EFFICACY AND MECHANISM EVALUATION

VOLUME 1 ISSUE 4 DECEMBER 2014
ISSN 2050-4365

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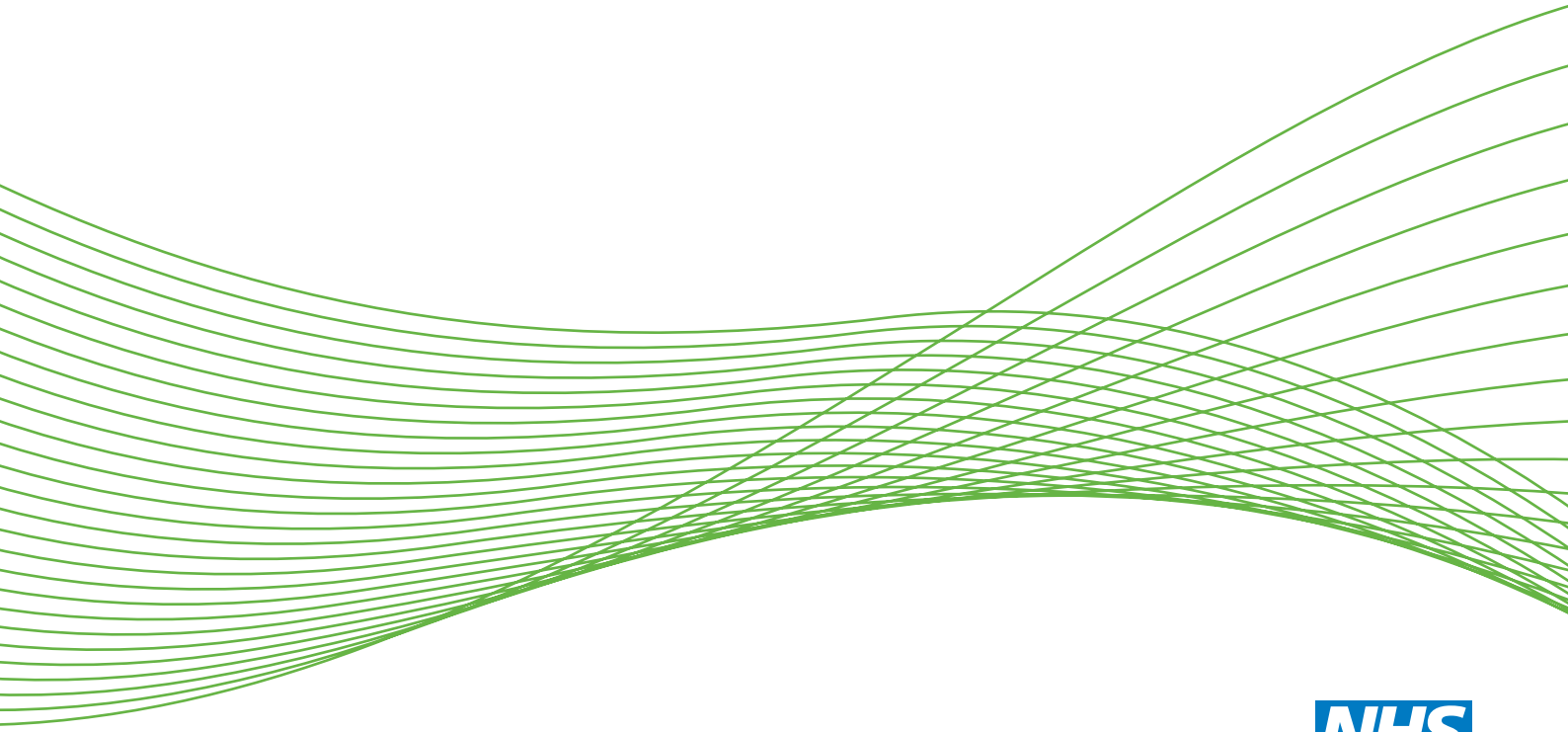

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DOI 10.3310/eme01040

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Katherine Anagnostou,[1] Sabita Islam,[1] Yvonne King,[2] Loraine Foley,[2] Laura Pasea,[3] Chris Palmer,[3] Simon Bond,[4] Pamela Ewan[1] and Andrew Clark[1]*

[1]Department of Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK
[2]Department of Allergy, Addenbrooke's Hospital, Cambridge, UK
[3]Centre for Applied Medical Statistics, Department of Public Health and Primary Care, University of Cambridge, Institute of Public Health, Cambridge, UK
[4]Cambridge Clinical Trials Unit, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge, UK

*Corresponding author

Declared competing interests of authors: Andrew Clark and Pamela Ewan are inventors on a patent application covering the peanut protein dose range.

Published December 2014
DOI: 10.3310/eme01040

This report should be referenced as follows:

Anagnostou K, Islam S, King Y, Foley L, Pasea L, Palmer C, *et al*. Study of induction of Tolerance to Oral Peanut: a randomised controlled trial of desensitisation using peanut oral immunotherapy in children (STOP II). *Efficacy Mech Eval* 2014;**1**(4).

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

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This report

The research reported in this issue of the journal was funded by the EME programme as project number 08/99/18. The contractual start date was in January 2010. The final report began editorial review in July 2013 and was accepted for publication in April 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Study of induction of Tolerance to Oral Peanut: a randomised controlled trial of desensitisation using peanut oral immunotherapy in children (STOP II)

Katherine Anagnostou,[1] Sabita Islam,[1] Yvonne King,[2] Loraine Foley,[2] Laura Pasea,[3] Chris Palmer,[3] Simon Bond,[4] Pamela Ewan[1] and Andrew Clark[1]*

[1]Department of Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK
[2]Department of Allergy, Addenbrooke's Hospital, Cambridge, UK
[3]Centre for Applied Medical Statistics, Department of Public Health and Primary Care, University of Cambridge, Institute of Public Health, Cambridge, UK
[4]Cambridge Clinical Trials Unit, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge, UK

*Corresponding author atclark@doctors.org.uk

Background: Peanut allergy is a common disease that causes severe and fatal food allergic reactions. Currently, the best treatment is avoidance as repeated reactions can occur. Quality of life (QoL) is reduced by fear of severe reactions and social limitations. Oral immunotherapy (OIT) is a novel treatment that may be an effective treatment for peanut allergy.

Objectives: To determine the efficacy of peanut OIT in children.

Design: A phase 2 randomised, controlled, crossover trial (open label).

Setting: Single UK centre study.

Participants: Children aged 7–15 years with peanut allergy diagnosed by double-blind, placebo-controlled food challenge (DBPCFC). No children were excluded because of anaphylaxis or asthma.

Interventions: Daily immunotherapy (2 mg, 5 mg, 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 400 mg and 800 mg of peanut protein) was administered as peanut flour (containing 50% peanut protein). Doses were increased at 2-weekly intervals to a maintenance dose of 800 mg of protein. The control group underwent peanut avoidance for 6 months during phase 1.

Main outcome measure: A peanut DBPCFC up to 1400 mg of peanut protein was performed in both groups at 6 months. The highest amount of peanut tolerated was the main outcome measure.

Randomisation: Randomised by online audited system to active or control group (1 : 1).

Blinding: The intervention arm allocation was not blinded.

Methods: We assigned 99 participants aged 7–16 years with peanut allergy of all severities to active OIT or control (peanut avoidance/current standard of care). The primary outcome was desensitisation, defined as negative peanut challenge (1400 mg of protein DBPCFC) at 6 months (phase 1). Control participants underwent OIT during phase 2, followed by DBPCFC. Immunological parameters and disease-specific QoL scores were measured.

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Results: The primary outcome, desensitisation, was observed in 62% (24/39) of the active group and none (0/46) of the control group after phase 1 [95% confidence interval (CI) 45% to 78% vs. 0% to 9%; $p < 0.001$]; 84% (95% CI 70% to 93%) of the active group tolerated daily ingestion of 800 mg of protein (≈ five peanuts). Median increase in peanut threshold after OIT was 1345 mg (range 45–1400 mg; $p < 0.001$) or 2.5-fold (range 1.82–280-fold; $p < 0.001$). After phase 2, 54% (95% CI 35% to 72%) tolerated a 1400-mg challenge (≈ 10 peanuts) and 91% (95% CI 79% to 98%) tolerated a daily ingestion of 800 mg of protein. QoL scores improved (decreased) after OIT (median change –1.61; $p < 0.001$). Side effects were mostly mild with gastrointestinal symptoms being the most common: oral pruritus occurred after 6.3% of doses, wheeze occurred after 0.41% of doses (one-fifth of participants) and intramuscular epinephrine was required after 0.01% of doses (one participant).

Conclusion: In children with peanut allergy of any severity, OIT successfully induced desensitisation in the majority, with a clinically meaningful increase in peanut threshold. QoL improved after intervention and there was a good safety profile. Immunological changes reflected clinical desensitisation. Peanut OIT should not be undertaken in non-specialist settings. Future work will include a phase 3 confirmatory study and studies of long-term tolerance; similar studies of other allergens are also required.

Trial registration: Current Controlled Trials ISRCTN62416244.

Funding: This project was awarded by the Efficacy and Mechanism Evaluation programme and is funded by the Medical Research Council (MRC) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC–NIHR partnership, and jointly sponsored by the University of Cambridge and Addenbrooke's Hospital [Cambridge University Hospital Foundation Trust (RD authorisation A091686)]. The project will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 1, No. 4. See the NIHR Journals Library website for further project information.

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List of abbreviations

AUC	area under curve
CI	confidence interval
DBPCFC	double-blind placebo-controlled food challenge
FAQLQ-PF	food allergy quality-of-life questionnaire – parent form
IgE	immunoglobulin E
MFI	mean fluorescent intensity
MRC	Medical Research Council
NIHR	National Institute for Health Research
NOAEL	no observed adverse effect level
OIT	oral immunotherapy
PBS	phosphate-buffered saline
QoL	quality of life
RCT	randomised controlled trial
SLIT	sublingual immunotherapy
SPT	skin prick test

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Plain English summary

Peanut allergy is a common disease in developed countries, affecting up to 1% of children in the UK, France, Germany and the USA. Peanut allergy is most often diagnosed in children, but it can appear for the first time at any age. Reactions vary in severity, and include mouth itching, nausea, stomachache and vomiting. Itchy nettle sting-like rashes and swelling also occur. More serious reactions involve wheezing, throat tightness and shortness of breath, requiring hospital treatment. It is not possible to predict who is at most risk of a severe reaction.

Peanut allergy does not usually resolve and most children will grow into adults with peanut allergy. Currently, the best treatment is peanut avoidance, and patients manage this with varying success. Accidental reactions happen frequently, and families have to carry emergency medication all the time, including injectable adrenaline.

The quality of life (QoL) of families with children who have a peanut allergy is reduced because of constant fear of reactions and the social limitations they put in place to keep their children safe (e.g. not eating out).

Based on the encouraging results of a small pilot study, we undertook a randomised trial of a new treatment: peanut oral immunotherapy (OIT). This involved children eating increasing amounts of peanut under supervision, starting with a tiny amount and building up to the equivalent of five peanuts a day.

The results showed that a high proportion (80–90%) of peanut-allergic children could eat 4–6 peanuts regularly after treatment and that many (50–60%) can eat the equivalent of up to 10 peanuts at a time (primary outcome measure of the trial). At least in the short term (up to 2 years), children need to continue eating peanuts on a daily basis to maintain desensitisation. Common side effects of treatment included mouth itching and stomachache. Wheeze occurred after less than 1 in 200 doses and was treated with asthma inhalers. This treatment protects children from accidental ingestion and they can relax their avoidance practice. There was a significant improvement in QoL measure by a standardised questionnaire.

Peanut OIT is a promising novel treatment that appears to work well and with acceptable side effects. As this is the first study of its type, the findings are relevant to the population studied, but will require confirmation using other patient subgroups. Because of the complex treatment and monitoring involved, OIT should be restricted to specialist centres. This technique may be applicable to other foods and further studies are warranted.

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Scientific summary

Background

Peanut allergy is a common and important medical condition, affecting 1% of children in developed countries, and rarely resolves. Peanut allergy is the most common cause of severe and fatal food allergic reactions and it is not possible to identify those at highest risk. The quality of life (QoL) of affected families is reduced because of constant fear over food choices and the likelihood of anaphylaxis. Despite the current best management, families of peanut-allergic children have poor knowledge of how to avoid and also treat food allergy emergencies. Accidental reactions are common (annual incidence rates for accidental reactions of up to 50% have been reported) and there is no disease-modifying treatment; therefore, the case is made for development of disease-modifying therapies. Oral immunotherapy (OIT) seems to be the most promising short- to medium-term solution to this problem, given its apparent efficacy in other allergies.

Grass pollen immunotherapy given by subcutaneous injection has been used for over a century to treat allergic rhinitis and has proven efficacy and safety. An early study of subcutaneous immunotherapy for peanut allergy showed a trend to benefit, but was terminated after severe adverse reactions. The oral route may be associated with increased safety and has been studied in cases of egg and milk allergy.

Subcutaneous peanut immunotherapy was first attempted in a small study in 1992, in which three subjects had a 67–100% reduction in symptoms induced by peanut challenge, suggesting that this is an effective therapy. No subject suffered anaphylaxis during immunotherapy. Sublingual immunotherapy for hazelnut allergy has been the subject of a more recent randomised controlled trial that showed significant increases in tolerance to hazelnut [assessed by double-blind, placebo-controlled food challenge (DBPCFC)] and systemic reactions were observed in only 0.2%. We chose to use the oral route as we expect this to induce fewer side effects than injection immunotherapy, while still being efficacious, as demonstrated for pollen immunotherapy. There are preliminary studies on desensitisation to other food allergens such as milk and egg.

