had also atopic dermatitis. Controls n=10 (4 girls; 6 boys aged 5-13 yrs) had only strict elimination diet for 18 months; the diagnosis of allergy on the basis of clinical	Quasi-RCT, not randomised, controls refused desensitization	Milk 18 cases; Egg 17; Fish 9; Wheat 2; Apple 1; Bean 1	Dilution: 10 drops of milk in 100 ml; from 1 drops/day at the beginning of the protocol and at the end of treatment days 175-177 130 ml/day; maintenance dose: 130 ml of milk at least two or three times a week; Egg dilution: 1 drop of raw	Desensitization was successful in 31/36 cases (85.7%)				In 11/36 cases (30.5%) had reactions such as, urticaria, vomiting, worsening of bronchial asthma or of atopic dermatitis, angioedema, and abdominal pain		SPT were performed at baseline and after treatment (18 months); In 27 /36 patients (75%) SPTs markedly decreased after the treatment and only 9 cases (25%) did not show any changes	SpIgE levels were measured at baseline; at 6, 12 and 18 months; During the treatment SpIgE decreased significantly after 6 (P<0.001); 12 (p=0.004), and 18 (P=0.002) months	IgG4 levels were measured at baseline; at 6, 12 and 18 months; IgG4 significantly increased after 6 (P<0.001), 12 (P<0.001), and 15 (P<0.001) months of oral desensitization	

Study	Patients characteristics/ diagnosis criteria	Design	Foods	Type of immunotherapy		Clinical outcomes					Immunologic outcomes			
				H1	H2	OD	OT	RR	Adverse events/ medication use		SPT	TIgE/ SpIgE	IgG/ IgG4	Other
									SRs	LRs				
	history, SPT, RAST, DBPCFC			shaken egg (albumin + yolk) in 100 ml of water; 1 drops from days 1-3 till 10 drops days 22-24; then dilution 10 drops of raw shaken egg (albumin + yolk) in 100 ml of water 1 drops in days 25-27 till 50 ml days 166-168; maintenance dose: 1 egg at least two or three times a week; Cooked fish (boiled cod) 0.000033 mg days 1-3 till 100 g days 154-156; maintenance dose: 100 g of boiled cod at least twice a week										

CM	Cows' milk
H1	Home-based immunotherapy
H2	Hospital-based immunotherapy
HE	Hens' egg
IgG	Immunoglobulin G
IgG4	Immunoglobulin IgG4
LRs	Local reactions
nsLTPs	non-specific Lipid Transfer Proteins
OD	Oral desensitization
OT	Oral tolerance
RR	Relapse Rate
SOTI	Specific Oral Tolerance Induction
SPT	Skin Prick Test
SpIgE	Specific IgE
SRs	Systemic reactions
TIgE	Total IgE

Appendix 4: Risk of bias assessment of included studies

Study, year	Food	Design	Adequate sequence generation	Allocation concealment	Blinding/ patient-related outcomes	Incomplete outcome data addressed?	Free of selecting reporting	Free of other bias*	Grade
Burks, 2012	Hens' Egg	RCT	Yes	Yes	No	Yes	Yes	Yes	B
Caminiti, 2009	Cows' Milk	RCT	No	No	Yes	Yes	Yes	No	C
Enrique, 2005	Hazelnut	RCT	No	No	Yes	Yes	Yes	No	C
Fernandez-Rivas, 2009	Peach	RCT	Unclear	Yes	Yes	Yes	Yes	No	B
Fleischer, 2013	Peanut	RCT	Yes	Yes	Yes	Yes	Yes	Yes	A
Kim, 2010	Peanut	RCT	Unclear	Yes	Yes	Yes	Yes	No	B
Lacono, 2013	Hens' Egg	RCT	Yes	No	No	Unclear	Unclear	Unclear	C
Longo, 2008	Cows' Milk	RCT	Yes	Yes	Yes	Yes	Yes	Yes	A
Martorell, 2011	Cows' Milk	RCT	Yes	Unclear	No	Yes	Yes	Yes	B
Meglio, 2013	Hens' Egg	RCT	Yes	No	No	Yes	Yes	Yes	C
Morisset, 2007 a	Cows' Milk	RCT	No	No	Single-blind	Unclear	Yes	No	C
Morisset, 2007 b	Hens' Egg	RCT	No	No	Single-blind	Unclear	Yes	No	C
Pajno, 2010	Cows' Milk	RCT	Yes	No	Yes	No	Yes	No	C
Patriarca, 1998	Cows' Milk Hens' Egg	RCT	Unclear	No	Yes	Unclear	Yes	No	C
Salmivesi, 2012	Cows' Milk	RCT	Unclear	Yes	Yes	No	No	No	C
Skripak,	Cows' Milk	RCT	Unclear	Yes	Yes	Yes	Yes	Yes	B

Study, year	Food	Design	Adequate sequence generation	Allocation concealment	Blinding/ patient-related outcomes	Incomplete outcome data addressed?	Free of selecting reporting	Free of other bias*	Grade
2008									
Staden, 2007	Cows' Milk Hens' Egg	RCT	No	No	Yes	Unclear	Yes	No	C
Varshney, 2011	Peanut	RCT	Yes	Yes	Yes	Yes	Yes	Yes	A
Mansouri, 2007	Cows' Milk	CCT	Unclear	No	Yes	No	Yes	No	C
Patriarca, 2003	Cows' Milk Hens' Egg Peanut, Fish Peach, Orange, Apple, Corn, Bean, Lettuce	CCT	No	No	Yes	No	Yes	No	C
Patriarca, 2007	Cows' Milk Hens' Egg Fish, Wheat Apple, Bean	CCT	No	No	Yes	No	Yes	No*	C

