ORKA-NL studie

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PROTOCOL TITLE: A randomized controlled trial to investigate the (cost)effectiveness of oral immunotherapy with different allergens in young children with an established food allergy.

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Inhoud

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IB	**Investigator's Brochure**
IC	**Informed Consent**
(s)IgE	**(specific) Immunoglobulin E**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
OIT	**Oral Immunotherapy**
(S)AE	**(Serious) Adverse Event**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Recent studies suggest that oral immunotherapy is associated with long-term tolerance development in food allergic children, but only when started early in life. Currently, no randomized controlled trials are performed for different kinds of food allergies in these young children.
Hypothesis: Early low-dose oral immunotherapy in young children with an established food allergy will induce long-term tolerance within one year in at least 50% more children compared to the percentage of children who achieve spontaneous tolerance in the routine care group (strict avoidance of the allergen).
Primary objective: What is the clinical- and cost-effectiveness of early low-dose oral immunotherapy aimed at long-term tolerance induction in children under the age of 30 months with an established food allergy compared to routine care?
Secundary objective: What is the effect of early low-dose oral immunotherapy in children under the age of 30 months with an established food allergy on (allergy specific) quality of life of parents and children compared to routine care?
Study design: randomized controlled superiority trial
Study population: Children between 9 and 30 months old with an IgE-mediated food allergy to peanut, tree nuts, cow's milk and/or hen's egg as proven by an oral food challenge. **Intervention**: 1-year low-dose oral immunotherapy (daily 300 mg allergenic protein) compared to strict avoidance in the control group.
Main study parameters/endpoints: Sustained unresponsiveness, defined as passing an exit oral food challenge at 4 weeks after discontinuation of the 12 months oral immunotherapy, and uncomplicated consumption of a full dose of the specific food at home, after 6 months unrestricted introduction of the specific food into the diet.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
Burden: in all children participating in the study, oral food challenges are performed, and two blood samples are obtained (both will completely or partially be part of routine diagnostic allergy care). Parents have to fill in 4 questionnaires each 6 months. Children whose allergy is assigned to the intervention group, have to visit the hospital for an additional 1 to 6 times during the build-up phase of the treatment and an additional blood sample is obtained after 6 months of therapy. Parents have to take care of daily ingestion of the allergenic food by their child at home.
Risks: the main risk of oral immunotherapy is the occurrence of allergic side-effects. Because a food allergy by definition is characterized by an allergic reaction in case of an accidental ingestion, parents have to be prepared for the risk of allergic reactions already. Inducing long-term tolerance, the main

goal of this treatment, would prevent a life-long risk of allergic reactions caused by accidental ingestions.

Group relatedness: current scientific knowledge suggests that only in food-allergic infants oral immunotherapy may be associated with long-term tolerance in contradiction to school-aged children.

1. INTRODUCTION AND RATIONALE

Many babies and toddlers with moderate to severe eczema develop a food allergy. While the eczema will disappear in more than half of the children, the food allergy may persist, causing lifelong dietary restrictions. The current lack of curative treatment options is therefore a substantial unmet need for these parents, and for children later on in life.[1]

Scientific research on treatment of food allergy has been focused on oral immunotherapy, because other treatment options have not proven significant profits. For oral immunotherapy, there is vast evidence that the therapy results in desensitisation of food-allergic children.[2] Desensitization is defined as a temporarily desensitisation while on therapy. Meaning that only during ongoing treatment the frequency and severity of allergic reactions could be decreased, with acute cessation of this effect after discontinuation of the therapy.[3] A second possible outcome of oral immunotherapy is curation of the food allergy, also named 'tolerance induction' or 'sustained unresponsiveness'. Sustained unresponsiveness is typically tested 2 to 8 weeks after discontinuation of the therapy by an oral food challenge using a full-dosage of the allergenic food. In many studies on oral immunotherapy for food allergy performed in adults and children > 4 years of age, this outcome is only achieved in a minority of patients.[32]

New promising perspectives have arisen during the past few years, suggesting that starting the therapy in the first years of life may increase the chance on curation of the food allergy. In babies with a high risk on development of food allergy, early introduction of high-allergenic food products has proven to prevent the development of food allergies to a very large extend.[4 5] This high effectiveness of early oral ingestion of food allergens to prevent the development of food allergy, has proven that food tolerance development in young children originates in the intestinal immune system. The next step to benefit from this strong tolerogenic capacity of the intestinal immune system early in life is to start oral immunotherapy at a very young age in children with food allergy. Results of the first studies on oral immunotherapy started before the age of 4 years, suggest that curation of food allergy is achievable in a high rate of babies and toddlers.

The first study on oral immunotherapy in young peanut-allergic children has shown very promising results, with more than 90% of children becoming tolerant for peanut. In this study, 37 children under the age of 3 years were included and randomized between high-dose (n=17) and low-dose (n=20) oral immunotherapy. A control group (n=154) was included in a cooperating hospital. No differences in effectiveness and immunological outcomes were observed between the two treatment arms. Sustained unresponsiveness was assessed after 4 weeks of discontinuation of the therapy and a survey five years later assessing regular consumption of peanut by the study participants. Long-term tolerance was achieved in 84% of the children receiving oral immunotherapy compared to an estimated spontaneous tolerance development between 4% and 31% in the control group.[6]

A recently published study on oral immunotherapy for peanut allergy is a randomized controlled study including 146 children between 12 and 48 months old with severe peanut allergy. The intervention consisted of two years of oral immunotherapy. Sustained unresponsiveness was the major outcome and was assessed after 6 months of withdrawal of the therapy. Long-term tolerance was achieved in 29 % of the children in the intervention group versus spontaneous tolerance development in 4 % of the children in de control group. The outcome appeared to be strongly related to the age of inclusion and the level of antibodies to peanut. Children who started the therapy before

the age of 24 months with a moderate level of peanut-specific antibodies, had the highest chance of achieving long term tolerance (up to 80%!). Unfortunately, only a minority of study participants started the therapy at such a young age, preventing from strong conclusions on this subgroup. However, the study suggests that starting oral immunotherapy after the age of 36 months is too late to achieve long-term tolerance in a significant proportion of the children, while starting the therapy at a very young age has very promising perspectives.[7]

In a large Canadian study, peanut-sensitized children from 9 to 71 months old received 1 year of oral immunotherapy. In this study, OIT was not discontinued to assess sustained unresponsiveness. According to the per-protocol analysis, 92 of 117 patients (78.6%) who did the follow-up oral food challenge were able to tolerate the food without allergic symptoms. It can be concluded that at least 21,4% of the children were still allergic after the therapy. The amount of children with no response to the therapy may be attributed to the higher age of these children.[8]

In the current feasibility study of the Deventer hospital, 62 children with a single or multiple food allergy completed the 1-year low-dose oral immunotherapy and were tested for sustained unresponsiveness after 4 weeks of discontinuation of the therapy. Of these 62 children, 16 were treated for a peanut allergy, 28 for a nut allergy and 16 for a hen's egg allergy. Only 3 children treated for peanut allergy, 1 treated for cow's milk allergy and 1 treated for hazelnut allergy showed signs of an allergic reaction during the exit oral food challenge, while all other children passed the test, which is a unique and remarkable finding. Long-term introduction into the diet has been assessed in 12 children. They all introduced the specific allergen into their diet. Two children have experienced mild allergic symptoms in the first year after completing the therapy. One child, who was treated for cashew nut allergy, experienced an itchy mouth after 6 months of no allergen intake, the other child, who was treated for hen's egg allergy, still experiences contact allergy, an itchy mouth and stomach pain after ingesting ½ hen's egg. All other children are eating the specific allergen weekly or monthly without signs of an allergic reaction.