We have pilot data on children aged 5–18 years, using a study design identical to that of the active arm in the proposed trial. All had peanut allergy confirmed by blinded challenge before progressing to OIT according to the current proposal. To date, 19 out of 22 children have reached the final dose of 800 mg of peanut protein and are taking this, the equivalent of five peanuts, at home with no reaction. OIT doses taken at home and on the research ward are well tolerated and no subject has had a severe or generalised reaction during up-dosing. There is a need for systematic study of peanut OIT.

Objectives

We previously performed a phase 1 study that showed good tolerability and an indication of good efficacy. The current study is a phase 2 randomised controlled study of the efficacy of peanut OIT in achieving desensitisation in a well-characterised population.

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Method

The overarching objective was to determine efficacy of OIT in desensitising children with peanut allergy. We aimed to determine whether or not the treatment was successful in the intervention group compared with the control (phase 1), and whether or not it is successful when offered to the control group (phase 2).

Eligible patients were aged between 7 and 15 years of age, of either sex, with peanut allergy confirmed by a clinical history of a typical rapid-onset immediate-type hypersensitivity reaction after peanut ingestion, positive skin prick test (SPT) to peanut (extract from ALK-Abelló; Hørsholm, Denmark) defined by a weal of ≥ 3 mm in the presence of a negative control and positive histamine control, and positive DBPCFC. We excluded patients if they had a clinically apparent immunodeficiency, but we did not exclude patients who had a previous reaction that was severe, or life-threatening.

Subjects were randomised in a 1 : 1 ratio via a central audited online response system to an active or control group. During phase 1, the active group underwent 6 months of active OIT and the control group underwent 6 months of standard care (peanut avoidance). At the end of phase 1 (6 months), all participants were assessed for peanut allergy by DBPCFC. During phase 2, participants in the control group still allergic to peanut after 6 months of standard care were given active OIT, followed by a DBPCFC after 6 further months.

The primary outcome of 'no reaction' during a DBPCFC was assessed using an objective, blinded measure. The primary end point was the proportion of desensitised subjects at the end of phase 1. Desensitisation was defined as 'no reaction' during peanut DBPCFC with a cumulative dose of 1400 mg of peanut protein.

The secondary end points were:

- proportion who responded to treatment after receiving OIT (a response to treatment was defined as ingesting 800 mg of peanut protein regularly for up to 6 months)
- proportion of the control group who were desensitised or responded to treatment during phase 2
- fold and absolute increase in threshold [maximum tolerated peanut protein (mg)] after OIT
- change in QoL scores [measured by food allergy quality-of-life questionnaire – parent form (FAQLQ-PF) 0–12 years] from baseline to the end of phase 1 and phase 2
- adverse events
- immunological outcomes [basophil area under curve (AUC) percentage of CD63 and mean fluorescent intensity (MFI), peanut immunoglobulin E (IgE), total IgE and SPT diameter].

Oral immunotherapy

The active intervention (OIT) was administered in daily doses throughout and was given in two phases. First, there was a gradual up-dosing phase with 2-weekly increments to 800 mg/day, followed by a maintenance phase in which the highest tolerated dose (with a target of 800 mg/day) was taken continuously to complete a total of 6 months' immunotherapy. The same characterised peanut flour used in the challenges was also used for up-dosing (light roast flour; Golden Peanut Company, LLC, Alpharetta, GA, USA). The same dose was administered at home daily for 2–3 weeks.

Flow cytometric analysis (fluorescence-activated cell sorting) of patient samples was undertaken on whole-blood specimens by study staff to quantify the percentage and MFI of CD63+ basophils. SPTs were undertaken using a standardised peanut extract from ALK-Abelló (Hørsholm, Denmark) and a single-point lancet. Peanut-specific serum IgE was measured using the ImmunoCAP system (Thermo Scientific, Hørsholm, Denmark).

Statistical analysis

Fisher's exact test was used to compare the proportion of those with desensitisation to peanut after 6 months in the active group with the control group at the end of phase 1. Multiple logistic regression

was used to adjust the odds of desensitisation for baseline characteristics. Secondary analyses tested for treatment differences with Fisher's exact test (proportion response to treatment in active group and control group at end of phase 2), paired and independent sample *t*-tests (absolute and fold change in threshold) and Mann–Whitney *U*-tests (change in QoL scores, basophil AUC of percentage of CD63 and MFI, peanut-specific serum IgE and SPT weal diameter). All statistical tests described in this section use a two-sided 5% significance level. We performed analysis on the intention-to-treat population that included all those who were randomised and participated in at least one post-baseline assessment.

Sample size was based on Fisher's exact test with 90% power and 5% significance (two-sided). A sample size of 49 in each group is sufficient to detect proportions of participants with desensitisation to peanut of 0.64 and 0.30 in the active and control groups, respectively, at the end of phase 1. Allowing for 5% dropout increased the required sample size to 52 participants in each group and 104 subjects overall. Based on the above, we would expect 35 waiting list group patients to proceed to the active intervention in phase 2. Non-parametric tests may be used instead of parametric tests if the assumptions are not appropriate.

Results

We enrolled 104 children, aged 7–16 years (median 12.4 years), to the study. Five children did not react during their baseline peanut challenge, thus not meeting the inclusion criteria, and were excluded from further participation in the study. Therefore, 99 out of 104 children were randomised: 49 out of 99 to the active group and 50 out of 99 to the control group. One child was discontinued and five withdrew from the active group during phase 1. In the control group, four children withdrew and one was discontinued during phase 1. Two further children withdrew from the control group when they underwent the intervention in phase 2.

Primary objective

There was a significant difference between the numbers of patients who tolerated 1400 mg of peanut protein during DBPCFC at the end of phase 1 in the active (24/39) compared with the control group (who underwent peanut avoidance for 24 weeks) (0/41) ($p < 0.001$). The proportions desensitised during phase 1 after 24 weeks were 0.62 (range 0.45–0.78) and 0 (range 0–0.091) in the active and control groups, respectively.

Secondary objectives

Response to treatment, defined by the ability to tolerate daily doses of 800 mg of peanut protein after 24 weeks of immunotherapy, occurred in 0.84 [95% confidence interval (CI) 0.70 to 0.93] of the active group at the end of phase 1 and 0.91 (95% CI 0.79 to 0.98) of the control group at the end of phase 2 (post immunotherapy). There was a significant increase in peanut no observed adverse effect level (NOAEL) in the active group after phase 1, with a median change in threshold of 25.5-fold ($p < 0.001$) compared with a small positive change in peanut threshold (NOAEL) in the control group during phase 1 (0.80, range 0.05–1.82).

The proportion of patients who achieved desensitisation (0.54, 95% CI 0.35 to 0.72) or response to treatment (0.91, 95% CI 0.79 to 0.98) in the control group after 24 weeks of OIT (end of phase 2) was similar to that in the active group [0.62 (range 0.45–0.78) and 0.84 (95% CI 0.70 to 0.93), respectively].

Quality-of-life end points

Quality-of-life scores assessed by the FAQLQ-PF measure were similar between active and control groups at baseline (2.28 vs. 3.61). After treatment in both groups there was a similar and clinically meaningful improvement (decrease) in QoL scores (control –1.41, 95% CI –4.83 to 1.38; active –1.61, 95% CI –4.87 to 0.24; $p < 0.001$).

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Immunological assessments revealed a significant small reduction in median SPT weal diameter (–1 mm, range –8 to 4 mm; $p = 0.0015$) and an increase in peanut-specific serum IgE (12.7 kilounit (kU)/l, range –18.6 to 1359 kU/l; $p < 0.001$) after 24 weeks' OIT in the active group. Basophil stimulation tests data were expressed as the AUC of plots of MFI and percentage of CD63-positive cells against concentration of peanut protein. No significant within-patient differences were found after treatment for AUC of MFI or percentage of CD63-positive cells although there was a reduction in MFI and percentage of CD63-positive cells at the lower peanut doses.

Logistic regression revealed that several baseline covariates had an influence on the final NOAEL (the highest amount of peanut tolerated after OIT). Treatment, log-baseline NOAEL, age, family history and log-transformed peanut-specific IgE have a statistically significant effect on log-transformed NOAEL at 6 months. On average, patients in the OIT group have a log-NOAEL at 6 months 4.12-fold higher than those in the waiting list group. For every unit increase in log-transformed baseline NOAEL, the log-transformed NOAEL at 6 months, on average, increases 0.33-fold. For every year increase in age at baseline, the log-transformed NOAEL at 6 months decreases, on average, by 0.17. Patients with a family history of peanut allergy have, on average, 0.64 lower log-transformed NOAEL at 6 months than patients who do not have a family history of peanut allergy.

The number of adverse events was similar in both groups after treatment. The majority of events were gastrointestinal, with oral itching being most common (occurring after 6.3% of all doses); cutaneous events were uncommon, appearing after only 0.16% of doses. Wheezing occurred after 0.41% of doses and was treated with inhaled beta-2 agonists or oral antihistamines in all cases except for one participant who also received intramuscular epinephrine on two occasions, with rapid resolution of his symptoms. There were no serious adverse reactions and no cardiovascular events.

Conclusions

In children aged 7–15 years with challenge-proven peanut allergy of any severity, peanut OIT successfully induced desensitisation in the majority with a clinically meaningful increase in peanut threshold. There was a high rate of response to treatment in both the active and control groups, after undergoing OIT. Immunological changes reflected clinical desensitisation. QoL improved after intervention and the safety profile was acceptable. Peanut OIT offers a highly efficacious treatment for peanut allergy in children.

Peanut allergy is a highly homogeneous disease, with well-validated diagnostic tests and minimal variation in phenotypic characteristics. Future confirmatory trials are desirable, but given the highly homogeneous nature of the illness and the strong effect size observed in this study, such trials are unlikely to require large numbers of patients.

This study provides a protocol for the study of OIT to other allergens that commonly cause food allergic reactions in adults and children. These include tree nuts, milk, egg, fish and shellfish. Similar studies of OIT using these allergens are required to demonstrate whether or not this treatment regime can be translated to treat other common and potentially severe food allergies.

Trial registration

This trial is registered as ISRCTN62416244.

Funding

This project was awarded by the Efficacy and Mechanism Evaluation programme and is funded by the Medical Research Council (MRC) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC–NIHR partnership, and jointly sponsored by the University of Cambridge and Addenbrooke's Hospital [Cambridge University Hospital Foundation Trust (RD authorisation A091686)].

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Chapter 1 Introduction

Peanut allergy is a common and important medical condition, affecting 1% of children in developed countries.[1–3] Unlike other common childhood food allergies (e.g. to hen's eggs), resolution is uncommon.[4] Peanut allergy is the most common cause of severe and fatal food allergic reactions and it is not possible to identify those at highest risk.[5] The quality of life (QoL) of affected families is reduced because of constant fear over food choices and the likelihood of anaphylaxis.[6,7] Despite the current best management, families of peanut-allergic children have poor knowledge of how to avoid and also treat food allergy emergencies.[8] Accidental reactions are common (annual incidence rates for accidental reactions of 3%, 14% and 50% have been reported).[9]

Peanut allergy puts patients at risk of severe reactions and death, and has a profound effect on their QoL. There is no disease-modifying treatment and spontaneous resolution is rare; therefore, the case is made for development of disease-modifying therapies. Oral immunotherapy (OIT) seems to be the most promising short- to medium-term solution to this problem, given its apparent efficacy in other allergies.

Grass pollen immunotherapy given by subcutaneous injection has been used for over a century to treat allergic rhinitis and has proven efficacy and safety.[10] An early study of subcutaneous immunotherapy for peanut allergy showed a trend to benefit, but was terminated after severe adverse reactions.[11] The oral route may be associated with increased safety and has been studied in cases of egg and milk allergy.[12–15]

The recent House of Lords Science and Technology Committee report on allergy stressed that allergy research directly related to health care is an area of unmet need that requires greater priority.[16] According to the report, 'immunotherapy is a valuable resource in the prophylactic treatment of patients with life threatening allergies . . . so its wider use could potentially result in significant long-term savings for the NHS',[16] © Parliamentary copyright 2007, Contains Parliamentary information licensed under the Open Parliament Licence v1.0, URL: www.parliament.uk/site-information/copyright/open-parliament-licence/.