*As described in Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration. Wiley-Blackwell, 2009 these included: recruitment bias; selection bias; information bias; publication bias; confounding; intervention bias; bias due to early stopping; performance bias; attrition bias; detection bias; reporting bias

Appendix 5: Additional forest plots

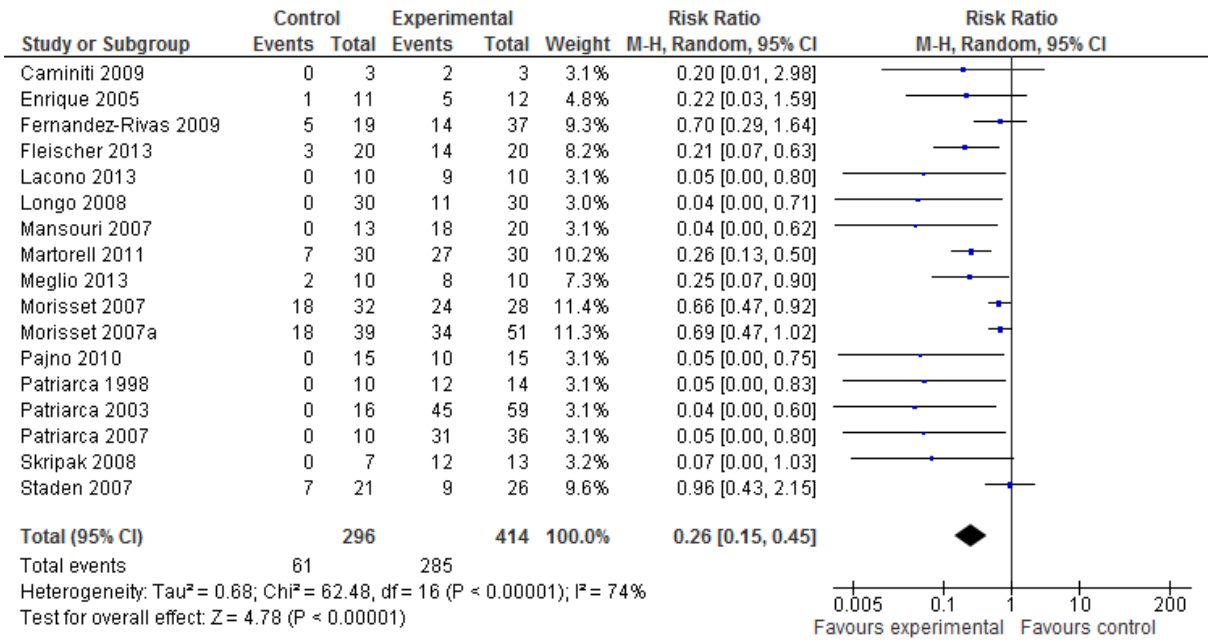

Figure S1: Sensitivity analysis RR of food allergy after OIT or SLIT (diagnosis of food allergy confirmed by DBPCFC)

