Appendix 6: Sample protocols

The following sample protocols are based on the protein content for the allergen(s) included in the OIT treatment. They actual amount of food given will therefore depend on the protein content of the allergen.

The following equivalency table provides protein content for foods frequently used for OIT, based on the USDA food database. Because variations in protein content are to be expected according to brand or nut size, patients should be advised to use the same product at home as the one used in clinic during the up-dosing phase. Ideally, new products are introduced during up-dosing visits. Once maintenance has been achieved and is well tolerated, patients can usually experiments with new food alternatives safely, provided they understand the concept of food equivalency. Consultation with registered dieticians experienced in OIT and teaching tools to that effect can be very helpful to assist patients with equivalent food alternatives.

For food containing heat-labile allergens, such as milk or egg, special consideration should be given to the product used in OIT. Where desensitization with raw forms will protect against cooked forms, the reverse may not be true. In practice, patient objectives regarding heat-labile and heat-resistant allergens are often not the same. Where patients often wish to achieve complete desensitization to cooked forms to allow their introduction in diet and reduce limitations, most only wish to achieve partial desensitization against raw forms to protect against accidental contamination. The choice of products should reflect those objectives, which can change during therapy as patients discover their love or dislike of the food they had been avoiding. For example, a target daily maintenance dose for milk allergy could be 15mL of fresh milk (0.5g protein) and 1 whole portion of string cheese (6g protein).

Measurement of daily doses

Whole units: With larger dose amounts, easily measurable of food units can be used (e.g. ¼ peanut snack stick, 1 cm of string cheese).

Weight: With smaller amounts, individual doses can be measured precisely with scale in soufflé cups or capsules. Usual practice aims for a level of precision of ± 10%. If this task is delegated, proper training is essential to avoid dosing errors and cross-contamination and ensure traceability.

Volume: A practical alternative to weighing individual doses consists in using syringes or measuring spoons for patient to calculate daily dose for liquid food or suspension.

The suspension media must be adapted to the food. For example, defatted peanut or sesame flour are best suspended in simple syrup suspension. Nut meals, on the other hands tend to float in simple syrup because of their oil content. Suspension vehicles with suspending and anti-foam agents (e.g. oral-blend or oral mix) are therefore better suited for nut meals.

Example of Recipe for 60 mL of peanut suspension at 250mg protein per 5mL (50mg/mL):

In a sterile specimen cup, add 6g of defatted peanut flour (or 7.2g of powdered peanut butter). Add simple syrup up to the 50mL line. Mix thoroughly with spoon. Complete with simple syrup up to the 60 mL line. Shake. Keep refrigerated.

On the label, make sure to indicate:

- Patient name
- Content and concentration (e.g. peanut 250mg/5mL)
- Date of production
- Peanut flour lot
- Peanut flour expiry date

Equivalency table: protein content per type of allergen

Protein content is based on the USDA database. Exact allergen content may vary according to brand. Food escalations in clinic should therefore be performed with the same product that will be used at home.

