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Supplementary File

Supplementary Table 1: Appendix A- EBL Critical Appraisal Checklist for Studies Included in the Systematic Review.

		Anagnostou et al. (2014)	Vickery et al. (2018)	Blumchen et al. (2019)	Hourihane et al. (2020)	Vickery et al. (2021)	Reier-Nilsen et al. (2018)	Reier-Nilsen et al. (2018)	Vickery et al. (2013)	Nagakura et al. (2018)	Howe et al. (2019)
Section A: Population	Is the study population representative of all users, actual and eligible, who might be included in the study?	Y	Y	Y	Y	Y	Y	Y	U	Y	Y
	Are inclusion and exclusion criteria definitively outlined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is the sample size large enough for sufficiently precise estimates?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is the response rate large enough for sufficiently precise estimates?	U	Y	Y	Y	Y	N	Y	U	Y	Y
	Is the choice of population bias-free?	Y	Y	U	Y	Y	N	N	Y	N	U
	If a comparative study:	Y	Y	Y	Y	N	Y	Y	N/A	N	Y
	Were participants randomized into groups?										
	Were the groups comparable at baseline?	Y	Y	Y	Y	Y	Y	Y	N/A	N	Y
	If groups were not comparable at baseline, was incomparability addressed by the authors in the analysis?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Y	N/A
	Was informed consent obtained?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Section B: Data Collection	Are data collection methods clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	If face-to-face survey, were inter-observer and intra-observer bias reduced?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Is the data collection instrument validated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	U
	If based on regularly collected statistics, are the statistics free from subjectivity?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Does the study measure the outcome at a time appropriate for capturing the intervention's effect?	Y	Y	Y	U	Y	Y	Y	Y	U	Y
	Is the instrument included in the publication?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Are questions posed clearly enough to be able to elicit precise answers?	Y	N/A	Y	Y	N/A	Y	N/A	Y	N/A	Y
	Were those involved in data collection not involved in delivering a service to the target population?	Y	Y	U	Y	U	U	U	U	Y	U

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Section C: Study Design	Is the study type / methodology utilized appropriate?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is there face validity?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is the research methodology clearly stated at a level of detail that would allow its replication?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Was ethics approval obtained?	Y	Y	Y	Y	Y	Y	Y	Y	Y	U
	Are the outcomes clearly stated and discussed in relation to the data collection?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Results	Are all the results clearly outlined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Are confounding variables accounted for?	Y	Y	Y	Y	U	Y	Y	U	Y	Y
	Do the conclusions accurately reflect the analysis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is subset analysis a minor, rather than a major, focus of the article?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Are suggestions provided for further areas to research?	Y	Y	Y	Y	Y	N	Y	Y	N	Y
	Is there external validity?	U	N	U	N	Y	N	N	Y	Y	N

Supplementary Table 2: Summary of articles.

Author (Year), location, title	Objectives	Study type, population, sample size	Methodology	Key findings	Strengths and limitations
Anagnostou et al. (2014), UK. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial.	To examine the efficacy of peanut oral immunotherapy for desensitisation in peanut allergic children.	Randomised Control Trial Participants: Children aged 7-16 with an immediate hypersensitivity reaction to peanuts n=104 Eligibility criteria: - Positive SPT - Positive DBPCFC Exclusion criteria: - Major chronic illness -If household member or care provider has an allergy to peanuts - Unwillingness or inability to comply with study	Phase I: Participants randomly assigned to receive active P-OIT or control OIT (peanut avoidance). Phase II: Control participants undergo active P-OIT Active P-OIT: Gradual updosing in 2 week increments of P-OIT from 2-800 mg/day. Followed by a maintenance period of the highest dose tolerated taken daily until 26 weeks reached. After 6 months: DBPCFC P-OIT product: peanut flour mixed into food	- 84% of active group in Phase I and 91% active group in Phase II (phase I control group) were able to tolerate daily ingestion of 800 mg protein (about 5 peanuts) for 26 weeks -Peanut NOAEL/peanut threshold: significant increase in active group after phase I -Clinically meaningful improvement in QoL scores after P-OIT (in active and control groups) -Most common adverse event was oral itching -19% of participants used a 2 agonist inhaler and 1 participant self-administered intramuscular adrenaline	Strengths -Including local and national participants increases generalizability for population studied - Statistical analyses were thoroughly explained Limitations -Participants were aware of their treatment allocation -Possible underreporting of symptoms by participants in active treatment -True response rate in phase I may be lower than estimated -Phase I response rate likely lower than estimated due to participants withdrawing or not reaching target maintenance dose