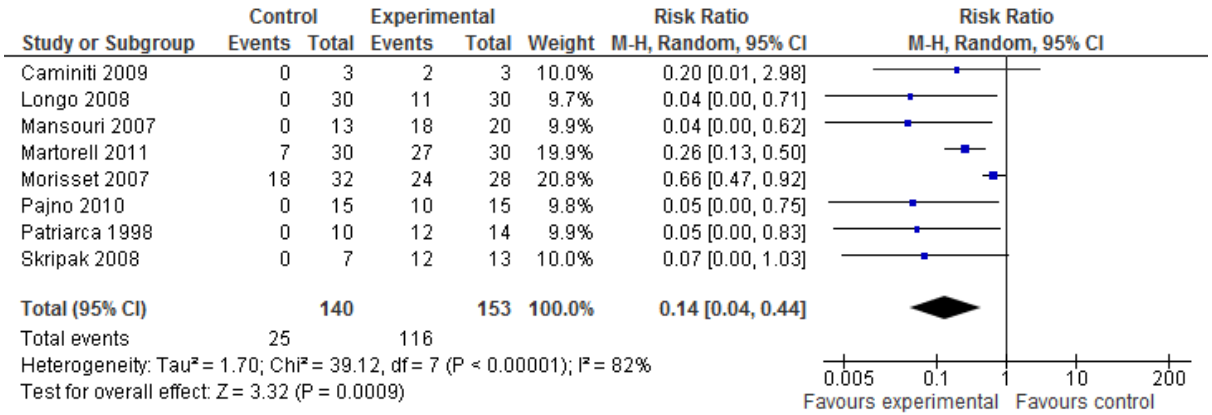

Figure S2: RR of CMA as assessed by DBPCFC in OIT vs. controls

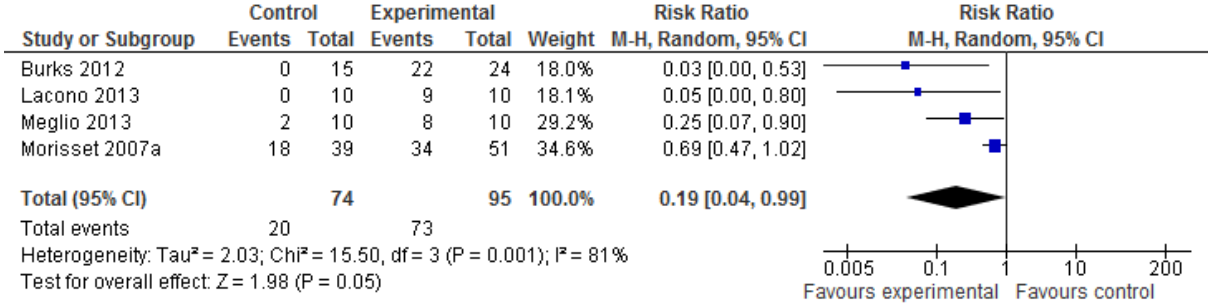

Figure S3: RR of HE allergy as assessed by DBPCFC in OIT vs. controls

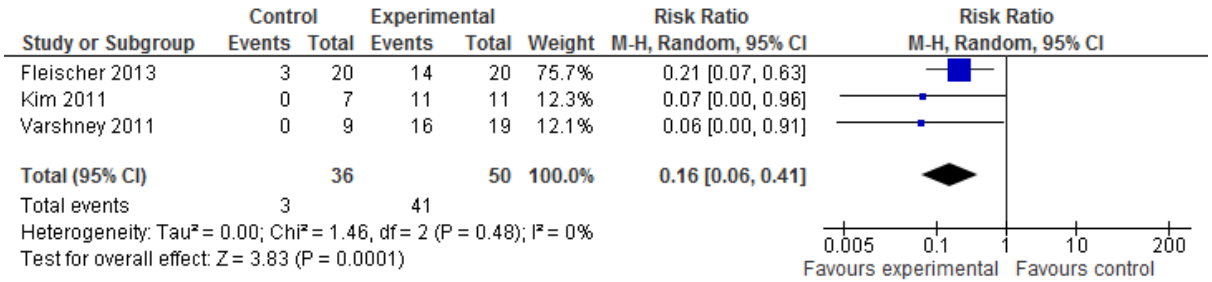

Figure S4: RR of peanut allergy as assessed by DBPCFC in OIT/SLIT vs controls

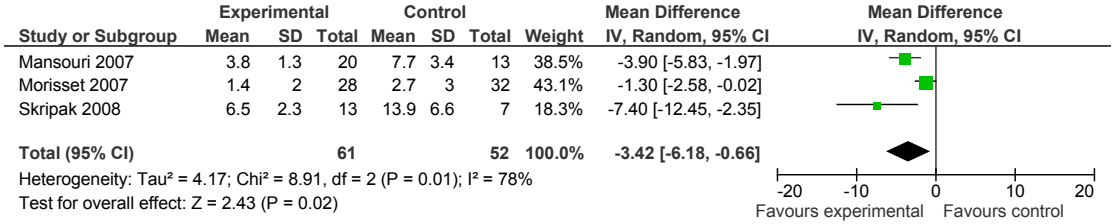

Figure S5: SPT (wheal in mm) following OIT for cows' milk allergy

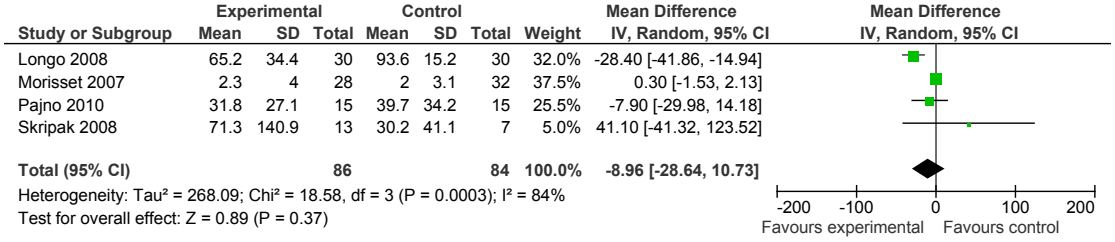

Figure S6: SpIgE (kU/L) following CMA

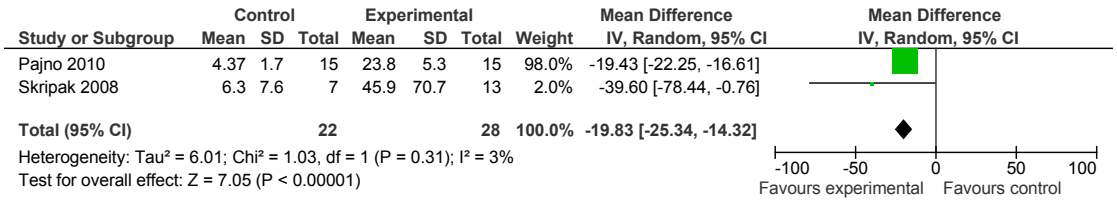

Figure S7: IgG4 (µg/ml) following OIT for cows' milk allergy