Taken together, the current feasibility study on oral immunotherapy in the Deventer hospital shows the same high rate of tolerance development in young food allergic children as previous studies. And not only for peanut allergy, but also for tree nuts and hen's egg allergy. This strongly contradicts to natural tolerance development rates for peanut and cashew nut allergy and to the inability to achieve long-term tolerance by oral immunotherapy in children > 4 years of age and adults. Apparently, the capacity of the intestinal immune system to contribute to tolerance development for foods only applies to young children. The age-related difference in clinical efficacy of oral immunotherapy correlates in time with recognition of conformational versus linear IgE epitopes, the latter being associated with persistent allergies and mainly developing after 30 months of life.[9]

The window of opportunity for a curative treatment therefore seems to be limited, oral immunotherapy probably needs to be started as young as possible and at least before the age of 2 or 3 years if aimed at curation.

Because a food allergy is caused by an increased susceptibility of the dermal immune system, many children have a food allergy for more than 1 food product. In most children this is limited to 3 or 4 products. Because of the need to start at a young age, oral immunotherapy for the different allergens should be started simultaneously. In children with multiple food allergy, an allergy for cow's milk or hen's egg is common. Particular in severe allergic children, the rate of persisting allergy to

cow's milk allergy or hen's egg is high. Oral immunotherapy for these allergens should therefore be involved in the treatment of those severe allergic children.
In less allergic children, spontaneous tolerance development for cow's milk or hen's egg allergy is more common. Children with a persistent cow's milk or hen's egg allergy, however, are confronted with major dietary restrictions, because a lot of food products contain these allergens. For these children is waiting for spontaneous tolerance development also losing a chance for successful treatment. It remains to be questioned, however, whether oral immunotherapy for cow's milk and hen's egg allergy is cost-effective in less allergic children.

In conclusion: oral immunotherapy is a highly promising treatment for young children with food allergy. It may prevent the food allergy from becoming a lifelong burden, which causes a substantial decrease in quality of life. Worldwide, scientific research to this promising treatment has still been performed to a limited extend, probably because of the vulnerability of young children, fear of the unknown and the risk of allergic reactions inherent to the therapy. However, since studies have shown that oral immunotherapy can be performed with low-doses of normal food products, with a lower risk of severe allergic reactions, and because of the recent findings about the safety and feasibility of the therapy (https://www.dz.nl/patient/afdelingen/kinderallergie-behandelcentrum/orka-studie), it is time to proceed with new studies on this promising treatment. A large randomized controlled trial on the clinical efficacy and cost effectiveness is needed to clarify whether all food allergic children should be offered this therapy. Oral immunotherapy is suspected to be cost-effective by saving life-long medication prescriptions and emergency care visits, and above all, a much better quality of life.

Hypothesis
1a) Early low-dose oral immunotherapy in young children with an established food allergy to peanut and/or nuts will induce long-term tolerance in at least 60% of the children after a treatment duration of one year compared to 20% in the routine care group (strict avoidance of the allergen).
1b) Early low-dose oral immunotherapy in young children with an established food allergy to cow's milk or hen's egg will induce long-term tolerance in respectively at least 75% and 65% of the children after a treatment duration of one year compared to respectively 50% and 35% in the routine care group (strict avoidance of the allergen).
1c) Early low-dose oral immunotherapy in young children with an established food allergy is expected to be cost-effective compared to routine care (strict avoidance of the allergen).
2) Early low-dose oral immunotherapy in young children with an established food allergy will increase (allergy specific) quality of life for both parents and children compared to the routine care group (strict avoidance of the allergen).

2. OBJECTIVES

Primary Objective

What is the clinical- and cost-effectiveness of early low-dose oral immunotherapy in children under the age of 30 months with an established food allergy on the induction of long-term tolerance compared to routine care (strict avoidance of the allergen) for each allergen?

Secondary Objective(s)

What is the effect of early low dose oral immunotherapy in children under the age of 30 months with an established food allergy on (allergy specific) quality of life of parents and children compared to routine care (strict avoidance of the allergen)?

3. STUDY DESIGN

Multicenter, randomized controlled superiority trial, performed in the Netherlands. Blinding is not possible, because general available food products are used. The risk of bias caused by the open-label character of the study is assessed as small, because the primary end-point on effectiveness is assessed by an oral food challenge with objective allergy symptoms as stop criteria (the test is only stopped and assessed as positive when objective signs of an allergic reaction occur, according to national and international guidelines).

The main risk is (self)selection bias, causing a difference in chance of spontaneous tolerance development, despite randomization. This may be caused by withdrawal of children by their parents who are disappointed about being randomized to the control group, with parents of children at a higher risk of a persisting allergy being more disappointed. The levels of allergy specific IgE and IgG4 are the strongest predictors of tolerance development[10], therefore these immunologic parameters will be assessed to check differences between the intervention and control group and added as confounding factors in a multivariate analyses.

4. STUDY POPULATION

4.1 Population

Children between 9 and 30 months of age with an IgE-mediated food allergy to peanut, tree nuts (i.e. hazelnut, cashewnut and walnut), cow's milk and/or hen's egg as proven by an oral food challenge are eligible for inclusion. Patients with different (combinations of) food allergies will be included, until the sample size for each allergen is achieved. The population will range from children with a mild allergy for 1 allergen to children with a severe food allergy characterized by multiple food allergies (mostly 3 to 5), low threshold levels and/or anaphylactic reactions. Consecutive children with a (suspected) food allergy referred to one of the participating paediatric allergy centres will be enrolled. Contraindications at the discretion of the including physician are language barriers and doubts about the capability of the family to perform the daily maintenance therapy at home according to the protocol in order to guarantee the safety of the child.

Enrolment of the intended number of patients is assessed as achievable based on:

- High parental motivation to participate in a study on oral immunotherapy with their young child as shown in a qualitative study and by the fact that in the current safety and feasibility study in our hospital, patients were participating with a travel distance of up to 2 hours from our hospital.
- The high number of patients diagnosed with food allergy by the four cooperating paediatric allergy centres. An indication of these numbers are the number of oral food challenges performed in these allergy centres, ranging from 400 up to 1200 oral food challenges per year in each . The majority of these oral food challenges are performed in pre-school aged children.
- Due to the screening of infants with a high-risk of food allergy, the number of infants diagnosed with a food allergy in these 4 centres largely exceeds the intended number of inclusions.