Vickery et al. (2018), USA. AR101 Oral Immunotherapy for Peanut Allergy (PALISADE)	To assess the efficacy and safety of AR101. AR101: peanut-derived oral drug (delivers target daily dose of 300 mg of peanut protein)	Randomised Control Trial Conducted at 66 sites in 10 countries in North America and Europe. Participants: 4-55 years of age (primary analysis population were 4-17 years old) n=499 Eligibility criteria: -Dose-limiting sx to 100 mg of peanut protein or less (1/3 of a peanut) during DBPCFC -Serum peanut-specific IgE of at least 0.35 kUA/L -Positive SPT Exclusion criteria: -Severely or poorly controlled asthma -Chronic gastrointestinal symptoms	Multicenter, double-blind, placebo-controlled trial Participants randomly assigned to active AR101 treatment group or matching placebo group. Active treatment (12 months total): -Initial dose-escalation phase – 1 day from 0.5 mg to 6 mg -Increasing dose phase - dose increased every 2 weeks from 3 mg to 300 mg -24-week maintenance phase at 300 mg End-of-trial visit: exit DBPCFC conducted with additional increased doses as tolerated	For participants aged 4-17 -67.2% in active treatment able to ingest at least 600 mg peanut protein during exit FC with no more than mild symptoms (4% in placebo group) -Increased peanut threshold: 50% in active treatment were able to complete the entire DBPCFC which increased up to 1000 mg (3-4 peanuts) -95% had adverse events 34.7% in active group had mild events (50% in placebo) 4.3% in active group had severe events (0.8% in placebo) - Decreased severity of symptoms in treatment group at each dose level - Severe adverse events occurred in less than 6% of treatment group participants and less than 2% in placebo group	Strengths -Multicenter, double-blind, placebo-controlled trial decreases risk of bias -Local, national and international subjects increase generalizability Limitations -Population may not be generalizable to entire peanut allergic population -Most participants were male and white -Can't draw long term conclusions
Blumchen et al. (2019), Netherlands. Efficacy, Safety, and Quality of Life in a Multicenter, Randomized, Placebo-Controlled Trial of Low-Dose Peanut Oral Immunotherapy in Children with Peanut Allergy	To investigate the safety, efficacy, quality of life and burden of treatment of low dose P-OIT.	Randomized Control Trial Participants: Children aged 3-17 with a challenge-proven clinically relevant peanut allergy n=62 Eligibility criteria: - Serum peanut-specific IgE of more than 0.35 kUA/L -Note: included children with controlled asthma or a history of severe allergic reaction after peanut ingestion Exclusion criteria: -Receiving any other immunotherapy -Severe disease (e.g. uncontrolled asthma)	Low dose P-OIT multicenter, double-blind, randomized placebo-controlled trial Participants randomized to active treatment group or placebo. Active treatment: Starting dose dependent on the eliciting dose patients reacted to at initial OFC à Dose taken daily with updosing every 2 weeks lasting up to 14 months à Maintenance phase for 8 weeks with doses ranging from 125-250 mg Post-OIT OFC after maintenance phase	-74.2% of P-OIT group tolerated 300 mg peanut protein or more (16.1% in placebo-OIT group) in final OFC - 41.9% of P-OIT tolerated maximum dose of 4.5 g peanut protein at final OFC (1 in placebo group) -Reaching a lower maintenance dose than planned still lead to reasonable efficacy 14 P-OIT patients did not reach their planned. maintenance dose but had a median maintenance dose of 50 mg. 64% of the 14 tolerated at least 300 mg peanut protein at final OFC. Safety 90% of P-OIT group had mainly mild to moderate subjective AEs (compared to 77% of placebo group) No difference between groups in dropout rate due to AEs, occurrence of objective AEs or severity of symptoms - Significant reduction in accidental reactions to peanuts in P-OIT group - Significant improvement in health related QoL after P-OIT - Low burden of treatment (most mothers and children reported positive feelings about the OIT and would do it again)	Strengths - Multicentre, double-blind, randomized control trial reduces risk of bias - Included children with highly sensitive peanut allergy - First study to assess burden of treatment Limitations - Unblinded OFC protocol could lead to overreporting of reactions during baseline OFCs and underreporting at final OFCs - Study used a different OFC protocol which could change the sensitivity of threshold and severity of reactions during OFC - possible impacting the efficacy data