Allergen		Amount of protein
Chicken's egg	1 mg of powdered-egg whites	1.25 mg
	1 whole egg	5000 mg
	1 ml raw egg* mixed	100 mg
	Note: Raw egg is not recommended under 1 year old unless pasteurized due to risk of bacterial contamination	
Peanut	1 peanut	250 mg
	1 ml Peanut butter (Kraft®)	200 mg
	2.4 mg of powdered peanut butter (PB2®)	1 mg
	2 mg of defatted peanut flour	1 mg
	0.1 mL of peanut flour suspension (50mg/mL)	5 mg
	1 peanut stick snack (Bamba®)	80 mg
Cow's milk	1 ml milk (any percent of fat)	35 mg
	2.8 mg of powdered milk	1 mg
	1 cm of string cheese stick (6g protein for 12cm stick)	500 mg
Mustard	1 ml yellow mustard	40 mg
	3.2 mg of mustard powder	1 mg
Hazelnut	1 table spoon of Nutella ®	300 mg
	1 hazelnut	180 mg
	Hazelnut meal	1 mg
Almond	1 almond	275 mg
	4.6 mg of almond meal/flour, non-defatted	1 mg
	2.6 mg of powdered almond butter (PB2®)	1 mg
Cashew	1 cashew	275 mg
	5.6 mg of cashew meal	1 mg
Pecan	1 pecan half	150 mg
	10 mg of pecan meal	1 mg
Pistachio	1 pistachio	150 mg
	4.6 mg of pistachio meal	1 mg
Walnut	1 walnut half	360 mg
	6 mg of walnut meal	1 mg
Salmon	5 mg of smoked or raw salmon	1 mg
Sesame	1 ml tahini	167 mg
	2.5 mg of defatted sesame flour	1 mg
	DO NOT USE whole sesame seeds unless crushed to allow release of the allergen contained in the seed.	
Shrimps	1 small shrimp (2.5g)	450 mg
Soy	1 ml soy milk (7g/250 ml)	28 mg
Oat	7.5 mg of oat flour	1 mg
Barley	9.3 mg of barley baby cereal	1 mg
Rye	7.5 mg of rye flour	1 mg
Buckwheat	7.5 mg of buckwheat flour	1 mg
Wheat	1 slice of whole wheat bread (32g)	4380 mg
	10 mg of white all-purpose flour	1 mg
	1 macaroni (elbow)	35 mg

Sample dosing schedules

Note: all schedules are meant as guidance and should be adapted to patient response and personal objectives. These are provided as examples to guide implementation of OIT and have not been shown superior to other published schedules.

CoFAR schedule

This protocol, published by Burks et al in 2012,[32] consists in an initial food escalation up to a dose of 6 to 50 mg of food protein. Followed by daily dosing with the highest tolerated dose and up-dosing every other week.
Food doses are initially doubled (+100%) at each step up to a dose of 50 mg protein. Percentage increments are then progressively decreased to increments of +25%.

Step	Protein amount	% increase
1	0.1 mg	-
2	0.2 mg	100%
3	0.4 mg	100%
4	0.8 mg	100%
5	1.5 mg	100%
6	3 mg	100%
7	6 mg	100%
8	12 mg	100%
9	25 mg	100%
10	50 mg	100%
11	75 mg	50%
12	100 mg	33%
13	125 mg	25%
14	156 mg	25%
15	195 mg	25%
16	245 mg	25%
17	306 mg	25%
18	383 mg	25%
19	479 mg	25%
20	599 mg	25%
21	749 mg	25%
22	936 mg	25%
23	1170 mg	25%
24	1463 mg	25%
25	1829 mg	25%
26	2286 mg	25%
27	2858 mg	25%
28	3572 mg	25%
29	4465 mg	25%
30	5582 mg	25%
31	7000 mg	25%

Omalizumab-enabled accelerated schedule

Adapted from Begin et al., 2014[23]
This up-dosing schedule follows the same structure as CoFAR schedule, but faster. The first steps for the initial escalation triple the amount of food (+200%) and latter up-doses consist in doubling the dose (+100%). This accelerated protocol was developed for patients having received omalizumab for at least 2 months prior to initiating OIT, which contributes to increase their reactivity threshold (off-label indication).

Step	Protein amount	% increase
1	5 mg	-
2	15 mg	+200%
3	50 mg	+233%
4	150 mg	+200%
5	300 mg	+100%
6	600 mg	+100%
7	1200 mg	+100%
8	2400 mg	+100%
9	4800 mg	+100%
10	9600 mg	+100%

Pre-school peanut schedule

This protocol was published in a cohort study of toddlers and pre-schoolers undergoing peanut OIT[9] but can be used for any patient with high baseline reactivity threshold to their food. It can be initiated with an initial escalation or directly at a dose that is expected to be below the patient's reactivity threshold (given in clinic). For convenience, the up-dosing steps were developed based on easily measurable portions of the Bamba peanut snack. The schedule should be adapted to the food used to remain convenient.