There are few data on desensitisation to foods; however, this is an established treatment for inhalant allergies (e.g. pollen-induced rhinitis) and insect venom anaphylaxis. Subcutaneous injection immunotherapy for pollen-induced rhinitis is effective and disease modifying in that it results in persistent tolerance after stopping therapy. Efficacy is confirmed by a recent Cochrane meta-analysis showing a clear benefit in symptom score and medication use against placebo.[17] Similarly, success is seen in subcutaneous injection immunotherapy for insect venom allergy, for which it is possible to safely desensitise patients with life-threatening reactions.[18]

Sublingual immunotherapy (SLIT), administering doses under the tongue, is a relatively recent development that has high efficacy and tolerability for pollen desensitisation (for severe hay fever). A Cochrane review confirmed the efficacy of SLIT compared with placebo in terms of a reduction in symptom scores and antiallergic medication requirements. Of particular note is the apparent safety of SLIT, which has encouraged us to pursue the oral route in the current proposal.[19]

Subcutaneous peanut immunotherapy was first attempted in a small study in 1992; three subjects exhibited a 67–100% reduction in symptoms induced by peanut challenge, suggesting that this is an effective therapy. No subject suffered anaphylaxis during immunotherapy.[11] SLIT for hazelnut allergy has been the subject of a more recent randomised controlled trial (RCT), which showed significant increases in tolerance to hazelnut [assessed by double-blind placebo-controlled food challenge (DBPCFC)] and systemic reactions were observed in only 0.2%.[20] We chose to use the oral route as we expect this to induce fewer side effects than injection immunotherapy, while still being efficacious, as demonstrated for pollen immunotherapy. There are also preliminary studies on desensitisation to other food allergens such as milk and egg.[12–15]

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We have pilot data on children aged 5–18 years using a study design identical to that of the active arm in the proposed trial. All had peanut allergy confirmed by blinded challenge before progressing to OIT according to the current proposal. To date, 19 out of 22 children have reached the final dose of 800 mg of peanut protein and are taking this, the equivalent of five peanuts, at home with no reaction. OIT doses taken at home and on the research ward are well tolerated and no subject has had a severe or generalised reaction during up-dosing.[21,22]

A recent systematic review of studies of peanut OIT identified a single small randomised controlled study in 28 children.[23] It suggested a positive effect of peanut OIT, but was too small to estimate efficacy.[23] There is a need for systematic study of peanut OIT. We performed a phase 1 study that showed good tolerability and an indication of good efficacy.[21,22] The current study is a phase 2 randomised controlled study of the efficacy of peanut OIT in achieving desensitisation in a well-characterised population.

Chapter 2 Method

Setting

We undertook this single-centre RCT at the Wellcome Trust Clinical Research Facility on the Cambridge Biomedical Campus between January 2010 and March 2013. The study was conducted according to the principles of Good Medical Practice for clinical trials.

Patient and public involvement

Patient representatives were involved from the outset. We surveyed the pilot study participants to gather feedback that informed the design of the current trial. The national patient support group, the Anaphylaxis Campaign, has reviewed the current protocol and they have ratified the design and confirmed the study end points are important and relevant to their membership. Furthermore, a representative of the Anaphylaxis Campaign joined as a member of the Trial Steering Committee.

The result will be disseminated by an article in the Anaphylaxis Campaign's newsletter and website.

Aims

The overarching objective was to determine efficacy of OIT in desensitising children with peanut allergy. We aimed to determine whether or not the treatment was successful in the intervention group compared with the control (phase 1) and whether or not it is successful when offered to the control group (phase 2) (*Figure 1*).

Participants

Participants were recruited both locally (allergy clinic) and nationally (through the national patient support group Anaphylaxis Campaign). Eligible participants were 7–16 years of age with an immediate-type hypersensitivity reaction after peanut ingestion, positive skin prick test (SPT) to peanut (extract from ALK-Abelló, Hørsholm, Denmark) defined by a weal of ≥ 3 mm in diameter in the presence of a negative saline and positive histamine control, and positive DBPCFC.[19] We excluded participants if they had a significant chronic illness (except for eczema, rhinitis and asthma) because this is an immunomodulatory therapy, if a care provider or current household member had suspected or diagnosed allergy to peanut, or if there was unwillingness or inability to comply with study procedures. We did not exclude participants who had a previous life-threatening reaction, tree nut allergy or a history of severe asthma.

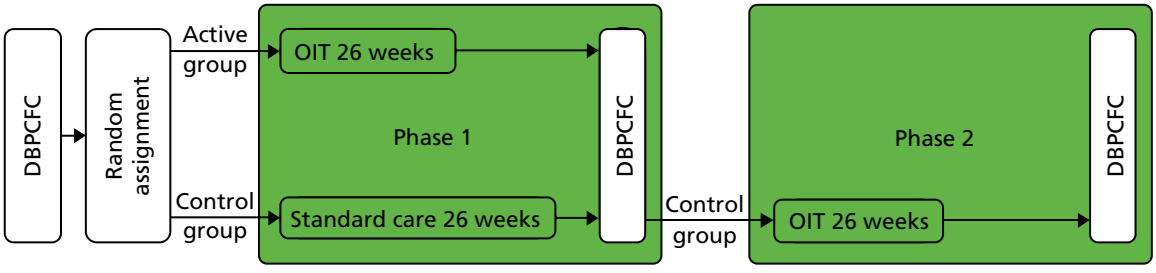

FIGURE 1 The Study of induction of Tolerance to Oral Peanut (STOP II) study design.

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The Cambridge Central Ethics Committee approved the study (09/H0308/154) and the guardian of each participant gave his or her informed consent. Children of an appropriate age (≥ 12 years) were encouraged to provide their own assent.

Randomisation

Subjects were randomised (1 : 1) via an audited online system (Randomizer, Medical University of Graz, Graz, Austria) to the active or control group (see *Figure 1*). Minimisation was used to reduce imbalance of baseline covariates, with a random element using a weighting probability of 0.8. Factors were sex, age, challenge threshold, peanut-specific serum immunoglobulin E (IgE), severity from history and presence of asthma or other food allergy. Group allocation was unblinded.

During phase 1, the active group underwent 6 months of active OIT and the control group underwent 6 months of standard care (peanut avoidance). Minimisation was used to avoid imbalance of baseline covariates, with a random element using a weighting probability of 0.8. At the end of phase 1 (6 months) all participants were assessed for peanut allergy by DBPCFC. During phase 2, participants in the control group still allergic to peanut after 6 months of standard care were given active OIT, followed by a DBPCFC after 6 further months (see *Figure 1*). There were no important changes to method after commencement.

Participants underwent an initial DBPCFC followed by 1 : 1 randomisation. During phase 1, participants in the active group underwent OIT for 26 weeks. Participants randomised to the control group were asked to continue normal peanut avoidance for the first 26 weeks of the study (standard care). Both groups then underwent a second DBPCFC. In phase 2, control group participants underwent active OIT for 26 weeks followed by a third DBPCFC at 52 weeks (end of phase 2).

Patients were not blinded to allocation groups; however, the primary outcome was assessed using an objective blinded measure, i.e. 'no reaction' during a DBPCFC. Challenge assessors were blinded to the challenge placebo/active arm, but not to the treatment allocation. Study personnel were the chief investigator, a clinical fellow, a study nurse and a scientist. All study personnel were masked to the randomised active/placebo assignment in the challenge except the scientist who prepared the challenge material but had no interaction with the participant or study team. Allocation was saved in a locked database accessible only to the unblinded scientist.

Procedures

The primary end point was the proportion of desensitised subjects at the end of phase 1. Desensitisation was defined as 'no reaction' during peanut DBPCFCs, with a cumulative dose of 1400 mg of peanut protein.

Oral challenges

All peanut challenges were undertaken as DBPCFCs according to best practice,[19] using separate active and placebo phases and masked using the validated EuroPrevall dessert food carrier recipe (range of doses: 5 mg, 50 mg, 100 mg, 300 mg and 1000 mg of peanut protein).[20] We chose a cumulative challenge dose equivalent to approximately 10 peanuts to demonstrate desensitisation to an amount of peanut that we considered unlikely to be encountered accidentally following OIT. Random number lists determined the order of DBPCFC placebo and active arms. All study personnel were masked to the challenge assignment except the unblinded scientist, who prepared the challenge material but had no interaction with the participant or study team.

Secondary end points were the proportion who responded to treatment after receiving OIT (a response to treatment was defined as ingesting 800 mg of peanut protein regularly for up to 6 months); the proportion of the control group who were desensitised or responded to treatment during phase 2; the fold and absolute increase in threshold [maximum tolerated peanut protein (mg)] after OIT; change in QoL [measured by food allergy quality of life – parent form (FAQLQ-PF) 0–12 years] scores from baseline to the end of phase 1 and phase 2; number and type of adverse events; and change in immunological outcomes [basophil area under curve (AUC) of percentage of CD63 and mean fluorescence intensity (MFI), peanut IgE, total IgE, and SPT diameter]. There were no changes to outcomes after commencement.

Oral immunotherapy

The active intervention (OIT) was administered in daily doses throughout and was given in two phases. First, there was a gradual up-dosing phase with 2-weekly increments to 800 mg/day, followed by a maintenance phase during which the highest tolerated dose (with a target of 800 mg/day) was taken continuously to complete a total of 6 months' immunotherapy. The same characterised peanut flour used in the challenges was also used for up-dosing (light roast flour; Golden Peanut Company, Alpharetta, GA, USA). The up-dosing phase increments were 2 mg, 5 mg, 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 400 mg and 800 mg of peanut protein (patent applied for dosing regime). All dose increases took place in the Wellcome Trust Clinical Research Facility and subjects were observed for 2 hours. The same dose was administered at home daily for 2–3 weeks. At the final two up-doses, subjects ingested the equivalent dose as whole-roasted peanuts.

Patients were provided with a symptom diary that they were asked to complete each day and hand back to the study team at each visit. Patients were asked to take their dose with food and instructed not to exercise for 1–2 hours after taking a dose. Families had 24-hour contact access to the study team. Patients were free to take antihistamines as they wished throughout the study.

Flow cytometric analysis (fluorescence-activated cell sorting) of patient samples was undertaken on whole-blood specimens by study staff to quantify the percentage and MFI CD63+ basophils. SPTs were undertaken using a standardised peanut extract from ALK-Abelló and a single-point lancet. Peanut-specific serum IgE was measured using the ImmunoCAP system (Thermo Scientific, Hørsholm, Denmark).

Basophil activation tests

Peripheral blood was collected into heparin and processed within 2 hours. Laboratory workers performing basophil activation tests were not blinded to treatment allocation. Briefly, 100 µl of heparinised whole blood aliquoted into 12 × 75 mm flow cytometry tubes (Becton Dickinson) was stimulated with interleukin 3 (3 ng/ml final concentration; R&D Systems, Minneapolis, MN, USA) in a 37 °C water bath for 10 minutes. The blood samples were then activated for 20 minutes at 37 °C, with the same volume of varying concentrations of endotoxin-free crude peanut extract (0.001–100 µg/ml) in Ca^{2+}- and Mg^{2+}-free phosphate-buffered saline (PBS) (Sigma, Santa Fe, MN, USA). Positive controls included *N*-formylmethionyl-leucyl-phenylalanine (2 µM; Sigma, Santa Fe, MN, USA) and polyclonal anti-IgE (1/10,000; AbD Serotec, Kidlington, UK) and PBS and endotoxin-free ovalbumin (1 µg/ml; Sigma, Santa Fe, NM, USA) as negative and food allergen-negative controls, respectively. Degranulation was stopped by incubating on ice for 5 minutes. Cells were stained with a saturating antibody cocktail of CD63-fluorescein isothiocyanate (clone H5C6; Becton Dickinson), CD123-phycoerythrin (clone 9F5; Becton Dickinson) and HLA-DR-PerCP (human leucocyte antigen peridinin-chlorophyll protein; clone L243; Becton Dickinson) in the dark, on ice, for 20 minutes. The whole-blood samples were lysed and fixed with Becton Dickinson FACS™ (Franklin Lakes, NJ, USA) lysing solution for 15 minutes, at room temperature. After two washes (0.26% weight per volume bovine serum albumin; 2 mM ethylenediaminetetraacetic acid in PBS), the cell pellet was resuspended in 1% paraformaldehyde and acquired on a FACSCalibur™ (Franklin Lakes, NJ, USA) flow cytometer (Becton Dickinson Biosciences, San Jose, CA, USA). At least 200,000 events were acquired for each sample. Activated basophils were identified as CD63+/CD123+/HLA-DR– and changes in the frequency (%CD63+) and expression (net CD63 MFI) was measured.

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Statistical analysis

The full analysis population was all subjects who were randomised and participated in at least one post-baseline assessment. The criteria for per-protocol analysis of the outcome of peanut challenge at the end of immunotherapy consisted of desensitisation and continuation of immunotherapy up to the maintenance dose of 800 mg of protein.

Fisher's exact test was used to compare the proportion of those with desensitisation to peanut after 6 months in the active group with the control group at the end of phase 1. Multiple logistic regression was used to adjust the odds of desensitisation for baseline characteristics. Secondary analyses tested for treatment differences with Fisher's exact test (proportion response to treatment in active group and control group at end of phase 2), paired and independent sample *t*-tests (absolute and fold change in threshold), and Mann–Whitney *U*-tests (change in QoL scores, basophil AUC of percentage of CD63 and MFI, peanut-specific serum IgE and SPT weal diameter). All statistical tests described in this section use a two-sided 5% significance level. We assessed analysis on the intention-to-treat population that included all those who were randomised and participated in at least one post-baseline assessment.

Sample size was based on Fisher's exact test with 90% power and 5% significance (two-sided). A sample size of 49 in each group is sufficient to detect proportions of participants, with desensitisation to peanut of 0.64 and 0.30 in the active and control groups, respectively, at the end of phase 1. Allowing for a 5% dropout increased the required sample size to 52 participants in each group and 104 subjects overall. Based on the above, we would expect 35 waiting list group patients to proceed to the active intervention in phase 2. Non-parametric tests may be used instead of parametric tests if the assumptions are not appropriate.

A statistical analysis plan, which embodies all the calculations performed, was agreed and signed off before any analysis was undertaken on the database (*see Appendix 1*).

Results

We enrolled 104 children, aged 7–16 years (median 12.4 years), to the study. Five children did not react during their baseline peanut challenge, thus not meeting the inclusion criteria, and were excluded from further participation in the study. Therefore, 99 children were randomised: 49 out of 99 to the active group and 50 out of 99 to the control group (*Figure 2*).