4.2 Inclusion criteria

In order to be eligible for participation in this study, a subject must meet all of the following criteria:

- 9 to 30 months of age at inclusion.
- an IgE-mediated food allergy to peanut, cashew, hazelnut, walnut, cow's milk and/or hen's egg as proven by sensitization to the specific allergen (sIgE > 0.35kU/l) and a positive oral food challenge.
- The fore-mentioned allergens are introduced into the diet of the child (the child is tolerant for the specific allergen(s)), or the child is diagnosed with a food allergy for the specific allergen(s).
- Informed consent is given by parent(s) or guardian(s).

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- (suspected) eosinophilic oesophagitis
- uncontrolled asthma/ viral wheeze.

- The inability of parents to follow instructions, recognize allergic reactions or administer emergency medication.
- Participation in any other intervention study at the time of the OIT study, with the exception of studies on guided early introduction of highly allergenic foods.

4.4 Sample size calculation

We estimate that a sample size of 500 children (250 intervention group and 250 control group) will be needed to provide 450 food specific immunotherapies, which was the minimum necessary for 90% power to detect an effect size of 50% induced food-specific tolerance development in children with a persisting allergy. This calculation was based on a two-sided significance level of 0.05 and the following assumptions: (1) providing a mean of 1.5 food-specific oral immunotherapy per patient, (2) spontaneous tolerance development rates as estimated on different levels of evidence (scientific literature and expert opinion), (3) the need to include 5% more children because of a mismatch of multiple-food allergies to the allergies needed for inclusion, and (4) loss to follow-up for no more than 10% of the participants.

Table 1. Power calculation per individual allergen

	spontaneous tolerance development after 12 months follow-up	Spontaneous + 50% induced tolerance development	Sample size intervention + control group based on alpha of 0.05 and a power of 90%
Cow's milk	50	75	77 + 77
Hen's egg	35	65	56 + 56
peanut	20	60	29 + 29
Cashew	20	60	29 + 29
hazelnut	20	60	29 + 29
Walnut	20	60	29 + 29
		total	249 + 249 allergies (in 200 + 200 children)

5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

Early low-dose oral immunotherapy will be executed by the daily intake of small amounts of generally available food products the child is allergic to (e.g. peanut butter). After confirming the diagnosis by an oral food challenge, children will start with the build-up phase of the therapy. The starting dose is 30% of the threshold level as determined by the oral food challenge (table 2). This dose is administered in the clinic, preferable within 4 weeks after the initial oral food challenge. After this initial dose, patients ingest the same amount of food on a daily basis at home. In patients with threshold levels below 1000 mg protein, increasing doses of the allergen are administered in the clinic every 2 weeks over 1 to 15 visits to achieve the maintenance dose of 300 mg allergenic protein (Table 2). Between clinic visits, patients ingest the last administered dose of food on a daily basis at home. On average, 4 visits are required to achieve the maintenance dose of 300 mg protein per day (approximately half of the children have threshold

levels above the 300 mg protein). During the maintenance phase, this dose of 300 mg protein will be administered daily by parents at home for a period of one year. Oral food challenges and build-up visits for dose escalation are performed by trained health care providers who will be supervised by an allergologist, because of the risk of allergic reactions.

Build-up schemes will be personalized based on threshold levels and the shared decision of parents and health care providers to build-up with a regular regimen (one build-up step per hospital visit) or a rush regimen (up to 5 build-up steps per hospital visit, Table 3).

Table 2. Regular build-up scheme depending on threshold levels

Threshold level	**0.001g = 1mg**	**0.003g = 3mg**	**0.010g = 10mg**	**0.030g = 30mg**	**0.1g = 100mg**	**0.3g = 300mg**	**1g = 1000mg**	**3g = 3000mg**
Step 1	0.3 mg	1 mg	3.3 mg	10 mg	33 mg	100 mg	300 mg	300 mg
Step 2	0.6 mg	2 mg	6.6 mg	20 mg	66 mg	125 mg		
Step 3	1.2 mg	4 mg	13.2 mg	40 mg	75 mg	160 mg		
Step 4	2.4 mg	8 mg	26.4 mg	75 mg	100 mg	200 mg		
Step 5	4.8 mg	16 mg	52.8 mg	100 mg	125 mg	250 mg		
Step 6	9.6 mg	32 mg	75 mg	125 mg	160 mg	300 mg		
Step 7	19.2 mg	64 mg	100 mg	160 mg	200 mg			
Step 8	38 mg	75 mg	125 mg	200 mg	250 mg			
Step 9	75 mg	100 mg	160 mg	250 mg	300 mg			
Step 10	100 mg	125 mg	200 mg	300 mg				
Step 11	125 mg	160 mg	250 mg					
Step 12	160 mg	200 mg	300 mg					
Step 13	200 mg	250 mg						
Step 14	250 mg	300 mg						
Step 15	300 mg							

Table 3. Examples of rush build-up schemes for 2 threshold levels

Threshold level	0.003g = 3mg	0.1g = 100mg
Dag 1	Step 1 1 mg	Step 1 33mg
Dag 2	Step 2 2 mg	Step 2 65mg
	Step 3 3 mg	Step 3 78mg
	Step 4 4 mg	Step 4 95mg
		Step 5 115mg
		Step 6 135mg
Dag 3	Step 5 6 mg	Step 7 170mg
	Step 6 10 mg	Step 200mg
	Step 7 15 mg	Step 9 230mg
		Step 10 260mg
		Step 11 300mg
Dag 4	Step 8 25 mg	
	Step 9 37,5 mg	
	Step 10 60 mg	
Dag 5	Step 11 90 mg	
	Step 12 135 mg	
	Step 13 200 mg	
Dag 6	Step 14 250 mg	
	Step 15 300 mg	

5.2 Use of co-intervention

Desloratadine 1.25 – 2.5 mg per dose

Levocetirizine 1.25 – 2.5 mg per dose

Cetirizine 1.5 – 5 mg per dose

5.3 Escape medication

Applicable for the intervention group and the control group

Epinephrine autoinjector, 0.15mg per dose

Desloratadine 1.25 – 2.5 mg per dose

(Levo)cetirizine 1.25 – 2.5 mg per dose

Cetirizine 1.5 – 5 mg per dose

6. INVESTIGATIONAL PRODUCT

It can be discussed if this chapter is applicable for the current study. Food products are used during the therapy, therefore some would argue that this is research on an investigational product. However, the food products are freely available, widely used food products, and regularly part of a normal infant's diet. This is apparently a strong argument as most studies on oral immunotherapy using standard food products are not labelled as studies on investigational medicinal products.[2] *Our previous feasibility study on oral immunotherapy was also not labelled as such. Therefore, we consider this study on oral immunotherapy not as a study with an investigational product. However, because of the young age of the children involved, we will discuss some aspects of oral immunotherapy based on freely available food products in this chapter and provide a risk analysis in chapter 11.*

6.1 Name and description of food products

Table 4. Examples of free available food products to be used in the ORKA-NL study