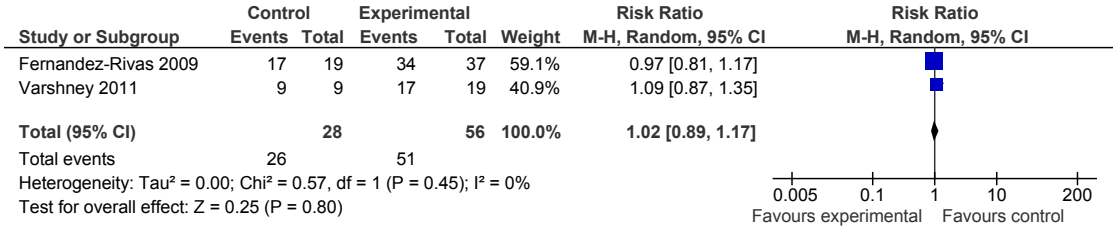

Figure S8: Safety data – absence of systemic reactions during OIT or SLIT for food allergy (only grade A and B studies)

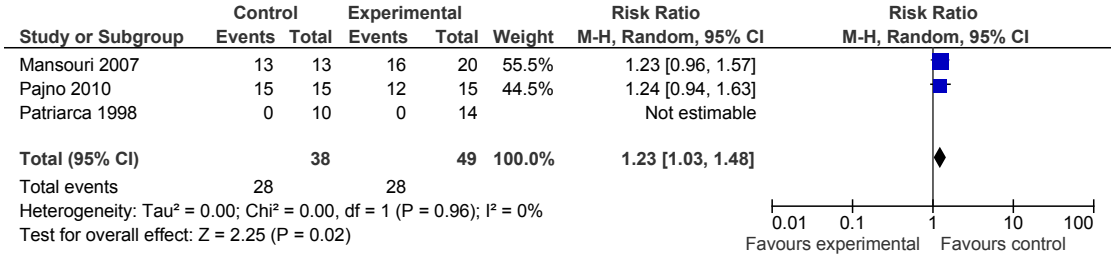

Figure S9: Safety data – absence of systemic reactions during OIT for cows' milk allergy

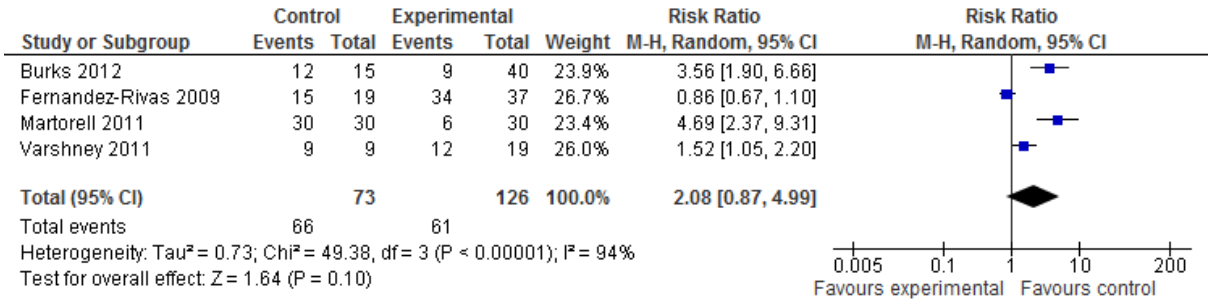

Figure S10: Safety data – absence of local reactions during OIT or SLIT for food allergy (only grade A and B studies)

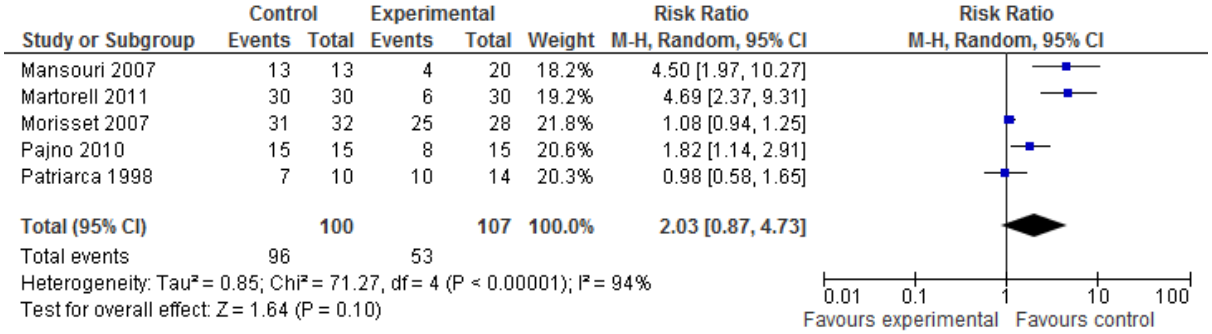

Figure S11: Safety data – absence of local reactions during OIT for cows' milk allergy

Appendix 6: Immunological assessment and outcomes (immunoglobulin analysis)