One child was discontinued and five withdrew from the active group during phase 1. In the control group, four children withdrew and one was discontinued during phase 1. Two further children withdrew from the control group when they underwent the intervention in phase 2.

There were no significant differences in baseline characteristics between allocation groups (*Table 1*).

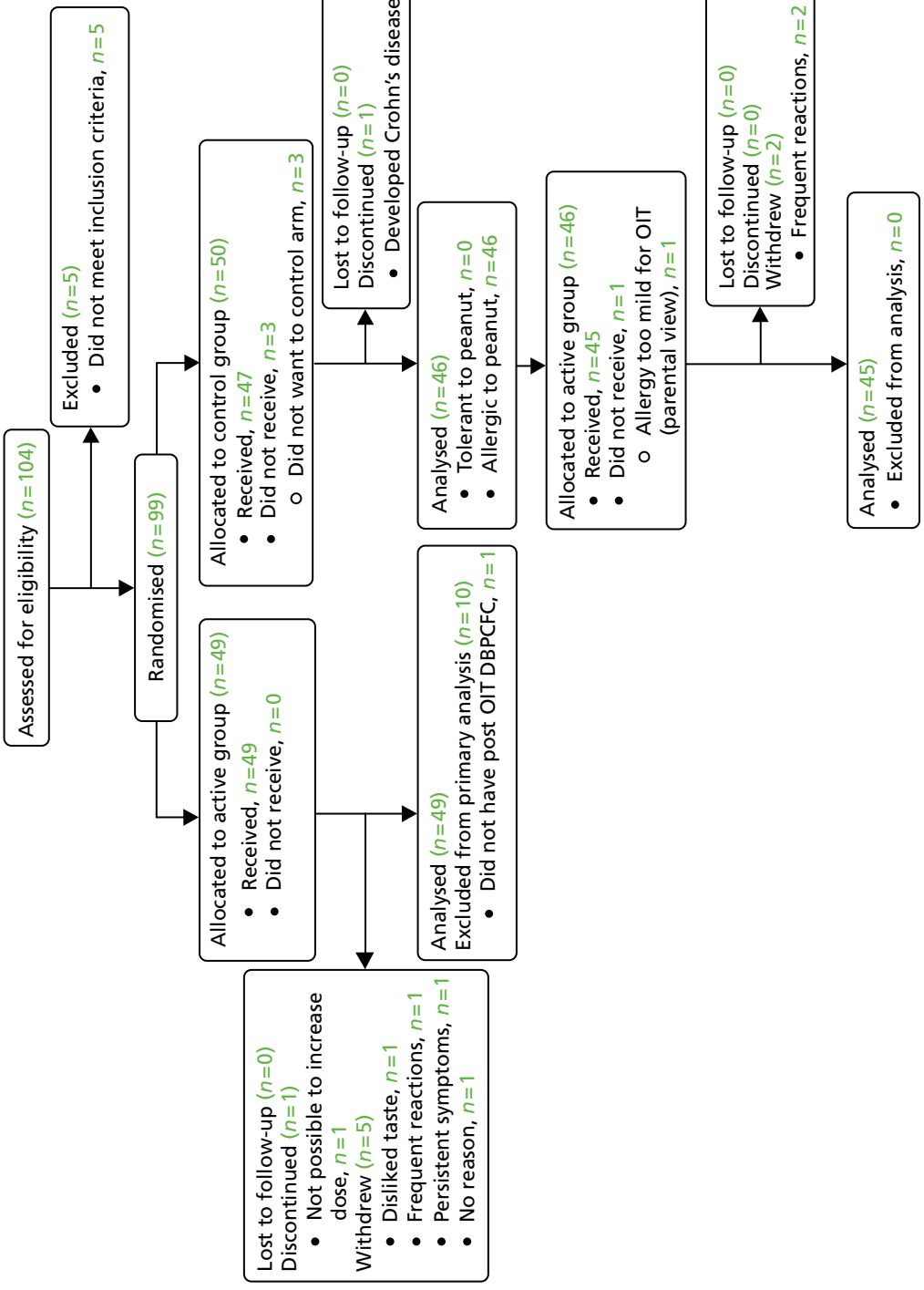

FIGURE 2 The CONSORT diagram of patient flow through the study.

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TABLE 1 Baseline characteristics of study participants

Characteristic	Control group (*N* = 50)	Active group (*N* = 49)
Age (years)		
n	50	49
Mean (SD)	11.9 (2.67)	12.4 (2.42)
Median (range)	12.3 (7.2–16)	12.3 (8.1–16.3)
Sex (male), *n* (%)	36 (72)	34 (69.4)
Weight (kg)		
n	47	49
Mean (SD)	44.3 (16.4)	45.7 (15.5)
Median (range)	39 (21–82)	43 (23–81)
Asthma, *n* (%)	29 (58)	29 (59.2)
Eczema, *n* (%)	27 (54)	24 (49)
Rhinitis, *n* (%)	27 (54)	29 (59.2)
Family history of peanut allergy, *n* (%)	35 (70)	31 (63.3)
Severity of worst clinical reaction WAO score[23]		
Grade 1, *n* (%)	25 (51)	20 (40.8)
Grade 2, *n* (%)	13 (26)	25 (51)
Grade 3, *n* (%)	9 (18.4)	3 (6.1)
Grade 4, *n* (%)	2 (4.1)	1 (2)
Other food allergy, *n* (%)	13 (26)	10 (20.4)
FAQLQ-PF QoL score		
n	20	19
Mean (SD)	2.69 (1.60)	3.26 (1.26)
Median (range)	2.28 (0.3–5.54)	3.61 (0.47–5.44)
Peanut SPT weal diameter (mm)		
n	50	49
Mean (SD)	8.54 (3.08)	8.92 (3.02)
Median (range)	9 (3–14)	9 (0–16)
Other nut SPT weal diameter		
< 3 mm, *n* (%)	34 (68)	38 (77.6)
≥ 3 mm, *n* (%)	16 (32)	11 (22.4)
Total IgE (kU/l)		
n	50	49
Mean (SD)	539 (467)	597 (844)
Geometric mean	385.9	312.9
Median (range)	355.5 (44–1942)	295 (20–3971)
Peanut-specific IgE (kU/l)		
n	50	49
Mean (SD)	79.5 (117)	202.9 (539)
Geometric mean	24.0	29.9
Median (range)	41.6 (0.39–463)	37.9 (0.35–3649)

TABLE 1 Baseline characteristics of study participants (*continued*)

Characteristic	Control group (*N* = 50)	Active group (*N* = 49)
Tryptase (ng/ml)		
n	26	33
Mean (SD)	4.55 (1.85)	5.10 (2.94)
Median (range)	4.5 (1.7–8.9)	4.9 (0–15.6)
DBPCFC WAO severity score[23]		
Grade 1, *n* (%)	11 (22)	13 (26.5)
Grade 2, *n* (%)	37 (74)	33 (67.3)
Grade 3, *n* (%)	2 (4)	3 (6.1)
Grade 4, *n* (%)	0 (0)	0 (0)
DBPCFC: total peanut protein consumed (mg)		
n	50	49
Mean (SD)	151.9 (274.0)	99.8 (76.8)
Geometric mean	66.2	63.9
Median (range)	55 (5–1400)	60 (5–400)
DBPCFC: LOAEL (mg)		
n	50	49
Mean (SD)	147.9 (274.6)	94.6 (77.4)
Geometric mean	63.5	58.1
Median (range)	55 (5–1400)	55 (5–400)
DBPCFC: NOAEL (mg)		
n	50	49
Mean (SD)	41.5 (80.1)	28.4 (36.8)
Geometric mean	14.3	0
Median (range)	5 (5–400)	5 (0–155)
Basophil AUC of CD63 MFI against peanut protein concentration		
n	22	13
Mean (SD)	34,039 (27,513)	40,198 (33,488)
Geometric mean	205,556	29,271
Median (range)	31,438 (1219–109,006)	34,955 (4930–118,532)
Basophil AUC of percentage of CD63-positive cells against peanut concentration		
n	22	13
Mean (SD)	6505 (2774)	7322 (1609)
Geometric mean	5205	7133
Median (range)	6958 (179–9553)	7107 (3828–9284)

LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level; U, unit; WAO, World Allergy Organization-adapted score.[23]
LOAEL refers to the lowest dose of peanut protein (mg) that caused a reaction during baseline challenge.
NOAEL refers to the highest dose of peanut protein (mg) tolerated during baseline challenge.

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Clinical end points

Primary objective

There was a significant difference between the numbers of patients who tolerated 1400 mg of peanut protein during DBPCFC at the end of phase 1 in the active (24/39) and the control groups (who underwent peanut avoidance for 24 weeks) (0/41) ($p < 0.001$) (*Table 2*). The proportion desensitised during phase 1 after 24 weeks was 0.62 (range 0.45–0.78) and 0 (range 0–0.091) in the active and control groups, respectively.

TABLE 2 Clinical end points for phase 1 and phase 2

End points	Control	Active	Control vs. active *p*-value[a]
Clinical end points			
	$n = 46$	$n = 39$	
Phase 1			
Number and proportion desensitised and able to tolerate daily ingestion after phase 1			
Desensitised	0	24	< 0.001[b]
Not desensitised	46	15	
Proportion desensitised (95% CI)	0 (0 to 0.091)	0.62 (0.45 to 0.78)	–
Proportion able to tolerate daily ingestion (95% CI)	0	0.84 (0.70 to 0.93)	–
Within-patient changes in NOAEL (mg), absolute and fold change			
Median (range) absolute change in NOAEL (mg)	0 (–95 to 45)	1345 (45–1400)	0.002, < 0.001[c]
Median (range) fold change in NOAEL (mg)	0.81 (0.05–1.82)	25.5 (1.82–280)	0.003, < 0.001[c]
NOAEL (mg) after phase 1			
NOAEL (mg) median (range)	5 (5–400)	1400 (100–1400)	< 0.001[d]
Median difference in NOAEL (mg) between groups			
Median (95% CI)	1395 (395 to 1395)		< 0.001[d]
Phase 2			
Proportion desensitised and able to tolerate daily ingestion after phase 2 (treatment)			
Proportion desensitised (95% CI)	0.54 (0.35 to 0.72)	–	–
Proportion able to tolerate daily ingestion (95% CI)	0.91 (0.79 to 0.98)	–	–
QoL end points			
	$n = 20$	$n = 19$	
Median (range) change in score from baseline to post-treatment	–1.41 (–4.83 to 1.38)	–1.61 (–4.87 to 0.24)	< 0.001, < 0.001

CI, confidence interval; NOAEL, no observed adverse effect level.
a First entry is for the control group fold change and the second entry is for the active group fold change.
b *p*-value obtained from Fisher's exact test.
c *p*-values are from Wilcoxon signed-rank tests.
d *p*-value from Mann–Whitney *U*-test.
QoL end points, FAQLQ-PF – parent form for 5–12 years. Scale 0 (best) to 6 (worst); median change in FAQLQ-PF scores from baseline to post treatment.
Desensitised defined as tolerates 1400 mg of protein DBPCFC.
Proportion able to tolerate daily ingestion defined as able to ingest 800 mg of protein regularly up to a total of 26 weeks' OIT.

Secondary objectives

Response to treatment, defined by the ability to tolerate daily doses of 800 mg of peanut protein after 24 weeks of immunotherapy, occurred in 0.84 [95% confidence interval (CI) 0.70 to 0.93] of the active group at the end of phase 1 and 0.91 (95% CI 0.79 to 0.98) of the control group at the end of phase 2 (post immunotherapy). There was a significant increase in peanut no observed adverse effect level (NOAEL) in the active group after phase 1, with a median change in threshold of 25.5-fold ($p < 0.001$) (*Figure 3*) compared with a small positive change in peanut threshold (NOAEL) in the control group during phase 1 (0.81, range 0.05–1.82).

The proportions of patients who achieved desensitisation (0.54, 95% CI 0.35 to 0.72) or response to treatment (0.91, 95% CI 0.79 to 0.98) in the control group after 24 weeks of OIT (end of phase 2) were similar to that in the active group.

Quality-of-life end points

Quality-of-life scores assessed by the FAQLQ-PF measure were similar between active and control groups at baseline. FAQLQ-PF (aged 5–12 years) was available from 19 children in the active group and 20 in the control group, before and after treatment. After treatment in both groups there was a similar and clinically meaningful improvement (decrease) in QoL scores (see *Table 2*).