Allergen	Food product, example 1	Food product, example 2	Food product, example 3
Hen's egg	Boiled hen's egg (10 minutes) (300 mg protein = 2,4 grams)	Hen's egg pancake (2 eggs in 10 pancakes) (300 mg protein = 19,6 grams)	X
Peanut	100% peanut butter (300 mg protein = 1,1 grams)	Ground unsalted peanut (300 mg protein = 1,2 grams)	Defatted peanut flour (300 mg protein = 0,6 grams)
Hazelnut	Terrasana pure hazelnut spread (300 mg protein = 2,2 grams)	Ground unsalted hazelnut (300 mg protein = 1,9 grams)	Hazelnut flour (300 mg protein = 2,0 grams)
Cashew nut	Terrasana cashew nut spread (300 mg protein = 1,5 grams)	Ground unsalted cashew nut (300 mg protein = 1,5 grams)	Cashew nut flour (300 mg protein = 1,7 grams)
Walnut	Terrasana walnut spread (300 mg protein = 1,3 grams)	Ground unsalted walnut (300 mg protein = 2,0 grams)	Walnut flour (300 mg protein = 2,1 grams)
Cow's milk	Semi-skimmed Cow's milk (300 mg protein = 8,8 grams/ml)	Low-fat yoghurt (300 mg protein = 6,4 grams)	Danoontje (300 mg protein = 4,8 grams)

6.2 Summary of findings from clinical studies

Having a food allergy is associated with a lifelong risk of (severe) allergic reactions due to accidental ingestions. This risk probably outweighs the risk of mild allergic reactions during immunotherapy. In addition, the allergic reactions during oral immunotherapy are predictable, because they are associated with the moment of administration of the food product, which will be at home or in the hospital. This contrasts with the accidental ingestions later on in life, which frequently don't occur at home.

6.3 Summary of known and potential risks and benefits

Benefits:

- Desensitization, starting within weeks after starting the therapy, will diminish the risk of allergic reactions caused by accidental ingestion of (small amounts of) the allergen.
- Increased chance on long-term tolerance induction (curation).

Risks:

- Increased risk of mild and moderate allergic side effects
- Slightly increased risk of severe allergic side effects
- Slightly increased risk of eosinophilic esophagitis or eosinophilic intestinal diseases, which are expected to recover after stopping the therapy

6.4 Description and justification of route of administration and dosage

Different routes of administration have been studied for immunotherapy for food allergy, including oral, epicutaneous and sublingual route of administration. Only oral administration is associated with long-term tolerance development in young children. While for a long period of time it was usual to provide high dose oral immunotherapy (3000 to 4500mg allergenic protein), recent studies have shown that a daily ingestion of 300 mg allergenic protein is sufficient to induce tolerance.[6] This low-dose immunotherapy favours the achievability of the therapy in young children and may reduce the risk of side effects.

6.5 Dosage, dosage modifications and method of administration

Maintenance therapy consists of daily ingestion of 300 mg allergenic protein for 1 year. Children with threshold levels below 1000 mg of allergenic protein as established by an oral food challenge, have to start the therapy with a lower dosage, followed by a build-up phase until the maintenance dose is achieved. Build-up schemes are personalised based on threshold levels, the choice for a regular or a rush build-up scheme and adapted in case of allergic side effects. In case of illness or other circumstances increasing the risk of allergic side effects, parents will provide half of the dose as used in the previous days or even stop the therapy for a few days. Parents will receive written information about such dosage modifications.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study endpoint

Intervention group: Sustained unresponsiveness defined as both

1. Passing an exit oral food challenge[#] performed at 4 weeks after discontinuation of the 1-year oral immunotherapy
2. uncomplicated (i.e. without any allergic symptoms) consumption of a full dose of the specific food (e.g. a glass of milk or a sandwich with peanut butter with a minimum of 4.4 gram allergenic protein) at home, after 6 months unrestricted introduction of the specific food into the diet of the participant following the exit oral food challenge.

Control group: Spontaneous tolerance development defined as both

1. Passing an exit oral food challenge 12 to 18 months* after inclusion
2. Uncomplicated (i.e. without any allergic symptoms) consumption of a full dose of the specific food (e.g. a glass of milk or a sandwich with peanut butter with a minimum of 4.4 gram allergenic protein) at home, after 6 months unrestricted introduction of the specific food into the diet of the participant following the exit oral food challenge.

[#] Challenge results are considered positive, and dosing is stopped when objective symptoms occur, following the recommendations of the 'PRACTALL consensus report'.[11]

** Since the chance of natural tolerance development possibly increases during a longer follow-up time, it is important to achieve a comparable follow-up time for allergies assigned to the intervention group and allergies assigned to the control group. The follow-up time for allergies assigned to the intervention group depend on the threshold level, because this determines the duration of the build-up phase. Therefore, the follow-up time for allergies assigned to the control group will be adjusted to the threshold level.*

7.1.2 Secondary study parameters/endpoints

- Quality of life (Food Allergy Quality of Life Questionnaire - parental form (FAQLQ-PF13), The 17-item Food Allergy Quality of Life– Parental Burden (FAQL-PB), the CarerQol-7D15.[111213]
- Health care resource use (measured by collecting data from medical records and by using parts of the iMTA Medical Consumption Questionnaire (iMCQ)[14]
- Productivity loss will be estimated through additional questions concerning parental absence from their work due to their child's disease and treatment
- Allergy-related immune parameters including food specific IgE and IgG4 (blood samples)[10]
- Safety, as measured by the frequency of treatment-related (serious) adverse events
- Therapy adherence, as assessed by monthly reports of a smartphone medication adherence app

7.1.3 Other study parameters

- Medical history of the patient (concomitant atopic diseases such as eczema, medical prescription history, food allergy history)

- Threshold level and severity of the allergy as determined by the entry oral food challenge
- Age of the patient at inclusion
- Data of skin prick tests, if performed.

7.2 Randomisation, blinding and treatment allocation

Randomization will be performed per participant. Castor EDC (Castor, Amsterdam, Ciwit BV the N. Castor electronic data capture 2017) will be used to randomize the children to oral immunotherapy (intervention group) or routine care (control group). In Castor, block randomisation will be used with computer generated variable block sizes. The sizes of the blocks will vary depending on the size of the group to be included which is different for the six allergens. The block sizes are unknown to the investigators of the different sites. An allocation ratio of 1:1,stratification per centre and stratification for each of the six allergens will be used.

Children with a multiple food allergy are included and randomized for their 'primary allergy'. The next sequence will be used to determine the 'primary allergy': cow's milk, hen's egg, walnut, hazelnut, cashewnut, peanut. The first allergy in this sequence, which is present in the participant will be the 'primary allergy'. Children randomized to the intervention group will receive treatment for all of their food allergies. (The sequence of allergies is based on the ratio of the prevalence and the number of participants to be included for that specific allergy)

Blinding is not possible, because general available food products will be used. The risk of bias caused by the open-label character of the study, such as detection bias, is assessed as small, because the primary end-point on effectiveness is assessed by an oral food challenge with objective allergy symptoms as stop criteria (the test is only stopped and assessed as positive when objective signs of an allergic reaction occur, according to national and international guidelines).