First author, year, country	Immunoglobulin measured	Method of measurement	Time parameters	Findings
RCTs				
Burks, 2012; USA	Specific IgE IgG4 (egg-specific)	Serum egg-specific IgE and IgG4 were measured with the use of the ImmunoCAP 100 (Thermo Fisher Scientific).	Baseline to month 10, 22 and 24	At 10 months, specific IgE levels were lower in children who were successfully desensitized at 22 months than in those who were not (p=0.02 and p=0.04, respectively) Median IgG4 levels at 10 months were higher in children who were desensitized at 10 months (p=0.0007), those who were desensitized at 22 months (p=0.005), and those who had sustained unresponsiveness at 24 months (p=0.02), as compared with children who did not pass the oral food challenge at these time points.
Caminiti, 2009; Italy	Specific IgE		Before the beginning of oral desensitization.	Measured only for the purpose of diagnosing CMA.
Enrique, 2005; Spain Enrique, 2008^	Specific IgE IgG4 (hazelnut specific)	Specific IgE against hazelnut was measured by an enzyme allergosorbent test.	Blood samples taken before treatment for in vitro studies. Blood samples were again drawn for in vitro studies 8-12 weeks later (at time of final DBPCFC).	Specific IgE showed no significant changes before and after SLIT in both groups. IgG4 levels: no statistical significance was found between the studied groups. However, there was an increase in the mean IgG4 levels in the active group (from 7.34 allergen units (AU)/mL to 9.84 AU/mL, $P < 0.05$).
Fernandez-Rivas, 2009; Spain	Specific IgE IgG4 (specific to Pru p 3)	Specific IgE to rPru p 3 was determined by the ADVIA Centaur	Serum samples were collected at T0, T1 and T6, and processed	Specific IgE showed a significant increase both in the active ($P < 0.001$) and placebo ($P = 0.025$) groups, although the increase

First author, year, country	Immunoglobulin measured	Method of measurement	Time parameters	Findings
Garcia, 2010^		platform and specific IgG4 to nPru p 3 by means of ELISA.	together at the end of the study by an investigator blinded to the treatment. (T0 = before treatment, T1= after 1 month of treatment, T6 = after 6 months of treatment).	remained only significant at T6 in the former (active 4.23, P < 0.001; placebo 4.04, P = 0.079, T-test). No significant inter-group differences were observed (P = 0.456). None of the patients with negative IgE to rPru p 3 at T0 converted to positive at T1 or T6. IgG4 to nPru p 3 showed a different evolution between groups (P = 0.022) with a significant increase in the active arm (P = 0.007) not observed in the placebo one (P = 0.185).
Fleischer, 2013; USA	Specific IgE IgG4 (peanut specific)	Serum egg-specific IgE and IgG4 were measured with the use of the ImmunoCAP 100 (Thermo Fisher Scientific).	Serum was obtained at baseline, at weeks 29, 44 and 68	Specific IgE week 44 peanut –specific IgE 35.8 (3.3 to 75.0) in SLIT versus 20.1 (4.1 to 80.3) in placebo (NS). Increase between baseline and week 44 in SLIT. IgG4 levels week 44 0.7 (0.4 to 2.3) SLIT versus 0.5 (0.2 to 0.7) placebo (NS). Increase between baseline and week 44 in SLIT.
Kim, 2010; USA	Specific IgE IgG4 (peanut specific)	Peanut-specific IgE and IgG4 levels were measured with the Phadia AB ImmunoCAP 100 instrument.	Serum was obtained at baseline, 4 months, 8 months, and the day of DBPCFC (after 12 months of SLIT).	After 12 months, peanut SLIT results in an increase in specific IgE levels over 4 months followed by a decrease over the subsequent 8 months. IgG4 levels in the active group increased significantly during 12 months compared to the placebo group.

First author, year, country	Immunoglobulin measured	Method of measurement	Time parameters	Findings
Lacono, 2013; Italy	Specific IgE (specific to HE)	Not specified	At baseline, after 6 months.	In SOTI group egg-specific IgE decreased significantly compared to controls at 6 months ($p=0.007$).
Longo, 2008; Italy	Specific IgE (CM specific)	Specific IgE levels were measured by using the Phadia CAP System FEIA.	Specific IgE levels in serum samples were measured at the time of enrolment, and after 6 and 12 months.	Specific IgE measured at 6 and 12 months showed a significant decrease after SOTI in 15 of 30 subjects. (cut-off point of 100 kUA/L)
Martorell, 2011; Spain	Specific IgE (CM specific)	Specific IgE levels were measured by using the Phadia CAP System FEIA.	At baseline and after 12 months	Specific IgEs decreased significantly in active group compared to controls after 12 months ($p<0.0001$).
Meglio, 2013; Italy	Specific IgE (specific to HE)	Specific IgEs and IgG4s to HE proteins were determined with Realtest (Reverse Enzyme Alergo Sorbent Test – Reast) (Lofarma) and an allergen microarray assay (Immuno Solid-phase Allergen Chip ISAC).	At baseline and after 6 months (pre and post desensitisation period).	The differences between specific IgEs before and after the treatment were significant only in the active group ($p=0.01$) (ISAC method). No comparisons between groups.
Morisset, 2007; France	Specific IgE (specific to CM and HE)	Specific IgE levels were measured by using the CAP system FEIA.	Specific IgE levels were assessed at: baseline and 6 months.	Specific IgEs decreased in both groups. However, the decrease in IgE was greater in the "recovery" sub-group: 3.07 vs. 1.6 kU/l ($p < 0.1$) and 8.21 vs. 6.7 kU/l in the "failure" sub-group (p ns).