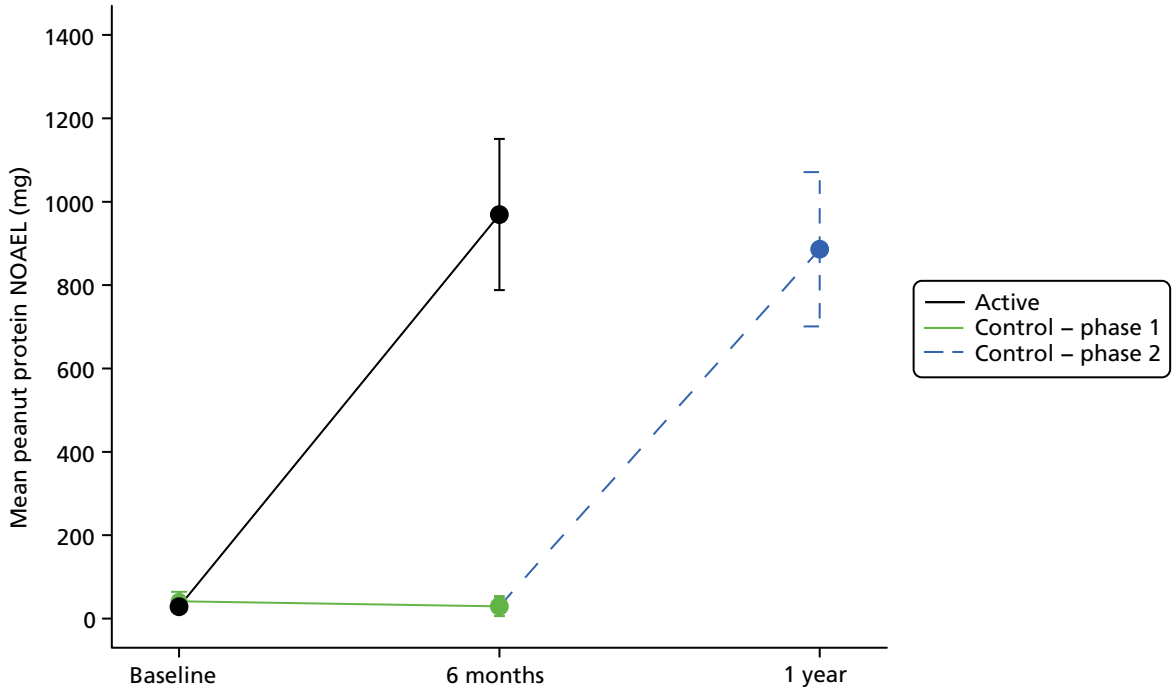

FIGURE 3 Mean and 95% CI peanut protein NOAEL (mg) by treatment group. NOAEL, highest dose of peanut protein tolerated in mg of protein during challenge or OIT (active treatment); difference at 6 months, $p < 0.001$. *p*-value from the Mann–Whitney *U*-test.

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Immunological end points

Immunological assessments revealed a significant small reduction in median SPT weal diameter (–1 mm, range –8 to 4 mm; $p = 0.0015$) and an increase in peanut-specific serum IgE [12.7 kilounit (kU)/l, range –18.6 to 1359 kU/l; $p < 0.001$] after 24 weeks' OIT in the active group. Basophil stimulation data were expressed as the AUC of plots of MFI and percentage of CD63-positive cells against concentration of peanut protein. No significant within-patient differences were found after treatment for AUC of MFI or percentage of CD63, although there was a reduction in MFI and percentage of CD63 at the lower peanut doses (*Table 3* and *Figure 4*).

Logistic regression

Logistic regression revealed several baseline covariates had an influence on the final NOAEL (the highest amount of peanut tolerated after OIT) (*Table 4*). Treatment, log-baseline NOAEL, age, family history and log-transformed peanut-specific IgE have a statistically significant effect on log-transformed NOAEL at 6 months. On average, patients in the OIT group have a log-NOAEL at 6 months 4.12-fold higher than those in the waiting list group. For every unit increase in log-transformed baseline NOAEL, the log-transformed NOAEL at 6 months, on average, increases 0.33-fold. For every year increase in age at baseline the log-transformed NOAEL at 6 months decreases, on average, by 0.17. Patients with a family history of peanut allergy have, on average, 0.64 lower log-transformed NOAEL at 6 months than patients who do not have a family history of peanut allergy.

For every unit increase in log-transformed baseline peanut-specific IgE, the log-transformed NOAEL at 6 months decreases, on average, by 0.31.

For every unit increase in log-transformed baseline total IgE, the log-transformed NOAEL at 6 months increases, on average, by 0.36.

A Tobit regression model was used to fit the data, showing OIT treatment and log-baseline NOAEL was associated with a statistically significant increase in log-transformed NOAEL after 24 weeks of OIT (see *Table 4*). On average, patients in the OIT group had a log-NOAEL at 6 months 4.66-fold higher than those in the control group after phase 1.

TABLE 3 Immunological end points

Immunological end points	Control ($n = 46$)	Active ($n = 39$)	p-value[a]
Within-participant changes in SPT weal diameter (mm)			
Median (range) change from baseline to post treatment	–1.5 (–8 to 9)	–1 (–8 to 4)	0.0693, 0.0015
Within-participant changes in total IgE (kU/l) by group			
Median (range) change from baseline to post treatment	24 (–303 to 1582)	99 (–164 to 1411)	0.0109, < 0.001
Within-participant changes in peanut-specific serum IgE (kU/l)			
Median (range) change from baseline to post treatment	74.5 (–55 to 637)	12.7 (–18.6 to 1359)	< 0.001, < 0.001

SPT performed with single-lancet technique using peanut extract, normal saline and histamine controls (ALK-Abelló; Hørsholm, Denmark).
a First entry is for the control group fold change and the second entry is for the active group fold change.
Peanut-specific IgE measured by ImmunoCAP (Thermo Scientific).

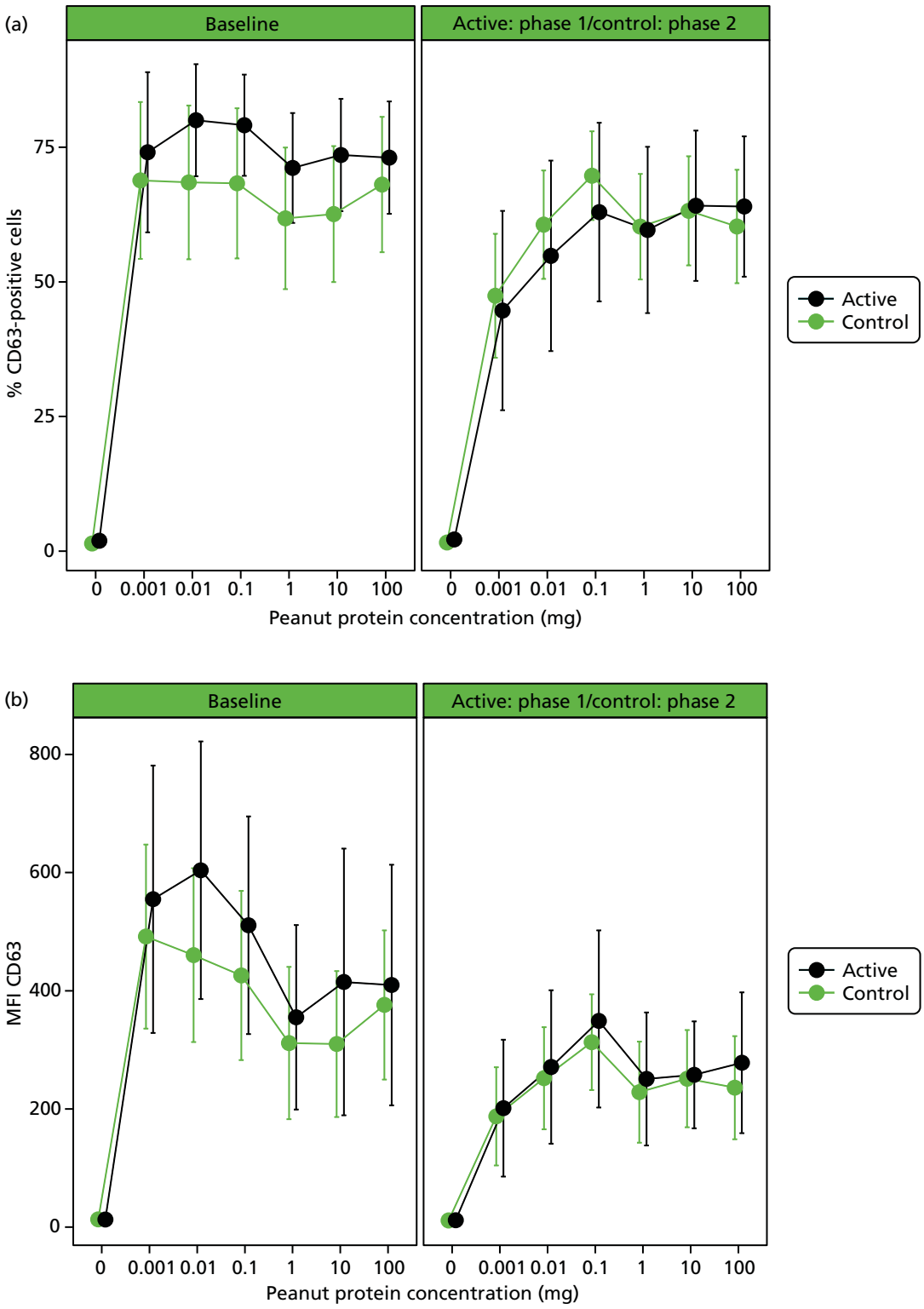

FIGURE 4 (a) In vitro basophil activation by peanut before and after desensitisation as percentage of CD63-positive cells. Heparinised whole blood was stimulated with a range of peanut protein concentrations (0.001–100 µg/ml) and flow cytometry was used to assess CD63 expression (%) within the basophil population. Differences in AUCs were not significant. (b) In vitro basophil activation by peanut before and after desensitisation as CD63 MFI (MFI of CD63 marker). Heparinised whole blood was stimulated with a range of peanut protein concentrations (0.001–100 µg/ml) and flow cytometry was used to assess CD63 expression (MFI) within the basophil population. Differences in AUCs were not significant.

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TABLE 4 Tobit regression model[22] exponentiated estimates – dependent variable natural log-6-month NOAEL

Covariates	Estimate	95% CI	*p*-value
OIT	105.5	67.73 to 164.40	< 0.001
Log (baseline NOAEL + 1)	1.40	1.15 to 1.69	< 0.001
Age	0.76	0.65 to 0.89	< 0.001
Female	1.42	0.87 to 2.31	0.16
Weight	1.04	1.01 to 1.06	0.004
QoL	1.12	0.89 to 1.42	0.32
Asthma	1.09	0.65 to 1.74	0.79
Eczema	0.82	0.53 to 1.26	0.36
Rhinitis	0.69	0.46 to 1.05	0.09
Other food allergy	0.84	0.52 to 1.36	0.48
Family history of peanut allergy	0.41	0.24 to 0.71	0.001
WAO grade 2	2.88	1.65 to 5.01	< 0.001
WAO grade 3	0.86	0.44 to 1.68	0.66
WAO grade 4	0.62	0.21 to 1.82	0.40
Peanut SPT weal diameter	1.02	0.94 to 1.11	0.60
Other nut SPT weal diameter > 3 mm	1.37	0.81 to 2.31	0.23
Tryptase	1.06	0.95 to 1.19	0.32
Log (peanut-specific IgE + 1)	0.60	0.51 to 0.71	< 0.001
Log (total IgE + 1)	1.74	1.35 to 2.23	< 0.001
Log (basophil activation CD63 MFI AUC)	0.98	0.73 to 1.32	0.91

WAO, World Allergy Organization score.
NOAEL the highest amount of peanut protein (mg) tolerated after OIT. The continuous variables can be interpreted as the percentage change in NOAEL expected from a unit increase of that variable when all other covariates are fixed. The categorical variable estimates can be interpreted as the percentage change compared with the reference group, when all other covariates are fixed. For logged covariates, the expected percentage change in 6-month NOAEL with a 10% increase in the logged covariate can be calculated as 1.10 log(exponentiated estimate). For example, for a 10% increase in baseline NOAEL (mg) we would expect a [1.1 log(1.40) = 1.032] 3.2% increase in 6-month NOAEL (mg). Similarly, for a 10% increase in baseline peanut-specific IgE (kU/l) we would expect a 4.8% decrease in 6-month NOAEL (mg).

A Tobit model allows for censoring in positive dependent variables, i.e. in this study the NOAEL (peanut threshold) was censored at 1400 mg, and the maximum cumulative dose of peanut protein administered to patients was 1400 mg and patients who did not react at 1400 mg may not react at even higher cumulative doses of peanut protein. A total of 24 out of the 85 patients included in this analysis achieved a NOAEL of 1400 mg at 6 months.

Adverse events

The number of adverse events was similar in both groups after treatment (*Table 5*). The majority of events were gastrointestinal, with oral itching being the most common (occurring after 6.3% of all doses). Cutaneous events were uncommon, appearing after only 0.16% of doses. Wheezing occurred after 0.41% of doses and was treated with inhaled beta-2 agonists or oral antihistamines in all cases, except for one participant who also received intramuscular epinephrine on two occasions, with rapid resolution of his symptoms. There were no serious adverse reactions and no cardiovascular events.

TABLE 5 Adverse events during treatment presented per participant ($n = 94$) and per dose (total doses = 17,793)

Events	*n* (%) of participants who experienced an adverse event	*n* (%) of adverse events per dose of OIT
Symptoms		
Mouth itch	76 (81)	1121 (6.30)
Abdominal pain	54 (57)	460 (2.59)
Nausea	31 (33)	393 (2.21)
Vomiting	31 (33)	134 (0.75)
Diarrhoea	1 (1)	5 (0.03)
Urticaria	12 (13)	29 (0.16)
Angiooedema	18 (19)	71 (0.40)
Erythema	20 (21)	41 (0.23)
Rhinitis	23 (24)	65 (0.37)
Wheezing	21 (22)	73 (0.41)
Laryngeal oedema	1 (1)	1 (0.01)
Cardiovascular collapse or fainting	0 (0)	0 (0.00)
Outcome		
Admission to ITU/SAR/SUSAR	0 (0)	0 (0.00)
Use of inhaled beta-2 agonist	18 (19)	63 (0.35)
Use of IM epinephrine	1 (1)	2 (0.01)

IM, intramuscular; ITU, intensive care unit; SAR, serious adverse reaction; SUSAR, serious unexpected suspected adverse reaction.