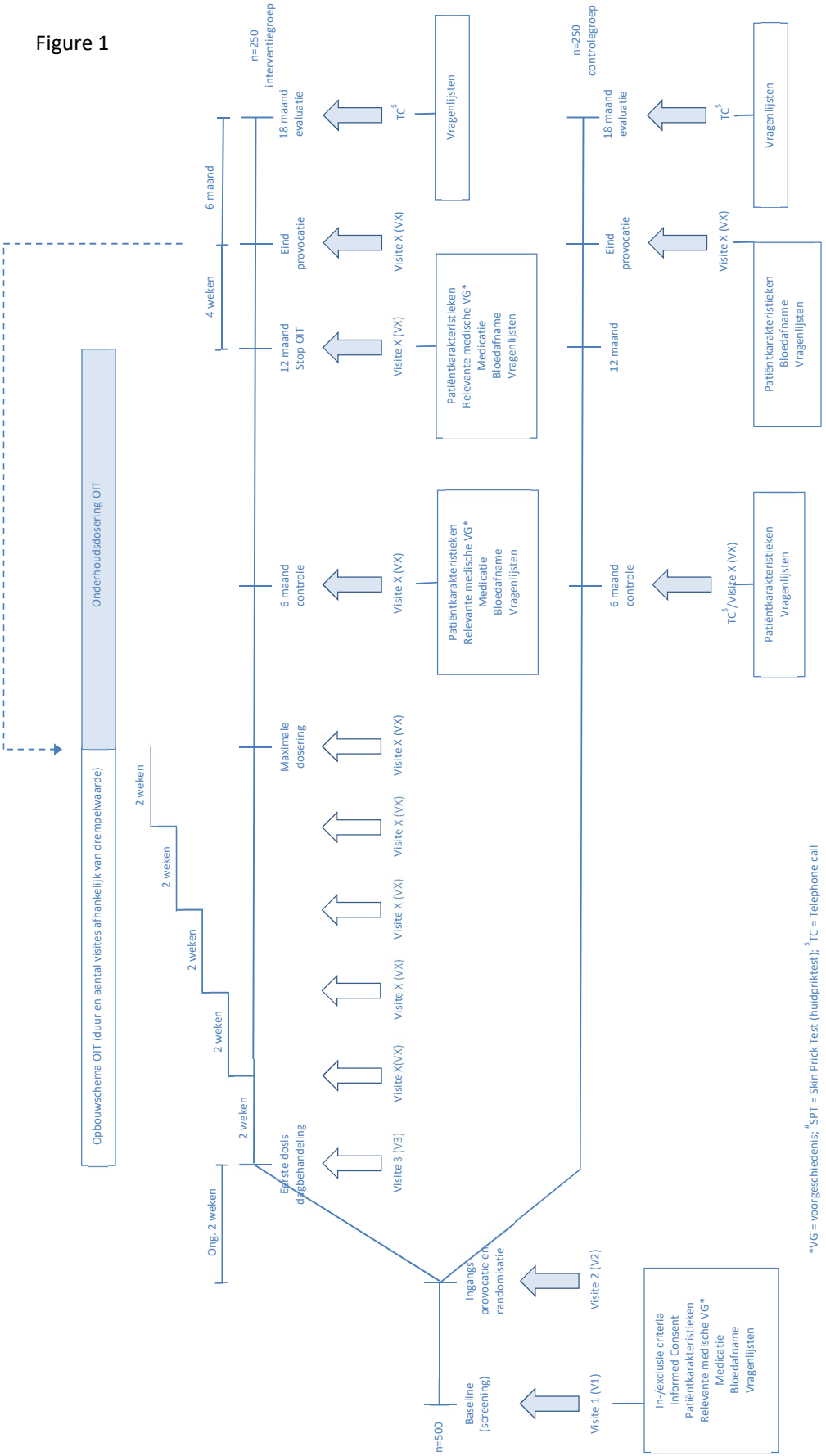
Because parents are aware of the assignment to the intervention group or the control group, the risk of performance bias is increased as discussed in more detail on page 12.

7.3 Study procedures

Early low-dose oral immunotherapy will be executed by the daily intake of small amounts of generally available food products the child is allergic to (e.g. peanut butter). After confirming the diagnosis by an oral food challenge, children will start with the build-up phase of the therapy (see Figure 1). To build-up, doses of the allergen are administered in the clinic every 2 weeks over 1 to 11 visits to 300 mg protein maintenance. Between clinic visits, patients ingest the same amount of food on a daily basis at home. On average, 4 visits are required to achieve the maintenance dose of 300 mg protein per day. During the maintenance phase, this dose will be administered daily by parents at home for a period of one year. Oral food challenges and build-up visits for increasing the dose are performed by trained health care providers and supervised by a paediatric allergologist, because of the risk of allergic reactions.

In clinics not familiar with providing oral immunotherapy for food allergy, paediatric allergologists will be trained in providing this new therapy, e.g. how to adjust the build-up scheme in case of side-effects. These paediatric allergologists are provided with all standard operating procedures and instructions needed to provide high quality of care.
Parents will receive a personal and extended instruction about the daily administration of the allergenic food to their child, together with written action plans containing instructions on how to manage at-home reactions, when to adjust the doses (e.g., during a viral illness), and when to administer medication including epinephrine. Parents will receive a precision scale and they will be instructed to use the smartphone medication adherence app to increase therapy adherence and to assess daily adherence to the protocol by monthly reports that will be generated by the app and send to the study investigator.
After one year, the OIT is stopped for 4 weeks, after which an exit oral food challenge is performed. In case of a negative food challenge, parents will be advised to introduce the food in the child's diet without limitations. Six months later, intake of the allergenic food will be assessed by a telephone survey. In case of a multiple food allergy, the above mentioned procedure will be performed in parallel.
Children whose allergy was assigned to the control group have to strictly avoid the specific allergenic food. At 12 to 18 months after inclusion, the allergic state of the child will be assessed, including an oral food challenge when indicated. In case children pass the exit oral food challenge without symptoms, 6 months later the consumption of the allergenic food will be assessed by a telephone survey.
In case of a positive oral food challenge, the primary end point has been reached. A telephone survey will be performed 6 months later, to confirm ongoing avoidance of the specific food.

Figure 1


n=500
Baseline (screening)
In-/exclusie criteria
Informed Consent
Patiëntkarakteristieken
Relevante medische VG*
Medicatie
Bloedafname
Vragenlijsten
Visite 1 (V1)
Visite 2 (V2)
Ingangs provocatie en randomisatie
Ong. 2 weken
Eerste dosis dagbehandeling
2 weken
2 weken
2 weken
2 weken
2 weken
Visite 3 (V3)
Visite X(VX)
Visite X (VX)
Visite X (VX)
Visite X (VX)
Visite X (VX)
Maximale dosering
6 maand
4 weken
Onderhoudsdosering OIT
Opbouwschema OIT (duur en aantal visites afhankelijk van drempelwaarde)
n=250 interventiegroep
6 maand controle
12 maand Stop OIT
Eind provocatie
18 maand evaluatie
Visite X (VX)
Patiëntkarakteristieken
Relevante medische VG*
Medicatie
Bloedafname
Vragenlijsten
TC$
Vragenlijsten
n=250 controlegroep
6 maand controle
12 maand
Eind provocatie
18 maand evaluatie
TC$/Visite X (VX)
Patiëntkarakteristieken
Vragenlijsten
Visite X (VX)
Patiëntkarakteristieken
Bloedafname
Vragenlijsten
TC$
Vragenlijsten
*VG = voorgeschiedenis; $SPT = Skin Prick Test (huidpriktest); $TC = Telephone call

Procedures

Allergy-related immune parameters including food specific IgE and IgG4:

- Capillary or venous blood sampling (maximal 5 ml) during diagnostic work-up/ entry oral food challenge, after 6 months of oral immunotherapy (only in the intervention group) and after 12 months of follow-up (both intervention and control group).
- Assessment of sensitization (sIgE in blood or a skin prick test) one year after diagnosing the food allergy is part of routine care for food allergic infants. For participants receiving routine care the blood sampling will be part of standard diagnostic work-up and follow-up care, when the assessment of sensitization by blood tests is the standard practice of the participating allergy centre. For children who receive care in allergy centres using skin prick tests as the standard method to assess sensitization, blood tests will be additionally performed.