First author, year, country	Immunoglobulin measured	Method of measurement	Time parameters	Findings
Pajno, 2010; Italy	Specific IgE IgG4 (CM specific)	Specific IgE and IgG4 were assayed using the ImmunoCAP system.	Blood samples were collected before randomization, when the dose of 8mL (volume of whole milk. Soy milk was the control treatment.) was reached (week13), and at the end of the study (18 weeks).	No significant difference in specific IgE levels between the active and control groups. At week 18 the levels of IgG4 in the active group was significantly higher than in the control group.
Patriarca, 1998; Italy	Total IgE Specific IgE (specific to CM, HE, fish and apple)	Total IgE was measured by employing PRIST (paper radioimmunosorbent test). Specific IgE was assessed by using a radio-immunoenzymatic assay. (RAST)	Both control and treated subjects were examined after a 6 month period (the desensitization protocol took 4 months on average). The treated subjects were then controlled periodically over a 3 to 6 year follow-up period.	No change was observed in IgE.
Skripak, 2008; USA	Total IgE Specific IgE IgG IgG4 (specific to CM)	Total IgE and the levels of IgE, IgG, and IgG4 antibodies were measured by using the Phadia CAP-system FEIA.	Blood samples were collected before immunotherapy, when the maintenance dose was reached, and after completion of immunotherapy.	Total serum IgE levels did not change, on average. Milk-specific IgE levels did not change significantly in either group. Although there was no significant change in CM IgG4 levels in the placebo group, there was a median increase from baseline of 767% in the active group (P = 0.002). CM-specific IgG antibody levels increased in parallel with the IgG4 antibody levels.

First author, year, country	Immunoglobulin measured	Method of measurement	Time parameters	Findings
Staden, 2007; Germany	Total IgE Specific IgE (specific to CM and HE)	Total IgE and specific IgE were measured using the Phadia CAP-system FEIA.	Blood sample was drawn prior to start of the intervention, prior to re-challenges or at final examination.	With respect to total IgE there was no significant alteration in values for either SOTI or elimination group (data not shown). Specific IgE decreased significantly over time in children who developed their natural tolerance under elimination diet as expected ($P < 0.05$). Under intervention with SOTI, children in the responder group and partial responder groups showed a similar response ($P < 0.001$). There was no significant change in specific IgE in children who had to stop SOTI and the ones who were non-responders under elimination diet. Children in the SOTI group who were responders had lower specific IgE levels than the non-responders at the beginning of the study ($P < 0.05$).
Varshney, 2011; USA	Specific IgE IgG IgG4 (peanut specific)	Peanut-specific IgE, IgG, and IgG4 levels were measured by using the ImmunoCAP 100 instrument (Phadia AB).	Serum immunoglobulin levels were analysed at regular intervals: baseline, 2 months, 6 months, 9 months and at OFC (week 48).	In the active group, median peanut-specific IgE increased nearly 3-fold by 2 months and was not significantly different from baseline at OFC; the placebo group showed no changes. The active group had significant increases in peanut-specific IgG at all time points. Peanut-specific IgG4 showed a significant increase from baseline at all time points with peanut OIT and did not change with the placebo group.
CCTs				
Mansouri, 2007;	Total IgE	Specific IgE was	Specific IgE levels were	IgE reduced after desensitisation (P =

First author, year, country	Immunoglobulin measured	Method of measurement	Time parameters	Findings
Iran	Specific IgE (CM specific)	measured qualitatively (an ELISA was performed).	measured during: pre-observational period & post-observational period (for the control group) and pre-desensitization & post-desensitization (for the case group). Total IgE was measured before the study but was not rechecked afterwards.	0.004); specific IgE reduced after desensitisation (P = 0.001).
Patriarca, 2003; Italy	Total IgE Specific IgE IgG4 (specific to CM, HE, fish, orange, peanut, corn, peach, apple, lettuce and beans)	Total and specific IgE and specific IgG4 in the serum were detected with an immuno-enzymatic assay (UniCAP was used to detect IgE and CAP FEIA was used to detect IgG4).	Specific IgE and IgG4 in the serum were measured at: baseline and after 6, 12 and 18 months.	During the oral desensitization, there was a significant decrease in specific IgE after 6 (P < 0.01), 12 (P < 0.01) and 18 months (P < 0.01), and a significant increase in specific IgG4 after 6 (P < 0.01), 12 (P < 0.01) and 18 months (P < 0.01).
Patriarca, 2007; Italy	Total IgE Specific IgE IgG4	UniCAP [Pharmacia] was used to detect IgE and CAP FEIA [Pharmacia] was used to detect IgG4.	IgE and IgG4 levels were monitored at: baseline and 6, 12, & 18 months after starting the protocol in all patients who completed the treatment successfully.	During the oral desensitizing treatment, a significant decrease was observed in specific IgE after 6 (P < 0.001), 12 (p = 0.004), and 18 (P = 0.002) months and a significant increase in specific IgG4 after 6 (P < 0.001), 12 (P < 0.001), and 18 (P < 0.001) months.