Discussion

Daily doses of peanut OIT up to a maximum dose of 800 mg of protein had a clinically meaningful effect on the disease, demonstrated by a high incidence of desensitisation, large absolute and fold increases in NOAEL threshold and a significant improvement in QoL score.

These results provide the first well-controlled and accurate estimate of the efficacy, benefits and risks of desensitisation using peanut OIT. Previous studies were either uncontrolled or too underpowered to estimate the effect size of the intervention.[20,21]

Peanut allergy is a common long-lived disease with onset in childhood. Fear of severe reactions and the effect this has on social behaviour reduces QoL, which can often be lower than it is for children with other chronic diseases such as type 1 diabetes or rheumatological conditions.[6,7] Parental perception of disruption in daily activities is mainly due to the perceived risk of their children's death,[6] leading to anxiety related to making food choices inside and outside the home.[7] Secondary effects of anxiety lead to socially disadvantageous behaviour in some, for example avoiding eating outside the home.[7]

This study confirms the improvement in QoL shown by an earlier uncontrolled study of peanut OIT.[24] Following OIT, our patients reported that they no longer avoid eating foods with precautionary labelling and they now eat out at restaurants without checking ingredients.

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Most peanut-allergic patients are able to avoid accidentally eating large amounts of peanut; however, if untreated, they are at constant risk of reacting to peanut hidden in foods. Without OIT, the attitude of both patients and families to selecting potentially contaminated foods varies widely and is determined mostly by subjective judgements and previous experience.[25] Consequently, accidental reactions are not uncommon, occurring in 14–55% per year.[9] A recent study combined published data on peanut thresholds, peanut contamination of chocolate and patterns of population food consumption using probabilistic modelling to estimate the absolute risk of reacting to precautionary-labelled foods.[26] The risk of a peanut-allergic child reacting after eating a chocolate with precautionary labelling was 0.61% (95% CI 0.47% to 0.81%). The authors showed that 36% (95% CI 31% to 42%) of chocolate bars for which peanut was not listed in the ingredients, sourced from France and the USA, contained detectable peanut protein, with a median of 8.25 mg/kg protein (95% CI 6.54 mg/kg to 10.54 mg/kg).[26] A study of 62 catering establishments in Northern Ireland found that 21% served a peanut-contaminated meal, despite a request for a peanut-free meal.[27] The highest level of contamination was found in a chicken curry containing 4.795 mg of peanut protein.[27] Our data show that peanut OIT can raise the reactive threshold by 25.5-fold so that 83–91% of patients can eat 800 mg of peanut protein regularly without reacting (approximately equal to four to six whole peanuts). In addition, 54–64% of children could tolerate a challenge with 1400 mg of protein without reacting, providing protection to approximately 10 peanuts. Raising the reactive threshold for patients is a key part of this treatment, protecting patients from greater amounts than they are likely to encounter on a day-to-day basis in contaminated snacks or meals.

Our primary end point was the proportion of patients desensitised after 6 months of OIT. Peanut allergy may resolve in up to 20% of children over several years,[4] but there are no data over a short period such as 6 months. There is currently no disease-modifying treatment for peanut allergy; therefore, the control group underwent the current best treatment for peanut allergy – peanut avoidance – to identify the proportion whose allergy resolved spontaneously over the 6-month period of phase 1, to reduce type 1 error.

We did not use a placebo during the control period because the risk of including it outweighed any potential benefit. During the pilot study, participants receiving peanut OIT reported that they significantly relaxed their peanut avoidance behaviour during the first 6 months of treatment, despite advice to the contrary. Therefore, we could not exclude the likelihood that a significant proportion of placebo-treated patients in this phase 2 study would relax their avoidance practice, guessing they were taking active treatment and, therefore, risking a severe reaction. Placebos in general are included to reduce the risk of type 1 error (i.e. false-positive results) in studies for which the primary end point can be influenced by knowing one is receiving a treatment, attention from health-care professionals, and the expectations of a treatment's effectiveness by those running the research study. However, the risk of a type 1 error in the context of this trial was acceptably low because the primary end point was measured using a blinded objective measure (i.e. 'no reaction' to a large amount of peanut during DBPCFC) that could not be influenced by these factors. A limitation of this study is that secondary outcomes such as QoL scores may have been influenced by knowledge of treatment allocation.

There was a small risk of bias as participants who knew they were receiving active treatment may have under-reported minor symptoms at the higher challenge doses, although these symptoms would have been infrequent and subjective. Additionally, during phase 1, 10 subjects did not undergo a post OIT challenge because they had withdrawn or not reached the target maintenance OIT dose at 6 months. It is probable that in phase 1 the true response rate is lower than estimated; however, in phase 2, for which there were few dropouts, we still observed a large effect. A very conservative sensitivity analysis was performed in which all the unobserved subjects in the active group were imputed as not desensitised and all the unobserved subjects in the control group were imputed as desensitised. The analysis gave a risk difference of 0.41 (exact 95% CI 0.21 to 0.58), which supports the conclusions of the main analysis.

It is probable that long-term peanut protein ingestion will be required to provide continued protection from accidental exposure and that long-term desensitisation rather than clinical tolerance is a realistic end point for treatment. During OIT, there is evidence of basophil and mast cell desensitisation (i.e. reduced SPT weal size), accompanied by a gradual change in peanut-specific T-cell surface markers from Th2 to Th1 phenotype (Dr Katherine Anagnostou, University of Cambridge, 2010, personal communication). Recent data from our group show that elevated peanut-specific serum IgE levels persist for several years after starting OIT, despite apparent clinical desensitisation (Dr Katherine Anagnostou, personal communication).

However, preliminary work suggests that extending the dose interval to 800 mg once weekly after 2–3 years of daily treatment is well tolerated, resulting in ongoing protective desensitisation (Dr Katherine Anagnostou, personal communication).

We chose a single maintenance treatment dose of 800 mg, pragmatically, as the largest amount of peanut that would be feasible/acceptable to take on a daily basis. From the limited data available in published studies, it is apparent that the rapidity of the up-dosing schedule has a greater effect on safety and efficacy than the magnitude of the maintenance dose, with semi-rush regimes showing poor efficacy and more frequent reactions. The starting dose of 2 mg of protein was developed from dose-ranging work in our pilot studies.[21,22]

Prognostic factors were explored using logistic regression revealing baseline covariates related to a change in log-transformed NOAEL threshold post OIT. Treatment with OIT was not surprisingly the most influential factor. Age, family history and peanut-specific serum IgE were associated with a significant decrease in log-transformed NOAEL after 24 weeks of OIT, implying that these might predict a less favourable outcome.

Not surprisingly, there were many more allergic events during active treatment than during periods of peanut avoidance. The safety data in this trial show that most adverse events were mild and due to gastrointestinal symptoms (e.g. oral itching), as expected from the route of administration. Skin reactions were uncommon (urticaria after 0.16% of doses). Reactions involving wheezing occurred after 0.41% of doses or approximately one-fifth of participants. Although wheezing could be taken as a sign of a more severe reaction, in all but one participant it was mild and responded to standard doses of inhaled bronchodilator drugs. A single subject self-administered epinephrine at home with good results on two occasions for wheezing after his peanut OIT doses; thus, he was withdrawn from the study. No one experienced hypotension.

There is no disease-modifying treatment for peanut allergy, meaning that families have to rely on avoidance practice and reduced QoL, leading to accidental reactions and carrying emergency medication. Peanut OIT is a promising novel treatment that shows good efficacy and an acceptable side effect profile. As this is the first study of its type, the findings are relevant to the population studied, but safety and efficacy will require confirmation using other patient subgroups and phase 3 trials. Because of the significant risks involved, OIT should be restricted to specialist centres.

Conclusions

We performed the first study with a design and size appropriate to derive an accurate estimate of the effect size of the treatment. We have demonstrated good efficacy and safety for peanut OIT, with a large effect size. Importantly, we studied a representative population of peanut allergic children, without excluding children with a history of severe reactions. The implication is that this treatment will be suitable for children with any severity of peanut allergy.

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Peanut allergy is a highly homogeneous disease, with well-validated diagnostic tests and minimal variation in phenotypic characteristics. Future phase 2 and 3 confirmatory trials are desirable, including other doses but, given the highly homogeneous nature of the illness and the strong effect size observed in this study, such trials are unlikely to require large numbers of patients. This cohort of patients, followed to 6 months, requires longer-term follow-up to determine the long-term adverse event profile and frequency of administration required to continue a state of desensitisation. Indicators of tolerance to peanut should be studied.

Research recommendations

- Confirmatory phase 3 trials for peanut OIT using this regime.
- Studies of long-term tolerance beyond 6 months' treatment.
- Application of this method to other allergens such as tree nuts and other foods.

Acknowledgements

The National Institute for Health Research/Wellcome Trust Cambridge Clinical Research Facility on the Cambridge Biomedical Campus supported the research. We are also grateful to Gareth Jones, Head of The Perse Prep School in Cambridge, and the Perse Prep Parents for fundraising to buy equipment used during this work. We would like to thank Clare Mills at the Institute for Food research, Norwich, UK for manufacturing the challenge meals. We thank our Data Monitoring Committee [Dr Nicola Brathwaite (chairperson), Dr Ken Ong and Dr Carlo Acerini] and members of our Trial Steering Committee [Dr Robert Boyle (chairperson), Dr Chris Palmer and Mrs Hazel Gowland]. We are extremely grateful to the Anaphylaxis Campaign who reviewed the study protocol, funding application and patient information sheets, and provided a patient representative (Hazel Gowland) as a member of the Trial Steering Committee. Finally, we thank our participants.

Contributions of authors

Katherine Anagnostou performed immunotherapy challenges and interpretation, and drafted, appraised and approved the submitted version.

Sabita Islam performed blinding of challenges and all laboratory work; prepared immunotherapy doses, and drafted, appraised and approved the submitted version.

Yvonne King performed recruitment, immunotherapy challenges and interpretation, and drafted, appraised and approved the submitted version.

Loraine Foley prepared immunotherapy doses, and drafted, appraised and approved the submitted version.

Laura Pasea designed and performed statistical analysis, and drafted, appraised and approved the submitted version.

Chris Palmer determined trial design, and drafted, appraised and approved the submitted version.

Simon Bond was responsible for oversight and design of statistical analysis; and drafted, appraised and approved the submitted version.

Pamela Ewan contributed to study design, and drafted, appraised and approved the submitted version.

Andrew Clark conceived the study, defined the primary objective, performed immunotherapy challenges, and drafted, appraised and approved the submitted version.

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References

1. Venter C, Arshad H, Grundy J, Pereira B, Clayton B, Voigt K, *et al.* Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK. *Allergy* 2010;**65**:103–8. http://dx.doi.org/10.1111/j.1398-9995.2009.02176.x
2. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol* 2003;**112**:1203–7. http://dx.doi.org/10.1016/S0091-6749(03)02026-8
3. Kanny G, Moneret-Vautrin DA, Flabbee J, Beaudouin E, Morisset M, Thevenin F. Population study of food allergy in France. *J Allergy Clin Immunol* 2001;**108**:133–40. http://dx.doi.org/10.1067/mai.2001.116427
4. Ho MH, Wong WH, Heine RG, Hosking CS, Hill DJ, Allen KJ. Early clinical predictors of remission of peanut allergy in children. *J Allergy Clin Immunol* 2008;**121**:731–6. http://dx.doi.org/10.1016/j.jaci.2007.11.024
5. Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999–2006. *J Allergy Clin Immunol* 2007;**119**:1018–19. http://dx.doi.org/10.1016/j.jaci.2007.01.021
6. Primeau MN, Kagan R, Joseph L, Lim H, Dufresne C, Duffy C, *et al.* The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. *Clin Exp Allergy* 2000;**30**:1135–43. http://dx.doi.org/10.1046/j.1365-2222.2000.00889.x
7. Avery NJ, King RM, Knight S, Hourihane JO. Assessment of quality of life in children with peanut allergy. *Ped Allergy Immunol* 2003;**14**:378–82. http://dx.doi.org/10.1034/j.1399-3038.2003.00072.x
8. Kapoor S, Roberts G, Bynoe Y, Gaughan M, Habibi P, Lack G. Influence of a multidisciplinary paediatric allergy clinic on parental knowledge and rate of subsequent allergic reactions. *Allergy* 2004;**59**:185–91. http://dx.doi.org/10.1046/j.1398-9995.2003.00365.x
9. Clark AT, Ewan PW. Good prognosis, clinical features and circumstances of peanut and tree nut reactions in children treated by a specialist allergy centre. *J Allergy Clin Immunol* 2008;**122**:286–9. http://dx.doi.org/10.1016/j.jaci.2008.05.015
10. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, *et al.* Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999 **12**;341:468–75. http://dx.doi.org/10.1056/NEJM199908123410702
11. Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J Allergy Clin Immunol* 1997;**99**:744–51. http://dx.doi.org/10.1016/S0091-6749(97)80006-1
12. Meglio P, Bartone E, Plantamura F, Arabito E, Giampietro P. A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. *Allergy* 2004;**59**:980–7. http://dx.doi.org/10.1111/j.1398-9995.2004.00542.x
13. Buchanan A, Green T, Jones S, Scurlock A, Christie L, Althage K, *et al.* Egg oral immunotherapy in non-anaphylactic children with egg allergy. *J Allergy Clin Immunol* 2007;**119**:199–205. http://dx.doi.org/10.1016/j.jaci.2006.09.016

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14. Staden U, Rolinck-Werninghaus C, Brewe F, Wahn U, Niggemann B, Beyer K. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. *Allergy* 2007;**62**:1261–9. http://dx.doi.org/10.1111/j.1398-9995.2007.01501.x

15. Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, *et al.* Specific oral tolerance induction in children with very severe cow's milk–induced reactions. *J Allergy Clin Immunol* 2008;**121**:343–7. http://dx.doi.org/10.1016/j.jaci.2007.10.029

16. House of Lords Science and Technology Committee 6th Report of Session 2007.

17. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev* 2007;**24**:CD001936.