Questionnaires to be completed by parents:

- At start of the study, and after 6, 12 and 18 months follow-up: Quality of life (Food Allergy Quality of Life Questionnaire - parental form (FAQLQ-PF13), The 17-item Food Allergy Quality of Life– Parental Burden (FAQL-PB), the CarerQol-7D15.
- At 6, 12 and 18 months of follow-up: parts of the iMTA Medical Consumption Questionnaire (iMCQ) and additional questions concerning parental absence from work due to their child's disease and treatment

Adherence

- Parents have to install a smartphone medication adherence app to register daily use of the therapy and have to send monthly reports (digital)

Oral food challenges

- Oral food challenges are performed in all participants, as part of the standard diagnostic work-up at the study entry. The exit oral food challenge is standard care for children receiving oral immunotherapy (a high chance of tolerance is an indication for a test). In participants receiving routine care, the exit oral food challenge would be part of standard care in approximately 65% of the children, for 35% of the children in the control group, the exit oral food challenge is a study procedure.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.5 Replacement of individual subjects after withdrawal

If achievable, taking health care costs into account, the individual allergy centres have the option to replace individual subjects after withdrawal. If the loss to follow-up exceeds 10% of inclusion for specific allergies, replacement of subjects is recommended.

7.5.1 Specific criteria for withdrawal (if applicable)

- Only withdrawal for OIT for the 'primary allergen' (see 7.2) will be defined as withdrawal of the subject providing the option to replace a patient for that specific allergen. After withdrawal for the primary allergen, the patient may complete OIT for other allergens if applicable and the data will be used for analysis.
  Failure to provide OIT because of child factors (such as food aversion) or medical factors (such as ongoing side effects), will not be defined as withdrawal but as treatment failure.
  In patients with multiple allergies, failure to provide OIT for a specific allergen does not imply the stop of OIT for other allergens.

7.6 Follow-up of subjects withdrawn from treatment

After withdrawal from treatment, follow-up will be continued to assess tolerance development, unless parents refuse follow-up.

7.7 Premature termination of the study

Taking into account the findings on safety parameters of the current feasibility study performed in the Deventer Ziekenhuis, reasons for premature termination of the study are not to be expected.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, considered related or possible related to oral immunotherapy. All such adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs:

- anaphylaxis as provoked by an oral food challenge (which will be reported in the annual progress report)

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

8.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

8.4 Data Safety Monitoring Board (DSMB)

A DSMB is established to perform ongoing safety surveillance. The DSMB will assess all (serious) adverse events periodically, every 6 months after start of the study. The DSMB may advice the study team to increase the safety for participants. The task and responsibility of the DSMB is described in more detail in the DSMB charter. The advice(s) of the DSMB will only be sent to the sponsor of the study, who will discuss the advice with the investigators of all participating centers. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

The DSMB consists of three members. Two are experienced paediatric-allergists, the third member who will also be the chair of the Board is a dermatologist providing food allergy care to adults and is experienced in performing food allergy studies. These members have no conflict of interest with the sponsor of the study.

(1) Dr. T.T.M. Le, Dermatoloog, afdeling Dermatologie/Allergologie, Universitair Medisch Centrum Utrecht
(2) Dr. E.C. Koffeman, kinderarts-allergoloog, Rijnstate Allergiecentrum, Arnhem
(3) Dr. I.F.A. Bocca-Tjeertes, kinderarts-allergoloog, afdeling inderlongziekten/allergologie, Universitair Medisch Centrum Groningen

9. STATISTICAL ANALYSIS

The statistical analyses will be performed with SPSS (version 26.0). Continuous data will be presented as means ± SD (normal distribution) or medians with IQR (non-normal distribution), categorical data will be presented as frequencies with percentages. As primary analysis, an intention to treat analysis will be performed. A per-protocol analysis will also be performed, based on parental information regarding actual administration of the allergen to their child.

9.1 Primary study parameter: tolerance induction

Differences in the primary parameter 'clinical effectiveness' will be analysed separately for each of the six allergens using univariate logistic regression analyses, followed by multiple logistic regression analyses in which we will adjust for potentially confounding factors, including but not limited to: age and level of sIgE at start of the therapy, threshold level and severity of the allergic reaction as assessed during the entry oral food challenge, number of allergies and study. For the multivariate logistic regression analyses, a minimum of 10 events per variable will be necessary to avoid bias. Results will be presented as odds ratios (OR) with 95% confidence intervals. Besides eyeballing, patterns of missing data will be analysed in SPSS with missing data analyses as well. Based on the pattern of missing data, the recommended approach for dealing with these missing data in a RCT will be chosen.

A trial-based cost-effectiveness analysis will be performed to compare early low-dose oral immunotherapy with usual care for the treatment of children between 9 and 30 months of age with an IgE-mediated food allergy. The analysis will be performed from a societal perspective, including cost inside and outside the healthcare sector. The main outcomes of this cost-effectiveness analysis will be total quality-adjusted life years (QALYs) and costs for both strategies, which will be compared through an incremental cost-effectiveness ratio (incremental costs/ incremental QALYs). To obtain quality of life estimates of the included patients, the Food Allergy Quality of Life Questionnaire-Parent Form (FAQLQ-PF),[12] will be completed by the patients' parents at the different measurement moments. Since the FAQLQ-PF is not a preference-based instrument, it will be mapped to utility values (which are needed to calculate QALYs) through the AQoL-6D instrument which is a preference-based instrument. [13]Additionally, the impact of caring for the patients on the parents' quality of life will be measured through the CarerQol -7D and Food Allergy Quality of Life-Parental Burden Questionnaire. [16,17] This disease-specific instrument will also be used because it is expected that the CarerQoL-7D does not capture all aspect of the children's disease which may have an impact on their parents' quality of life. Health care resource use due to the patients' allergy and treatment will be measured by collecting data from medical records and by using parts of the iMTA Medical Consumption Questionnaire, which will be filled in by the patients' parents to assess the productivity loss of parents due to caring for the patients, questions concerning their absence from work will be added to the iMCQ16. For this trial-based economic evaluation, the measurement moments for both quality of life and resource use are at the start of the study, and at 6, 12, and 18 months follow up. The uncertainty surrounding the cost-effectiveness results of the trial-based economic evaluation will be assessed through bootstrapping. The time horizon of the cost-effectiveness analysis will be two years (study duration). The outcomes of the trial-based analysis will be extrapolated (via a health economic model) using literature and external sources, if deemed

necessary to obtain an accurate estimation of the (differences in) total costs and QALYs of immunotherapy and usual care. All analyses will be performed according to the Dutch guidelines for performing health economic evaluations.[14]

9.2 Secondary study parameter(s)

Quality of life as assessed by four questionnaires will be scored by adding up the scores on each item to yield a total score. In case of sufficient normally distributed data, or possibly after transformation, a mixed model repeated measurements analyses will be performed or a Wilcoxon signed rank test (depending on the distribution of the data). Allergy-related immune parameters (e.g. sIgE en sIgG4) will be analysed for the six different allergens separately on baseline and on 12 months after starting the maintenance phase. Differences between the intervention and the control group will be analysed using Student T-tests or Mann Whitney U test (depending on the distribution of the data). Adherence will be calculated as provided doses/ days on oral immunotherapy and presented as a percentage. Safety as measured by treatment-related (serious) adverse events will be presented as frequencies of number and severity.