Appendix 7: Immunological assessment and outcomes (cytokine analysis)

First author, year, country	Cytokines measured	Method of measurement	Time parameters	Findings
RCTs				
Enrique, 2005; Spain Enrique, 2008^	IL-4, IL-5, IL-10, TGF-β, and IFN-γ.	ELISA	Blood samples taken before treatment for in vitro studies. Blood samples were again drawn for in vitro studies 8-12 weeks later (at time of final DBPCFC).	An increase in IL-10 levels after SLIT was found only in the active group, rising from 1.62 pg/mL to 2.24 pg/mL ($P < 0.05$). No differences were observed between the placebo and active groups. Unable to obtain results for the other cytokines because of the low sensitivity of the tests used.
Kim, 2010; USA	IL-5, IL-10, IL-13, and IFN-γ.	ELISA	Cytokine levels measured at baseline and after 12 months of peanut SLIT or placebo.	After 12 months, peanut SLIT results in a decrease in IL-5 secretion. After 12 months, IL-13 levels in the active treatment group decreased from a median of 147.1 pg/mL at baseline to 62.1pg/mL. However, this level was not significant compared with that in the placebo group ($P= 0.06$), which also decreased from a median baseline of 369.6 pg/mL to 149.55 pg/mL after 12 months. No differences between the 2 groups were found in IL-10 or IFN-γ levels at baseline or at 12

First author, year, country	Cytokines measured	Method of measurement	Time parameters	Findings
				months (data not shown).
Meglio, 2013; Italy	IL-4, IL-5, IL-6, Il-10, IL-13, IFN-γ, TNF-α, TGF-β1 and TGF-β2	ELISA	Pre and post desensitisation period	Only a significant increase of IL-5 in the active group was observed (pre: mean, 19.00 ± 9.4 pg/ml; range, 5.00-32.00; post 28.13 ± 14.7 pg/ml; range, 12.00-56.00 – p=0.03). All other differences were not significant
Varshney, 2011; USA	IL-5, IL-10, IL-13, IFN-γ, and TGF-β.	ELISA	Cytokine analysis occurred at: baseline, 9months, and the time of oral food challenge (OFC performed after approximately 1 year of OIT).	IL-5 and IL-13 decreased in peanut OIT subjects. Also, there was a transient increase in TGF-β in the active group at 9 months but levels returned to the baseline at OFC. No change in IL-5, IL-13, or TGF-β in placebo group. No significant change in IL-10 or IFN-γ in either the active or placebo group.

Appendix 8: On-going/unpublished studies

PI, country	Title	Study design	ClinicalTrials.gov identifier	No. of participants	Intervention	Primary outcome measures	Started reporting	Estimated study completion date	Status
Burks W, USA	Oral immunotherapy for childhood egg allergy	Allocation: Randomized	NCT00461097	NA	Oral egg immunotherapy	Percent of participants who can tolerate 10,000 mg of egg white solid	Yes	October 2013	Active, not recruiting
Burks W, USA	Sublingual immunotherapy for peanut allergy and induction of tolerance (SLIT 2)	Allocation: Randomized	NCT01373242	50	Liquid peanut extract	Percentage of subjects on placebo vs peanut SLIT who pass the 54 month DBPCFC to assess tolerance	No	June 2021	Recruiting
Burks W, USA	Mucosal immunotherapy for peanut allergy (MIT)	Allocation: Randomized	NCT00597675	45	Peanut flour	An outcome measure will be determined by a comparison of the result of the DBPCFC at the starting and at the end of the study for each of the subjects	No	December 2012	Active, not recruiting
Burks W, USA	Double blind peanut sublingual	Allocation: Randomized	NCT00597727	80	Peanut protein	Subject will successfully pass a	Yes	December 2014	Active, not recruiting

PI, country	Title	Study design	ClinicalTrials.gov identifier	No. of participants	Intervention	Primary outcome measures	Started reporting	Estimated study completion date	Status
	immunotherapy (PN SLIT)					DBPCFC at the end of the study after having been off the SLIT for 2 to 4 weeks			
Burks W, USA	Peanut oral immunotherapy	Open label: single group assessment	NCT00598039	40	Peanut flour	Subject will pass a DBPCFC at the end of the study and a second food challenge 1 month later after being off peanut for 1 month	Yes	July 2012	Active, not recruiting
Burks W, USA	Mucosal immunotherapy for peanut allergy in young children (DEVIL)	Allocation: Randomized	NCT00932828	60	Peanut and placebo flour	To treat peanut-allergic subjects with PMIT and to determine whether this protocol lowers their risk of anaphylactic reactions and causes long-term tolerance	No	December 2014	Active, not recruiting
Burks W,	Immunotherapy for peanut	Non-randomized	NCT00429429	40	Sublingual peanut	A negative DBPCFC at the	Yes	May 2011	Completed

PI, country	Title	Study design	ClinicalTrials.gov identifier	No. of participants	Intervention	Primary outcome measures	Started reporting	Estimated study completion date	Status
USA	allergy				immunotherapy	completion the two years of the study			
Burks W, USA	Egg oral immunotherapy (Egg OIT)	Open label: single group assessment	NCT00597558	12	Egg white protein	Subjects on egg OIT will have a negative DBPCFC to egg when the IgE is < 2 kU/l	Yes	July 2012	Active, not recruiting
Burks W, USA	Pilot oral immunotherapy (OIT) – initial pilot study in adults	Open label: single group assessment	NCT01274429	20	Powdered peanut protein	To treat peanut-allergic subjects with POIT and to determine whether this protocol lowers their risk of anaphylactic reactions and causes long-term tolerance	No	September 2014	Recruiting
Burks W, USA	Peanut oral immunotherapy and anti-immunoglobulin E (IgE) for peanut allergy	Allocation: Randomized	NCT00932282	10	Peanut oral immunotherapy; omalizumab	The percentage of subjects who pass the 20 gm peanut flour (≈ 50% peanut protein) oral food challenge following the desensitization	No	July 2014	Recruiting