18. Boyle RJ, Elremeli M, Hockenhull J, Cherry MG, Bulsara MK, Daniels M, *et al.* Venom immunotherapy for preventing allergic reactions to insect stings. *Cochrane Database Syst Rev* 2012;**10**:CD008838. http://dx.doi.org/10.1002/14651858.CD008838.pub2

19. Wilson DR, Torres LI, Durham SR. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2003;**2**:CD002893.

20. Enrique E, Pineda F, Malek T, Bartra J, Basagaña M, Tella R, *et al.* Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. *J Allergy Clin Immunol* 2005;**116**:1073–9. http://dx.doi.org/10.1016/j.jaci.2005.08.027

21. Clark AT, Islam S, King Y, Deighton J, Anagnostou K, Ewan P. Successful oral tolerance induction in severe peanut allergy. *Allergy* 2009;**64**:1218–20. http://dx.doi.org/10.1111/j.1398-9995.2009.01982.x

22. Anagnostou K, Clark A, King Y, Islam S, Deighton J, Ewan P. Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. *Clin Exp Allergy* 2011;**41**:1273–81. http://dx.doi.org/10.1111/j.1365-2222.2011.03699.x

23. Nurmatov U, Venderbosch I, Devereux G, Simons FE, Sheikh A. Allergen-specific oral immunotherapy for peanut allergy. *Cochrane Database Syst Rev* 2012;**9**:CD009014. http://dx.doi.org/10.1002/14651858.CD009014.pub2

24. Factor JM, Mendelson L, Lee J, Nouman G, Lester MR. Effect of oral immunotherapy to peanut on food-specific quality of life. *Ann Allergy Asthma Immunol* 2012;**109**:348–52. http://dx.doi.org/10.1016/j.anai.2012.08.015

25. Rimbaud L, Heraud F, La Vieille S, Leblanc J, Crepet A. Quantitative risk assessment relating to adventitious presence of allergens in food: a probabilistic model applied to peanut in chocolate. *Risk Anal* 2010;**30**:7–19. http://dx.doi.org/10.1111/j.1539-6924.2009.01322.x

26. Barnett J, Leftwich K, Muncer K, Grimshaw R, Shepherd M, Raats MM, *et al.* How do peanut and nut-allergic consumers use information on the packaging to avoid allergens? *Allergy* 2011;**66**:969–78. http://dx.doi.org/10.1111/j.1398-9995.2011.02563.x

27. Leitch S, Walker MJ, Davey R. Food allergy: gambling your life on a take-away meal. *Int J Environ Health Res* 2005;**15**:79–87. http://dx.doi.org/10.1080/09603120500062052

Appendix 1 Statistical analysis plan

Statistical Analysis Plan

TRIAL FULL TITLE	Study of Tolerance to Oral Peanut: Determining the efficacy of oral immunotherapy in peanut allergy
SAP VERSION	1.0
ISRCTN NUMBER	62416244
SAP VERSION DATE	17-May-2013
TRIAL STATISTICIAN	Laura Pasea
TRIAL CHIEF INVESTIGATOR	Dr Andrew Clark
SAP AUTHOR	Laura Pasea

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2 Abbreviations and Definitions

AE	Adverse event
AUC	Area under curve
CRF	Case report form
DBPCFC	Double blind placebo controlled food challenge
IgE	Immunoglobulin E
LOAEL	Lowest observed adverse effect level
NOAEL	No observed adverse effect level
OIT	Oral Immunotherapy
QoL	Quality of life
SAP	Statistical analysis plan
SPT	Skin prick test
SUSAR	Suspected unexpected serious adverse reaction
WAO	World Allergy Organisation

3 Introduction

The aim is to develop a new treatment for a common, serious and currently untreatable condition. We propose a definitive study of the efficacy of peanut oral immunotherapy (OIT) as a treatment for peanut allergy. Immunological mechanisms will be studied. We have conducted a pilot which demonstrated proof of concept; the present study includes larger numbers and a control group, with power to detect outcome at the 0.05 significance level. There will be two inter-dependent work packages. Package 1 will be a randomized comparison of intervention versus the current best management. Package 2 will confirm efficacy in the waiting list group when subsequently treated and allow an estimate of the overall success rate to within 10%.

4 Study Objectives and Endpoints

4.1 Study Objectives

The overarching objective is to determine efficacy of oral immunotherapy in peanut allergy. We will determine whether the planned intervention is successful in the intervention group compared to control (package 1), and whether it is successful when offered to the control group (package 2). Other objectives include identification of immunological changes over time, and improvement in quality of life scores.

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4.2 Endpoints

4.2.1 Primary Endpoint

Incidence of desensitisation to peanut at the end of six months.

4.2.2 Secondary Endpoints

- Incidence of desensitisation to peanut in waiting list patients after receiving the active intervention (end of phase 2)
- Incidence of response to treatment(end of phase 1 (intervention group) and end of phase 2 (waiting list group))
- Fold and absolute increase in threshold (maximum tolerated peanut protein (mg))
- Change in quality of life (QoL) scores from baseline to the end of phase 1
- Change in QoL scores before and after immunotherapy (Baseline to phase 1(intervention group) or phase 1 to phase 2 (waiting list group).
- Change in immunological outcomes (Basophil histamine release, Peanut IgE, Total IgE, and skin prick test diameter (SPT))
- Change in severity of symptoms (World Allergy Organisation (WAO) score) from baseline to the end of phase 1

4.3 Derived variables

- Desensitisation to peanut – able to ingest 1400mg peanut protein without reacting
- Response to treatment – able to ingest 800mg protein without reacting, after immunotherapy

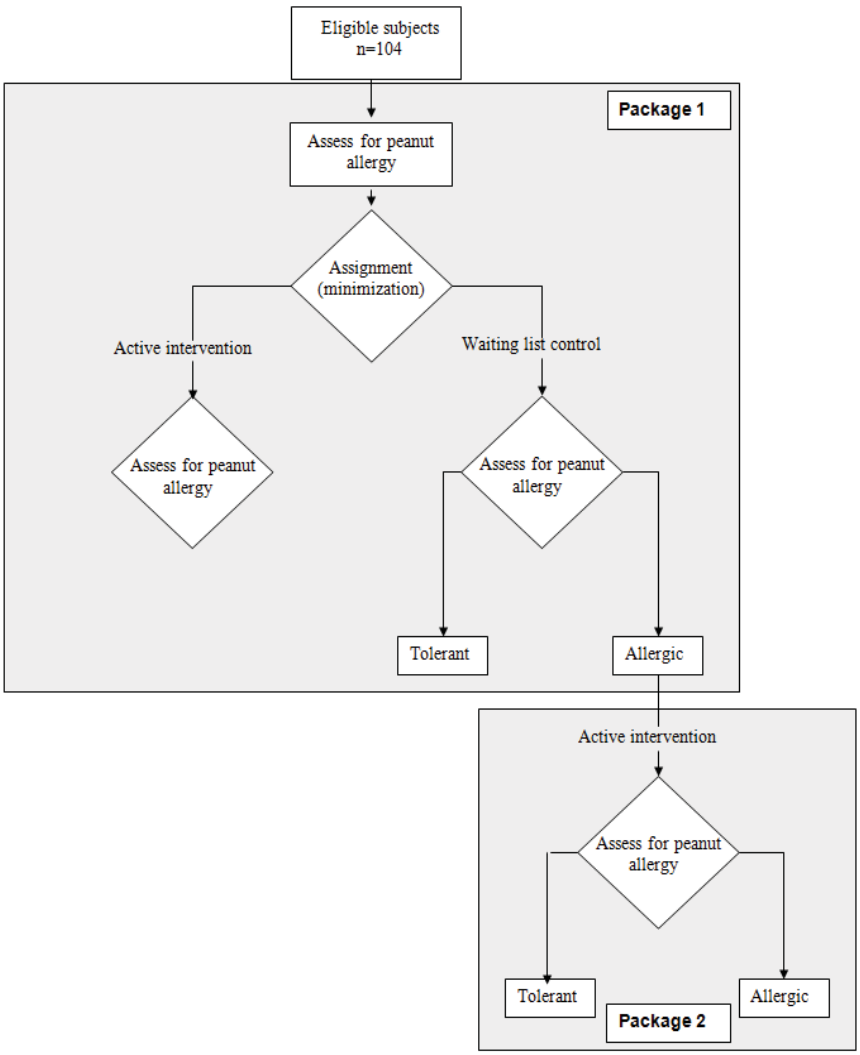
5 Study Methods

5.1 General Study Design and Plan

Single centre, randomized controlled trial of a novel active intervention (peanut oral immunotherapy) versus the status quo (peanut avoidance) in patients with peanut allergy. Two phase (package) design.

- Phase 1: Subjects randomly allocated (using minimisation methods – 80% chance of being assigned to imbalance minimising arm) to active intervention arm or waiting list arm. After 6 months all patients will be assessed for peanut allergy.
- Phase 2: Participants in waiting list arm still allergic to peanut at the end of phase 1 will be given the active intervention.

The figure below shows the study design.



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5.2 Inclusion-Exclusion Criteria and General Study Population

5.2.1 Inclusion Criteria

1. Subjects aged between 7 and 15 years of age

2. Subjects with peanut allergy confirmed by a clinical history of a typical rapid onset immediate type hypersensitivity reaction to definite peanut ingestion.

3. Positive skin prick test to peanut (extract ALK-Abello, Hørsholm, Denmark) defined by wheal ≥3mm in the presence of a negative control and positive histamine control.

4. Positive double blind placebo controlled food challenge performed according to international consensus guidelines

5. Informed consent obtained from parent / guardian or participant, as appropriate.

5.2.2 Exclusion Criteria

1. Clinically significant chronic illness, except for eczema, rhinitis or asthma.

2. Suspected or diagnosed allergy to peanut protein in care provider or current household member.

3. Unwillingness or inability to comply with study requirements and procedures.

5.3 Randomisation and Blinding

Subjects were allocated using minimisation to avoid imbalance of confounding factors between groups, with a random element using a weighting probability of 0.8 – i.e. patients were allocated to the group which would provide optimal balance with 80% probability.

The minimising variables were age (7-<12, 12-15), sex, allergy severity (mild, moderate, severe, never eaten), asthma, serum peanut IgE (≤28kU/l, >28kU/l), challenge threshold (>5mg, 50-200mg, >200mg) and other current food allergies.

Patients are not blinded to their randomised groups. However the primary outcome will be assessed using a double blind placebo controlled food challenge (DBPCFC). On the challenge neither the investigator, nurse not the participant will know whether the participants dose is peanut or placebo.

5.4 Study Variables

The visit schedule is shown below:

		Phase 1										*Phase 2*									
Week	0	2	4	6	8	10	12	14	16	18	24	*26**	*28**	*30**	*32**	*34**	*36**	*38**	*40**	*42**	*48**
Active immunotherapy visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	–	–	–	–	–	–	–	–	–	–
Waiting list visit*	**(Baseline)**	–	–	–	–	–	–	–	–	–	**2**	***3****	***4****	***5****	***6****	***7****	***8****	***9****	***10****	***11****	***12****
Demographics	x																				
Other allergies	x																				
WAO score (historical)	x																				
DBPCFC (NOAEL, LOAEL, WAO score)	x										x										*x*
Peanut SPT	x										x										*x*
Other nut SPT	x										x										*x*
Peanut specific IgE	x										x										*x*
Total IgE	x										x										*x*
Basophil histamine release	x										x										*x*
Tryptase	x																				
QoL questionnaire	x										x										*x*
OIT updose*		x	x	x	x	x	x	x	x	x		*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	

**Only waiting list patients who are not desensitised to peanut after 24 weeks undergo immunotherapy from week 26 to 48*

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DOI: 10.3310/eme01040 EFFICACY AND MECHANISM EVALUATION 2014 VOL. 1 NO. 4

5.4.1 Important Variable Definitions

- Peanut threshold (mg) – The no observed adverse effect level (NOAEL) – the highest cumulative dose of peanut that does not cause a reaction in a DBPCFC
- The lowest observed adverse effect level (LOAEL) is the lowest cumulative dose that causes a reaction (mg) in a DBPCFC
- Peanut IgE (kU/l 0 –1000) – Specific allergy antibody against peanut protein. Higher titres of IgE antibodies indicates higher probability of clinical allergy
- Basophil histamine release – Donor basophils stimulated in vitro by peanut extract at a range of concentrations. Basophil stimulation is detected by the mean fluorescent intensity of a cell surface marker (CD63). Area under the curve (AUC) of mean fluorescent intensity of CD63 (arbitrary units) and of the %CD63 positive cells against dose of peanut protein in milligrams.
- Tryptase (ng/ml) – a marker of background mast cell activation
- SPT diameter (mm 0–20) – A small amount of purified peanut is pricked on to the skin, and the diameter of the resulting wheal is recorded.