The full description of all analyses is described in the statistical plan, which will be final before the database lock.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

10.2 Recruitment and consent

Parents of (possible) eligible children will be informed about the study by a member of the Allergy Care Team providing allergy care to the child during outpatient clinic visits or during clinically performed oral food challenges. Oral and written information is provided to these parents. Parents will have at least 1 week to decide about participation and providing informed consent.

10.3 Objection by minors

The burden associated with participation will be minimised. Blood sampling by finger prick or vena punction is part of the therapy in children in the intervention group. In children in the control group, blood sampling can be part of the normal diagnostic work-up of a food-allergic child, but can also be an additional study-based procedure. If in the context of such research-based procedure, a child objects to a procedure, the procedure will be discontinued. Ongoing participation in the study is encouraged, despite missing blood samples. Oral food challenges and a blood sample to assess the level of sIgE at entry of the study are mandatory because these are inclusion criteria. If a child objects to this procedure, the child is not eligible for inclusion.

10.4 Benefits and risks assessment, group relatedness

This study will include participants between 9 and 30 months of age, to study the effectiveness of oral immunotherapy when started at a young age. Current scientific knowledge has been showing that this therapy, when started in children older than 3 or 4 years of age, is not effective regarding the achievement of long-term tolerance, whether a superior outcome is presumed when the therapy is started at a young age (as described in the introduction section).
Participants assigned to the intervention group may benefit by achieving long-term tolerance (curation of the allergy). These participants have an increased risk for mild allergic reactions related to the daily ingestion of the allergen, as shown by previous studies and the current feasibility study in the Deventer ziekenhuis. The risk for severe allergic reactions not responding to epinephrine is very low.
Participants assigned to the control group have no benefit regarding an increased chance on tolerance induction, and no increased risk for allergic reactions.

10.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor also has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

Castor data management system is used as a validated electronic case report form (eCRF) to collect clinical data for the study. Access and training for the ecRF will be made available to the participating sites. An explanation for missing (required) data should be displayed on the appropriate eCRF page.
The sponsor/principle investigator will perform data validation according to standard operating procedures and as described in the data management plan (DMP). The investigators of the different sites are responsible for maintaining and entering complete and correct data and has to respond to questions/queries within agreed timelines.
All information recorded in the eCRF must be traceable in the (medical) files of the subjects, except for the data from the electronic diaries (MediSafe app) and the different questionnaires (Castor data management system); these data are transferred directly to the database and are considered as source data.

The sponsor/investigator will provide the researchers on the other sites with an Investigator Site File (ISF). The investigator is responsible for keeping this ISF up-to-date and will keep it available for review by the study monitor.

The handling of personal data will comply with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. (in Dutch: Uitvoeringswet AVG, UAVG). Accordingly, the researcher is responsible for treating study data confidentially and has to ensure that the subject's identity is not made public. All study data (including blood samples) are coded to maintain subject confidentiality (subjects' patient numbers do not include patient initials or birthdate). The Subject Identification Log that links the patient numbers to the subjects' identities must be stored locally on a password protected server or in the Investigator Site File that is only accessible to the local researcher, research coordinators of the sites and to regulatory authorities.

Study documents may not be destroyed without prior written agreement between the sponsor/investigator and the researcher at the site. All documents related to the conduct of the study must be kept by the researcher for a period of 15 years. Moreover, blood samples are not destroyed immediately after use. They will be stored in order to be able to determine new biomarkers in the field of oral immunotherapy for food allergy during or in the period after the study. It can be stated on the consent form whether permission is provided for this. If consent is not provided by the parents, the child can simply participate in the current study and the blood will be destroyed.

By the use of the principles of FAIR data we will achieve a maximum impact from our research, increasing the visibility, improving the reproducibility and reliability and reaching a broader public, enabling also new research questions to be answered. We will make our data findable by assigning a persistent identifier (DOI) and ensuring the registry in a
searchable resource. Moreover, a trusted and well-suited repository will be used to publish our data (e.g. Yoda) and a personal persistent author identifier will be used in all our publications.

Metadata will be added as rich as possible (description of context, quality, condition and characteristics). Data will be made accessible by using a persistent identifier by which data can be retrieved. The repository that will be used allows us to share data and to collaborate with external parties. Publications are directly accessible via Open Access. To make the data interoperable README files will be used containing a description what data it includes. Moreover, controlled vocabularies and keywords and standard measurement units will be used. Wherever possible programming scripts will be added that were used to analyse the data. We will make our data reusable by ensuring that our data is well-documented to support a proper interpretation. We will provide information needed to make clear how, why and by whom the data have been created and processed. In addition, documentation will be provided on project level, file level as well as item level.

11.2 Monitoring and Quality Assurance

Prior to participation in this study, investigational sites will be evaluated for appropriate qualifications and ability to properly execute the study. Each investigational site must undergo proper training on the study protocol and ancillary study procedures/documents through participation in an initiation visit and/or Investigator meeting. Such training must take place before any subjects are enrolled at that site. Moreover, the study will only start if:

- the METC/local authorities have given their approval to conduct the study.
- essential documents are available, such as the ISF, CV of the investigator and of the research personnel on the site, and the Consortium agreement/ Clinical Trial Agreement.

The sponsor/investigator or designee will make periodic visits to the investigational site to assess compliance with study procedures and regulatory requirements; to ensure that the safety, welfare and privacy of subjects are being protected; and to verify the accuracy and integrity of the study data.
In addition, the study data will periodically be review to ensure that data are being appropriately collected and reported. Logic checks will be also programmed and run to identify errors and data discrepancies. Discrepancies will be reviewed with investigational site personnel, corrections will be made to the database, and a validated audit trail will be maintained. The database will be locked and audited before it is released for analysis.

Study monitoring will take place at various times during the study by an independent person/monitor that is qualified to monitor under the responsibility of the sponsor/investigator as described in the monitoring plan.
Monitoring includes both on- and off-site visits to check whether the rights and well-being of the subjects are protected, such as checking the presence of informed consent statements and the inclusion and exclusion criteria used. It also serves to verify that the data from the study reported is accurate and fully verifiable in the source documents. The third purpose is to verify that the conduct of the study is in accordance with the currently approved protocol(s), with GCP and with the relevant legal requirements.
The researcher at the site has to permit study-related monitoring, audit, review by the METC and regulatory authorities (inspection) and thereby provide direct access to source data and source documents subject to the protection and safeguarding of the subject's privacy.