Step	Protein amount		% increase
1	10 mg	1/8 sticks	-
2	20 mg	¼ sticks	100%
3	40 mg	½ sticks	100%
4	80 mg	1 sticks	100%
5	120 mg	1 ½ sticks	50%
6	160 mg	2 sticks	33%
7	240 mg	3 sticks	50%
8	320 mg	4 sticks	33%

Individualized symptom-driven up-dosing

This approach consists of individualizing up-dosing speed according to patient tolerance. There is no predetermined schedule. Home dosing is started at the highest tolerated dose from an initial escalation customized based on patient's baseline allergy profile (i.e. allergy testing, previous challenges or clinical reactions) and personal tolerance to the risk of reacting on that first introduction.

Intervals between dosing visits

The approach generally assumes constant intervals between up-dosing visits (2 weeks to 3 months). In some patients, longer intervals may improve chances of tolerating a given escalation but the extent to which length of interval between up-dosing visits contributes to preparedness for next escalation is unknown and most likely varies between patients. At a minimum, new symptoms from the previous escalation should have abated before proceeding with the next escalation. Greater intervals between intervals can also contribute to decreasing the logistical burden of therapy for patients and providers.

First up-dosing visit:

When the starting dose was well tolerated, both in clinic and at home, the first up-dosing visit will usually consist of an attempt to double the dose (+100%). An additional +100% can be added 30 minutes later during the same visit if it was well tolerated, for a total +200% escalation. A more conservative initial increment of +50% can also be considered based on specific context and shared-decision making.

Example A: *First up-dosing after starting OIT at a daily dose of 10mg.*

Step	Amount	% of current dose	Cumulative
1	20 mg	+100%	20 mg
	10 mg	+100%	30 mg

If the escalation is not tolerated in clinic: Patient should remain on the current dose and rescheduled for an attempt to escalate with half the failed % increment (+50% in the example above, 15 mg). Alternatively, in absence of systemic symptoms to the failed escalation, the patient could also attempt to increase to half the failed % increment at home.

Following visits:

If the dose was well tolerated at home since the last escalation: The subsequent escalation should use the same percent increment.

Example A*: Escalation to 30 mg (+200%) was well tolerated in clinic and at home.*

Step	Amount	% of current dose
2	90	+200%
3	270	+200%
4	2 hazelnuts	

If the escalation was not well tolerated at home after the last escalation: The subsequent escalation should use half of the % increment

Example B*: Escalation to 20mg (+100%) was tolerated in clinic but patient was bothered by moderate symptoms during the first week of home dosing at that dose.*

Step	Amount	% of current dose	Outcome
2	30	+50%	Moderate symptoms at home
3	38	+25%	No symptoms

4	48	+25%	No symptoms
5	60	+25%	No symptoms

If following escalations are completely symptom-free: Re-attempting higher percent increments can be considered. Assessment of dosing tolerance should take into account whether or not pre-medication is used prior to food dosing. Transient mild symptoms with home dosing are frequent in the first week following an escalation and are an indication that treatment speed is most likely optimal.

Example B (cont'd)

Step	Amount	% of current dose	Outcome
6	90	+50%	Oral pruritus for 4 days
7	135	+50%	No symptoms*
8	200	+50%	No symptoms*
9	300	+50%	No symptoms*
10	2 hazelnuts		No symptoms

*Patient advised to take cetirizine 60 minute before dose for the first 4 days after an escalation.

When patients are using pre-medication before taking food dose at home, the same medication should be used prior to the up-dosing. When patients are symptom-free with medication, ability to tolerate the dose without the pre-medication should be assessed before considering further increasing the up-dosing speed.

Pre-medication

Note: The following protocol on the use of pre-medication is meant as an example to help support implementation of OIT and has not been shown superior to other clinical approaches to pre-medication in OIT. Recourse to and choice of mediation should be individualized based on patient specific symptoms and context and should be adapted to patient response and personal objectives. Apart from disodium cromoglycate, which is specifically indicated for the prevention of gastro-intestinal IgE-mediated symptoms of food allergy, the uses described below constitute off-label uses.