Blumchen et al. (2019), Netherlands.	To investigate the safety, efficacy, quality of life and burden of treatment of low dose P-OIT.	Randomized Control Trial	Low dose P-OIT multicenter, double-blind, randomized placebo-controlled trial	- 74.2% of P-OIT group tolerated 300 mg peanut protein or more (16.1% in placebo-OIT group) in final OFC	Strengths
Hourihane et al. (2020), Ireland, France, Germany, Italy, Spain, Sweden and UK. Efficacy and safety of oral immunotherapy with AR101 in European children with a peanut allergy (ARTEMIS): a multicentre, double-blind, randomised, placebo-controlled phase 3 trial	To evaluate efficacy of AR101 in European peanut allergic children.	Randomized Control Trial Participants: Children aged 4-17 with a clinical history of peanut allergy n=175 Eligibility criteria: - Development of dose-limiting symptoms to 300 mg or less peanut protein	Participants randomly assigned to daily doses of AR101 OIT or placebo group. 2-day dose-escalation phase: from 0.5 mg to 6 mg on day 1 and 3 mg on day 2 Up-dosing phase: 20 to 40 weeks long, AR101 or placebo taken daily at home with dose escalations every 2 weeks (from 3 to 300 mg) Maintenance dosing phase: take daily placebo or 300 mg/day AR101 for 12 weeks	- 58% of AR101 group (n=132) able to tolerate 1000 mg peanut protein with no dose-limiting symptoms at exit FC (2% in placebo group, n=43) - 68% of AR101 group tolerated 600 mg peanut protein and 74% tolerate 300 mg - During exit DBPCFC ▯ AR101 participants who developed dose-limiting symptoms did so at higher doses than placebo ▯ AR101 group less likely to develop severe symptoms at any challenge dose - 99% of AR101 group (98% in placebo) had one or more treatment related AEs - 11% of AR101 group (2% in placebo) discontinued treatment due to AEs (mostly during up-dosing phase) - Self and caregiver reports of food allergy-related QoL noted greater improvements compared to placebo	Strengths -Clearly and thoroughly outlined how they monitored participant safety during the length of the trial Limitations - Participants predominantly white and male -Food allergy-related QoL assessed immediately after exit FC so participants may not have had enough time to evaluate the OIT's effect
Vickery et al. (2021), North America, EU and UK. Continuous and Daily Oral Immunotherapy for Peanut Allergy: Results from a 2-Year Open-Label Follow-On Study	A follow-up study of the PALISADE trial (listed above). To evaluate the long term OIT with peanut allergen powder-dnfp (PTAH) and alternative dosing regiments in peanut allergic children.	- Positive SPT - Peanut-specific IgE concentration of at least 0.35 kUA/L Exclusion criteria - Severe or life-threatening episodes of anaphylaxis within 60 days of screening DBPCFC - Severe or uncontrolled asthma - History of eosinophilic oesophagitis - Chronic, recurrent or severe GI symptoms with undiagnosed cause Exploratory open-label extension trial Participants: Participants from PALISADE trial who tolerated 300 mg peanut protein at exit DBPCFC + placebo participants; (primary analysis population were 4-17 years old) n=358	Exit DBPCFC Definition of tolerated dose: dose ingested with no more than mild symptoms that did not require pharmacological treatment PTAH-naïve group: participants from placebo group in PALISADE trial - Initial dose escalation updosing for 22-40 weeks à maintenance dosing at 300 mg daily for 24 weeks - After 6 months of maintenanceàmaintenance DBPCFC with 2000 mg PTAH-continuing group: participants from active treatment arm of PALISADE who successfully completed the 300 mg exit DBPCFC - Cohorts 1 and 3A à daily dosing regimens - Cohorts 2, 3B, 3C à non-daily dosing regimens Exit DBPCFC up to 2000 mg peanut protein	PTAH-continuing participants - Daily dosing cohorts appeared to have higher desensitization rates than non-daily dosing cohorts - AE rates: 12.94-17.54 per participant-year in daily dosing cohorts and 25.95-42.49 per participant year in non-daily dosing cohorts - 83% experienced mild or moderate AEs Treatment-related anaphylaxis occurred in daily dosing periods in 2 participants in cohort 1 and 3 in cohort 3C - All were female aged 5-15 years - 4 had a history of systemic allergic reaction at baseline Observed ongoing immunomodulation during 2nd year of treatment After 2 years of continued daily PTAH treatment, 80% were desensitized to 2000 mg peanut protein.	Strengths - Increased generalizability to real world peanut encounters due to the long-term structure of the trial - Offered more guidance on administration of P-OIT in paediatric population - Good sample size Limitations - Exclusion of those with uncontrolled asthma or chronic gastrointestinal disorders - Participants not randomized into treatment groups - risk of bias