11.3 Amendments

All substantial amendments are reported to the METC and the competent authority.
Non-substantial amendments will not be reported to the accredited METC, but will be registered and filed by the sponsor.

11.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last telephone interview 6 months after the last exit oral food challenge.
The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.6 Public disclosure and publication policy

The clinical trial will be registered in a public trial registry before the first patient is recruited. The results of this study will be disclosed unreservedly, preferably by submitting for publication to peer-reviewed scientific journals. If these journals do not consider the results for publication, the research results will be disclosed at least by publication in the trial register. Taken the basic principles into account of the rules of the Vancouver convention and the editors' statements of a number of authoritative biomedical scientific journals, one author of the 3 cooperating allergy centres will be involved in publication.

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

a. Level of knowledge about mechanism of action

Oral immunotherapy (OIT) involves daily consumption of a vast amount of allergenic food during a given time period. It can result in sustained unresponsiveness (absence of allergic symptoms when the food allergen is ingested after a period of therapy discontinuation). This clinical outcome has been associated with alterations in the allergen-specific immune response during the therapy. Various cell types are involved, including T-cells. Tregs are considered to be key contributors to tolerance induction and maintenance, by producing the anti-inflammatory IL-10. It is therefore likely that changes in allergen-specific T-cells are a main component to the clinical effectiveness of OIT. In mouse OIT-studies, Tregs are induced by allergenic exposure during OIT and have been associated with sustained unresponsiveness. Prolonged antigenic stimulation during the maintenance phase of OIT has also shown epigenetic modification of Tregs. Syed et al demonstrated an association between Foxp3 hypomethylation during Treg cell differentiation and sustained unresponsiveness [19]. Mouse models showed suppression of IL-5, IL-13, IgE production and effector T-cell responses with induction of CD4+CD25+FoxP3+ Tregs in the lamina propria.[20] Although more research is needed, allergen specific T-cells and in particular allergen specific Tregs play a pivotal role in achieving long-term tolerance.

b. Previous exposure of children to oral immunotherapy

Studies on the safety and feasibility of low-dose oral immunotherapy in infants with a peanut or cow's milk allergy have shown a high rate of mild allergic reactions.[8,6,21] 40% to 90% of participants are experiencing at least once a mild allergic reaction such as angioedema of the lips, facial urticaria or vomiting during their treatment. The rate of severe allergic reactions differs in these studies between 0,4% to 7%. Authors of these studies have regarded these rates of side-effects as safe. Safety data for patients (aged 1 to 18 years of age) undergoing (e-)OIT (early-oral immunotherapy) for multiple foods (up to 12 food products) haven been published very recently. Allergic reactions occurred in 22 patients (49%) during up-dosing or in the first 3 months of maintenance therapy during clinical visits or with a home dosage. No patients reported reactions after the first 3 months of daily maintenance therapy. All allergic reactions in this study were of mild to moderate severity. The study suggests that OIT for multiple foods has a comparable safety profile.[22]

Results from our current study on safety and feasibility of e-OIT started in children at an age between 9 and 24 months (https://www.trialregister.nl/trial/7663), show a similar pattern of frequent but mainly mild side effects of the oral immunotherapy; 61 % of the children experienced at least one mild allergic symptom. Patients undergoing e-OIT for multiple foods (2 to 4 products) had a similar risk of adverse events. Only a few severe adverse events were reported by parents. Moreover, parents considered the therapy as safe and feasible to perform. These data were examined by the Data Safety Monitoring Board of the study and assessed as an acceptable safety profile in June 2021 (the Safety report is available on https://www.dz.nl/patient/afdelingen/kinderallergie-behandelcentrum/orka-studie). Low-dose OIT in young children displays at least a similar (and probably a more favorable) safety profile

than the same therapy in older children and adults. It is important to consider that high-dose OIT is recommended for older children and adults by a recent European guideline.[2]

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

The primary mechanism of long-term tolerance can be induced in mouse-models.[23]

d. Selectivity of the mechanism to target tissue in human beings

Allergen immunotherapy is a very specific therapy: changes of the immune-system are allergen specific, with no effect on tolerance for other allergens. This is widely proven, both for immunotherapy for inhalant allergens and food allergens.

e. Analysis of potential effect

A dose-finding study compared 2 maintenance doses of oral immunotherapy for peanut allergy in young children: 3000 mg vs 300 mg peanut protein.[6] This study shows similar effectiveness regarding the achievement of long-term tolerance and a similar rate of side effects. In this study, oral immunotherapy will be provided by a maintenance dose of 300 mg. If this dose is accidentally increased, no major effect is to be expected on efficacy or side effects. A lower dose may affect the efficacy of the therapy.

g. Study population

Children between 9 to 30 months of age with an IgE-mediated food allergy. Many of these children also have eczema, because eczema is the main risk factor for developing a food allergy.

h. Interaction with other products

There are no interactions with other (food) products to be expected.

i. Predictability of effect

A higher level of food specific IgE at the start of the study is associated with a higher risk of a persisting allergy despite oral immunotherapy. A decrease of food specific IgE after 6 to 12 months of therapy and an increase in food specific IgG4 are associated with long-term tolerance development. An accurate prediction of the individual outcome of oral immunotherapy based on IgE or IgG4 levels is not possible.

The risk of allergic side effects is related to the threshold level: children with lower threshold levels are more at risk. The risk of developing eosinophilic esophagitis can not be predicted.

j. Can effects be managed?

Most allergic side-effects can be treated by antihistamines, anaphylaxis can be treated by administering epinephrine by an auto-injector.

Eosinophilic esophagitis will disappear by stopping the oral immunotherapy.

12.2 Synthesis

The main risk of oral immunotherapy is the occurrence of allergic side effects. High-dose oral immunotherapy has been studied widely in older children and is a recommended therapy (European guideline). Currently available evidence strongly suggests that low-dose oral immunotherapy in young children has a favourable safety profile.
Allergic side-effects can be treated very well with appropriate medicines, when administered without delay. To ensure this timely treatment of allergic side-effects, procedings with a higher risk of severe allergic side-effects are performed in-hospital (including oral food challenges and up-dosing of the therapy). Additionally, to ensure appropriate treatment of allergic side-effects at home, parents are provided with a written self-management plan, antihistamines and the epinephrine auto-injector. Extensive instructions are provided to parents to reduce the risk of allergic side-effects at home, including instructions about lowering the dose or stopping the therapy for a few days in case of infectious diseases or other health problems.

Having a food allergy is characterized by a lifelong risk of (severe) allergic reactions due to accidental ingestions. This risk probably outweighs the risk of mild and moderate allergic reactions during immunotherapy. In particular because the allergic reactions during oral immunotherapy are predictable, as they are associated with the moment of administering the food product, which will be at home or in the hospital. This contradicts to the accidental ingestions later on in life which frequently don’t occur at home.

13. REFERENCES

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