PI, country	Title	Study design	ClinicalTrials.gov identifier	No. of participants	Intervention	Primary outcome measures	Started reporting	Estimated study completion date	Status
						phase of the study			
Burks W, USA	Oral immunotherapy (OIT) for peanut allergy	Allocation: Randomized	NCT00815035	60	Peanut flour	To treat peanut-allergic subjects with peanut OIT and to determine whether this protocol lowers their risk of anaphylactic reactions and causes long-term tolerance	Yes	November 2013	Active, not recruiting
Burks W, USA	Peanut sublingual immunotherapy	Allocation: Randomized	NCT00580606	40	Peanut powder	Percentage of desensitized participants (while on daily SLIT) as measured by the 5 gm OFC or a 10-fold increase in the amount of peanut powder, compared to baseline oral food challenge	Yes	September 2013	Active, not recruiting
Clark AT, UK	Study of tolerance to oral	Open label: single group assessment	NCT01259804	22	Peanut oral immunotherapy	Pass/fall peanut challenge	Yes	January 2012	Active, not recruiting

PI, country	Title	Study design	ClinicalTrials.gov identifier	No. of participants	Intervention	Primary outcome measures	Started reporting	Estimated study completion date	Status
	peanut (STOP)								
Clark AT, UK	Study of tolerance to oral peanut:	Allocation: Randomized	ISRCTN62416244	104	Peanut oral immunotherapy	Proportion of subjects in the active group and control groups who pass a peanut challenge	No	August 2013	Active, recruiting
Dupont C, France	Sublingual milk immunotherapy in children (Lactaide)	Allocation: Randomized	NCT00874627	51	Milk sublingual immunotherapy	Reactive milk dose at inclusion; 6 mo and 12 mo	Yes	December 2012	Active, not recruiting
Lollar KW, USA	Sublingual immunotherapy for food allergy	Active, not recruiting	NCT00736281	150	Food drops; food allergens (peptides)	Validated Questionnaire will be administered to trial participants at 3,6,9,12 months after achieving the maintenance dose of food drops	No	October 2010	Active, not recruiting
Paassilta M, Finland	Safety of oral immunotherapy for cows' milk allergy in school-aged children	Active, not recruiting	NCT01361347	28	Milk oral immunotherapy	Number of participants with adverse events as a measure of safety and	No	December 2014	Active, not recruiting

PI, country	Title	Study design	ClinicalTrials.gov identifier	No. of participants	Intervention	Primary outcome measures	Started reporting	Estimated study completion date	Status
						tolerability			
Spergel JM,. USA	Milk oral immunotherapy in children	Allocation: Randomized	NCT01162473	40	Milk oral Immunotherapy	The percentage of children completing desensitization in each study group	No	June 2011	Enrolling by invitation
Sampson HA, USA	OIT and Xolair (Omalizumab) in cows' milk allergy	Allocation: Randomized	NCT01157117	76	Xolair (omalizumab) placebo/milk OIT	Percentage of subjects in the Xolair (omalizumab) group vs placebo group developing clinical tolerance to milk	No	December 2014	Recruiting
Shreffler WG, USA	Oral peanut immunotherapy (PNOIT)	Allocation: Randomized	NCT01324401	32	Peanut flour OIT	Tolerance	No	March 2014	Recruiting
Wood R, USA	A randomized, double-blind, placebo-controlled study of oral milk immunotherapy for cows' milk allergy	Allocation: Randomized	NCT00465569	20	Milk oral Immunotherapy	The percentage of patients who can tolerate four times the initial OFC threshold dose or the maximum OFC dose of 8 grams after therapy	Yes	June 2008	Completed

PI, country	Title	Study design	ClinicalTrials.gov identifier	No. of participants	Intervention	Primary outcome measures	Started reporting	Estimated study completion date	Status
Wood R, USA	The safety and efficacy of sublingual/oral immunotherapy for the treatment of milk protein allergy	Allocation: Randomized	NCT00732654	30	Milk Immunotherapy	The primary endpoint is clinical response to treatment, defined as (1) tolerating ten times the initial oral food challenge threshold dose, OR (2) tolerating the maximum oral food challenge dose at the OFC, at completion of immunotherapy	Yes	June 2010	Active, not recruiting
Wood R, USA	A randomized, double-blind, placebo-controlled pilot study of sublingual/oral immunotherapy for the treatment of peanut allergy	Allocation: Randomized	NCT01084174	30	Peanut powder/extract	The primary endpoint is to determine if sublingual administration of peanut extract and oral administration of peanut powder can induce a 10-fold increase in	Yes	January 2013	Active, not recruiting

PI, country	Title	Study design	ClinicalTrials.gov identifier	No. of participants	Intervention	Primary outcome measures	Started reporting	Estimated study completion date	Status
						tolerance as measured by food challenge			