Reier-Nilsen et al. (2018), Norway. Parent and child perception of quality of life in a randomized controlled immunotherapy trial	To investigate if P-OIT improved child QoL, as reported by parents and/or the children. To identify factors influencing change in QoL	Randomized Control Trial Participants: Subjects aged 5-15 years old with anaphylaxis to peanuts. n=77 Eligibility criteria: -Positive DBPCFC with objective symptoms in minimum two-organ systems	Open-labeled TAKE-AWAY P-OIT trial Randomization to P-OIT (n=57) and observation group (n=20). Pediatric QoL Inventory Version 4.0 completed by parents and children at enrollment (Y0), after 1 year (Y1) and after 2 years (Y2) of OIT. Perceived treatment burden recorded by visual analogue scales – including AEs.	At Y2: - 18 children discontinued OIT - 35/37 desensitized to 7500 mg peanut protein Y0 to Y2: - Mean change in QoL was 4.4 among child self-reports and twice as large on parental reports (no sig improvement among controls) - Change in QoL only significantly different from controls for parental reports - Suggests that parents may overestimate improvement in child-QoL by OIT	Strengths - Standardized QoL assessments - Detailed information of AEs - Visual analogue scale of perceived treatment burden Limitations - Allocating controls for observation only (no placebo) – increases risk of bias - Limited sample size may have contributed to non-significant differences in children self-reports of QoL - 32% of OIT children discontinued treatment and no QoL assessment was taken.
Reier-Nilsen et al. (2018), Norway. Feasibility of desensitizing children highly allergic to peanut by high‐dose oral immunotherapy	To determine the feasibility of reaching the maximum maintenance dose (MMD) of 5000 mg peanut protein or a lower individual maintenance dose (IMD) by updosing.	Randomized Control Trial Participants: Subjects aged 5-15 years old with anaphylaxis to peanuts. n=77 Eligibility criteria: -Positive DBPCFC with objective symptoms in minimum two-organ systems	The open-labeled TAKE-AWAY P-OIT trial. Randomization to P-OIT (n=57) and observation group (n=20). P-OIT group: biweekly updosing until reach MMD or IMD Demographic and biological characteristics, AEs, medication and protocol deviations investigated.	21.1% reached MMD and 54.4% reached an IMD of median 2700 mg peanut protein. 24.5% discontinued OIT. 19.4% experienced anaphylaxis during updosing. Reasons for not reaching MMD: distaste (majority), unacceptable AEs, social reasons Increased peanut s-IgG4/s-IgE ratio associated with MMD.	Strengths -Calculated objective LOAEL allowed for comparison between other studies Limitations - Switching from defatted peanut flour to whole peanuts could influence efficacy of OIT - No placebo arm - increases risk of bias.
Vickery et al. (2013), USA. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy	To determine if P-OIT can induce sustained unresponsiveness after withdrawal of OIT. Sustained unresponsiveness: ability of a subject to pass an OFC after stopping OIT and successfully introduce the allergenic food into the diet.	Exploratory pilot study Participants: Subjects aged 1-16 years n=39 (24 with evaluable outcomes) Eligibility criteria: - Clinical history of reaction to peanuts within 60 minutes of ingestion - Positive SPT - Peanut-specific IgE concentration of at least 15 kU/L or greater than 7 kU/L with a clinical reaction in the past 6 months Exclusion criteria - Clinical anaphylaxis if deemed severe or life-threatening (e.g. with hypotension) - Severe or poorly controlled asthma - Medical condition preventing OFC			