For oral pruritus:

- Consider a trial of non-sedating oral H1 antagonists one hour before taking the food dose.

For immediate gastro-intestinal symptoms (<30 minutes):

- Consider taking the food dose with along with a bulky meal or snack
- Consider a trial of oral H2 antagonists and/or non-sedating oral H1 antagonists one hour before taking the dose.

For delayed gastro-intestinal symptoms (>45 minutes):

- Consider taking dose in the morning, as sleep cycle/deprivation can contribute to decreased dose tolerance.
- Consider a trial of oral montelukast, one hour before taking the doses[104].
- Consider taking misoprostol before the dose, once a day. Finding optimal dosage of misoprostol can be challenging as it can cause confusing symptoms of intestinal cramping and diarrhea. Determining the right therapeutic index in the context of OIT requires close follow-up with patient and adjustments. It is usually reserved for patients where delayed symptoms appear to progress rather than abate over time following a food dose increase, presumably from the local cumulative amplifying effect of prostaglandins, and mast cell stabilizers are insufficient or not covered.

For either immediate or delayed gastro-intestinal symptoms, or both:

- Consider a trial of disodium cromoglycate no more than 15 minutes before taking the dose (once a day, unless food dose is taken multiple times).

In the context of an unavoidable co-factor (e.g. NSAIDs following dental procedure), to decrease the risk of systemic reactions to the dose:

- Consider a transient decrease in the daily dose
- Consider transiently adding disodium cromoglycate, taken once a day, no more than 15 minutes before the food dose. In mice models, disodium cromoglycate prevented the loss of barrier functions resulting from mast cell activation in the gastro-intestinal tract that is exacerbated by co-factors such as NSAIDs, which in turn protected against co-factor induced systemic reactions to the food dose.[105]

To prevent the occurrence of isolated bronchospasms following food dosing:

- The presentation of isolated bronchospasm without other systemic manifestation of anaphylaxis following food dosing suggests localized increased sensitivity of mast cells in bronchial tissue.
- If known asthma, reassess control and need to increase inhaled corticosteroids.
- If no asthma, consider the diagnosis and consider a trial of inhaled corticosteroids.
- Assess and address potential contribution of environmental allergens.
- Consider performing FeNO. The objective measure of a local inflammatory process with FeNO is particularly useful to confirm the presence of underlying “sub-clinical” asthma when patient has no manifestation of asthma other than with food dosing. It can be

helpful to demonstrate the concept to the patient and to monitor response to therapy in this particular context.

For gastro-intestinal symptoms which timing is not related to food dosing:

- Consider the possibility of a cellular-mediated allergic reaction to the food allergen. This can be difficult to differentiate from delayed type IgE-mediated reactions. Response to trials with the above-mentioned medications can help distinguish the underlying process.
- Consider adding a proton-pump inhibitor.
- Consider transiently or permanently decreasing the food dose.
- Consider performing endoscopy. In the context of OIT, the presence of eosinophils on biopsy could result from both recurrent delayed type IgE-mediated reactions or from a cellular-mediated reaction and should therefore not be the sole basis on which to orient management.
- Consider performing an atopy patch test (APT) with the food allergens. Where many patients with IgE-mediated food allergy can present mild infiltrate on APT, a strong reaction to one or more specific food is unusual and can be useful to guide management.

- *For patient with symptoms compatible with eosinophilic oesophagitis (EoE),*
    - Discuss the options of discontinuing or continuing OIT with patient. In a previous cohort of patients with cellular-mediated symptoms with OIT, those with symptoms compatible with EoE were generally able to continue treatment.
    - Consider a trial of swallowed topical corticosteroid after discussing.

- *For patients with symptoms compatible with eosinophilic gastro-intestinal disease (EGID),*
    - Consider discontinuing OIT. In a previous cohort of patients with cellular-mediated symptoms with OIT, those with symptoms compatible with EGID were unable to complete treatment.
    - For patients already receiving another biologic therapy indicated for their asthma, consider switching to dupilumab, which could contribute to a better control of cellular-mediated allergic response in the gastro-intestinal tract[106].