Nagakura et al. (2018), Japan. Low-dose oral immunotherapy for children with anaphylactic peanut allergy in Japan	To explore the efficacy of low dose OIT for anaphylactic peanut allergy.	Prospective clinical trial Participants: Subjects aged 5-18 years P-OIT n=24 Eligibility criteria: - History of anaphylaxis or high levels of peanut-specific IgE (>50 kUA/L) - Objective symptoms during an OFC of 133 mg peanut protein Exclusion criteria: - Poorly controlled bronchial asthma - Atopic dermatitis - Participation in other immunotherapy	24 children with anaphylaxis to peanuts were gradually fed increasing amounts of peanut powder up to 133 mg/day. Control group was a historical control group. Selected subjects aged 5 to 18 presenting with objective symptoms during baseline OFC of 133 mg peanut and who completely avoided peanuts before second OFC over a year after first OFC. OFC completed 1 year later after 2 weeks of peanut avoidance. If asymptomatic after ingesting 795 mg peanut: achieved sustained unresponsiveness. Measured peanut-specific IgE and IgG4 levels 5 times over the year. Sustained unresponsiveness: passing the OFC and successfully ingesting peanut protein once a week at home without symptoms	1 year later: 8 children in P-OIT group demonstrated sustained unresponsiveness (none in control group). After 1 month, P-OIT group had a significant increase in peanut-specific IgE followed by a significant decrease at 12 months.	Strengths -Participants from all around Japan increasing its generalisability Limitations - Differences between P-OIT group participants and historical control group - Sustained unresponsiveness was assessed after only 2 weeks of avoidance - may not have been sufficient time
Howe et al. (2019), USA. Changing Patient Mindsets About Non-Life-Threatening Symptoms During Oral Immunotherapy: A Randomized Clinical Trial	To determine if promoting the mindset that non-life-threatening symptoms during P-OIT can suggest desensitization improves treatment outcomes and experiences.	Randomized Clinical Trial Participants: Subjects aged 7-17 years n=50 Eligibility criteria: - Peanut specific blood IgE level >60 Ku/L, or - Peanut specific blood IgE levels >5 and <60 Ku/L with SPT >3 mm Exclusion criteria: -Diagnosis of anxiety and/or mood disorders	Patients consumed peanut doses at home over 24 weeks. Families randomly assigned to either: - "Symptoms as Positive Signals" (SAPS) ▯ Encouraged to think of symptoms positively and associated with increasing desensitization (using written information and activities at monthly clinic visits) - "Symptoms as Side Effects" (SASE) Both groups received: - Identical OIT instructions - Identical training medication use and instructions for recognizing life-threatening symptoms - Same access to resources - Monitoring of symptoms Treatment experience and treatment outcomes were measured by completing daily online questionnaires through REDCap	SAPS families demonstrated - Less anxiety over symptoms during the course of treatment - Decreased likelihood to contact staff about symptoms - Less non-life-threatening symptoms as dose increased - Decreased likelihood to skip or reduce doses - A greater increase in patient peanut-specific blood IgG4 levels Both groups ▯ Clinic sessions evaluated positively with no difference in perceptions of treatment efficacy	Strengths -Demonstrated the importance of prioritizing patient mindsets in altering patient experience and outcomes Limitations - Research conducted at a single site under supervision of one healthcare worker - Possible underestimation of the effect of changing symptom mindsets as the SASE families began to agree more than symptoms could be a positive signal