6 Sample Size

Based on Fisher's exact test with 90% power and 5% significance (two-sided) a sample size of 49 in each group is sufficient to detect proportions of participants with desensitisation to peanut of 64% and 30% in the intervention and control group respectively. Allowing for 5% drop out increases the sample size to 52 participants in each group and 104 subjects overall.

Based on the above we would expect 35 waiting list group patients to proceed to the active intervention in phase 2. To confirm efficacy of immunotherapy the success rate of all participants (intervention and phase 2 waiting list) should be within 10% of the success rate seen in intervention participants alone in phase 1.

7 General Considerations

7.1 Analysis Populations

7.1.1 Full Analysis Population

All subjects who were randomised and participated in at least one post-baseline assessment

7.1.2 Per-Protocol Population

The criteria for per-protocol analysis of the outcome of peanut challenge at the end of immunotherapy will consist of: desensitisation and continuation of immunotherapy up to the maintenance dose of 800mg protein.

7.1.3 Safety Population

All subjects who received any study treatment (including control) and are confirmed as providing complete follow-up regarding adverse event information.

7.2 Covariates and Subgroups

The covariates that are recorded at baseline are:

- Demographics (age, sex, weight, family history of allergy)
- Other allergic diseases (asthma, eczema, rhinitis)
- Sensitisation to tree nuts
- Severity of worst reaction before enrolment (WAO score)
- DBPCFC – WAO score, LOAEL, NOAEL
- Peanut SPT wheal diameter
- Other nut SPT wheal diameter
- Peanut specific IgE
- Total IgE
- Basophil AUC of CD63MFI against peanut protein concentration
- Basophil AUC of %CD63 positive cells against peanut protein concentration
- Tryptase
- QoL score

7.3 Missing Data

The frequency of missing data for all variables used in analysis will be summarised in a table.

To avoid using only complete case data for regression analysis when baseline covariates are missing, the 'missing indicator' method will be used. That is, we will include a binary indicator variable for the missingness of each covariate in regression models and we will 'fill in' all missing baseline covariate values with a fixed arbitrary number, say 0, to avoid software programs automatically omitting non complete cases from analysis.

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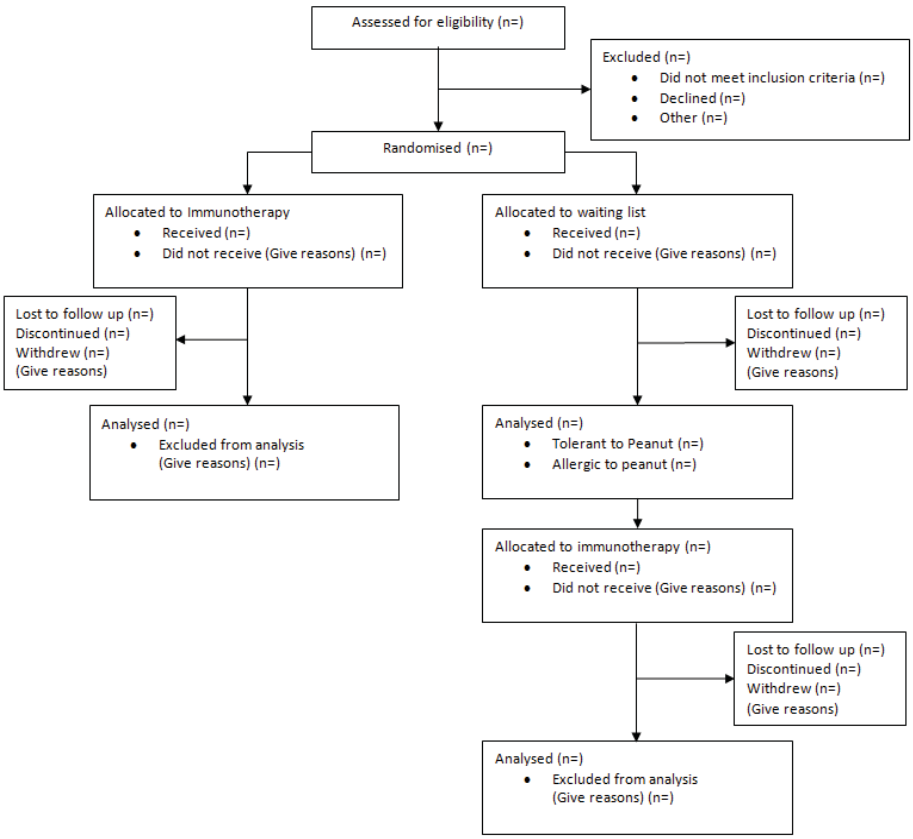
8 Summary of Study Data

Summaries of the study data will be presented as tables with separate columns for randomised group. All randomised patients will be included regardless of those who may not have completed the study. A table of baseline characteristics of patients will be included with a row for each covariate described in section 7.2.

Continuous variables will be summarised using means and standard deviations (or median and interquartile range if more appropriate) and categorical variables will be summarised using frequencies and percentages. The extent of missing data will be reported using annotations for the table and graphically using plots

8.1 Subject Disposition

Below is a blank example of a CONSORT diagram to include in the final report



8.2 Protocol Deviations

The summary statistics will be produced in accordance with section 8.

8.3 Demographic and Baseline Variables

The summary statistics will be produced in accordance with section 8.

8.4 Concurrent Illnesses and Medical Conditions

The summary statistics will be produced in accordance with section 8.

8.5 Prior and Concurrent Medications

The summary statistics will be produced in accordance with section 8.

8.6 Treatment Compliance

The summary statistics will be produced in accordance with section 8.

9 Efficacy Analyses

All statistical tests described in this section use a 2-sided 5% significance level. Non-parametric tests may be used instead of parametric tests if the assumptions are not appropriate. Sensible transformations of data may be used to allow the data to fulfil assumptions.

Plots (e.g. histograms, residuals) will be used to assess the assumptions and fits of regression models.

Tests will be accompanied with a measure of effect size (e.g. difference, odds ratio etc.) and a 95% confidence interval.

All analyses will be performed on an intention to treat (ITT) basis.

9.1 Primary Efficacy Analysis

Fisher's exact test will be used to compare the incidence with desensitisation to peanut after 6 months between the intervention and waiting list group.

Multiple logistic regression will be used to adjust the odds of desensitisation for baseline characteristics described in section 7.2.

9.2 Secondary Efficacy Analyses

- The incidence of desensitisation to peanut in the waiting list group after receiving the active intervention (end of phase 2) will be reported and compared with the incidence of desensitisation to peanut in the intervention group (end of phase 1) using Fishers exact test.

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- Incidence of response to treatment (i.e. desensitisation to the maintenance immunotherapy dose of 800mg) will be compared between the intervention and waiting list groups using Fishers exact test. Multiple logistic regression will be used to adjust the odds ratio of response to treatment for baseline characteristics described in section 7.2.
- The absolute and fold change in threshold will be compared within and between groups using paired and independent sample t-tests respectively. This may be extended to a linear regression adjusting for baseline covariates (section 7.2)
- QoL scores at the end of phase 1 will be compared between groups using a Mann Whitney U test.
- Change in QoL scores before and after intervention in both groups (Intervention: Phase1 – baseline; Waiting list: Phase 2– Phase 1) will be investigated within groups using a Wilcoxon sign rank test and then between groups using a Mann –Whitney U test.
- Change in peanut IgE from baseline to end of phase 1 will be compared between groups using a Mann–Whitney U test.
- Change in AUC (CD63MFI and %CD63 positive cells) of Basophil histamine release from baseline to end of phase 1 will be compared between groups using a Mann–Whitney U test
- Change in SPT results (peanut and other nuts) from baseline to end of phase 1 will be compared between groups using a Mann– Whitney U test
- Change in WAO score from baseline to end of phase 1 will be compared between groups using a Mann – Whitney U test

10 Safety Analyses

10.1 Extent of Exposure

The summary statistics will be produced in accordance with section 8.

10.2 Adverse Events

A table summarising the incidence of the following adverse events per peanut dose will be produced: mouth itching, abdominal pain, nausea, vomiting, diarrhoea, urticaria, angioedema, erythema, rhinitis, wheezing, laryngeal oedema, cardiovascular collapse, fainting, admission to intensive care unit (ITU), serious

adverse reaction, suspected unexpected serious adverse event (SUSAR), use of nebulised beta 2 agonist and use of intramuscular adrenaline.

10.3 Deaths, Serious Adverse Events and other Significant Adverse Events

The summary statistics will be produced in accordance with section 8.

11 Figures

The figures that will be produced include, but are not limited to:

Box plots:

- Peanut threshold at baseline and end of phase 1 (and phase 2 for waiting list group) by group
- Serum peanut specific IgE (log) at baseline and end of phase 1(and phase 2 for waiting list group) by group
- SPT at baseline and end of phase 1 (and phase 2 for waiting list group) by group

Plot of basophil histamine release CD63MFI and %CD63 positive cells against peanut protein concentration (baseline and phase 1 (and phase 2 for waiting list group)) by group

Plot of probability of desensitisation to peanut according to logistic regression model with a continuous independent covariate on the x-axis (possibly baseline peanut IgE, threshold or age), separate lines for treatment groups and appropriate constants chosen for all other covariates.

Plot of probability of response to treatment to peanut according to logistic regression model with a continuous independent covariate on the x-axis (possibly baseline peanut IgE, threshold, or age), separate lines for treatment groups and appropriate constants chosen for all other covariates.

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12 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

13 Listing of Tables and Figures

A summary of the tables and figures to be included in the final report are given in the tables in this section

13.1Tables

Table Title	No.	Population	Endpoint	Time Points or how to conglomerate	Covariates or Subgroups	Summary Statistics	Formal Analysis
Summary of patient characteristics	1.1	Full analysis	Age	Baseline	Treatment	n, mean, SD	NA
			Sex			n, %	
			Weight			n, mean, SD	
			Asthma			n, %	
			Eczema			n, %	
			Rhinitis			n, %	
			Other food allergy			n, %	
			Tryptase			n, mean, SD	
			WAO score (historical)			n, median, range	
			Sensitisation to tree nuts			n, %	
			QoL score			n, median, range	
			Peanut specific IgE			n, median, range	
			Total IgE			n, median, range	
			Peanut SPT wheal diameter			n, mean, SD	
			Other nut SPT wheal diameter			n, mean, SD	
			Family history of peanut allergy			n, %	
			DBPCFC total peanut protein consumed			n, median, range	
			DBPCFC peanut threshold (NOAEL)			n, mean, SD	
			DBPCFC WAO score			n, median, range	
			DBPCFC LOAEL			n, mean, SD	

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DOI: 10.3310/eme01040 EFFICACY AND MECHANISM EVALUATION 2014 VOL. 1 NO. 4

			Basophil AUC of CD63MFI against peanut protein concentration			n, mean , SD	
			Basophil AUC of %CD63 positive cells against peanut protein concentration			n, mean, SD	
Desensitisation to peanut after 6 months	2.1	Full analysis	Allergy desensitised or undesensitised	6 months	Treatment	n, %, odds ratio, 95% CI	Fishers exact test
Logistic regression – adjusted odds of desensitised peanut allergy	2.2	Full analysis	Allergy desensitised or undesensitised	6 months	Treatment Age Sex Asthma Eczema Rhinitis Weight Sensitisation to tree nuts Peanut specific IgE Peanut SPT wheal diameter Basophil AUC of CD63MFI against peanut protein concentration QoL score Family history of allergy Baseline NOAEL	odds ratios, 95% CI	Logistic regression
Comparison of change in threshold between treatment groups	2.3	Full analysis	Threshold	Baseline and 6 months	Treatment	mean, SD, absolute and fold difference, 95% CI	t-test

Comparison of change in quality of life score between treatment groups	2.4	Full analysis	Quality of life score	Baseline and 6 months	Treatment	median, range, difference, 95% CI	Mann–Whitney U test
Comparison of change in quality of life score before and after intervention within and between treatment groups	2.5	Full analysis	Quality of life score	Baseline and 6 months (immunotherapy) 6 and 12 months (Waiting list)	Treatment	median, range, difference, 95% CI	Wilcoxon sign rank test Mann–Whitney U test
Comparison of change in peanut immunological outcomes between treatment groups	2.6	Full analysis	Peanut IgE Total IgE Peanut SPT Other nut SPT Basophil histamine release CD63MFI (AUC) Basophil histamine release %CD63 positive cells (AUC)	Baseline and 6 months	Treatment	median, range, difference, 95% CI	Mann–Whitney U tests
Comparison of change in WAO score between treatment groups	2.7	Full analysis	WAO score	Baseline and 6 months	Treatment	median, range, difference, 95% CI	Mann–Whitney U tests
Predictors of treatment response	2.8	All patients who underwent immunotherapy	Response to immunotherapy	6 months (or 12 months for Waiting list group)	Treatment Age Sex Asthma Eczema Rhinitis Weight	odds ratios, 95% CI	Logistic regression

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					Sensitisation to tree nuts Peanut specific IgE Peanut SPT wheal diameter Basophil AUC of CD63MFI against peanut protein concentration QoL score Family history of allergy peanut Baseline NOAEL		
Adverse events per dose	2.9	Safety population	Mouth itching Abdominal pain Nausea Vomiting Diarrhoea Urticaria Angioedema Erythema Rhinitis Wheezing Laryngeal oedema Cardiovascular collapse Fainting Admission to ITU Serious adverse reaction SUSAR	End of study	Treatment	n, %	NA

	Use of nebulised beta 2 agonist Use of intramuscular adrenaline	

13.2 Figures

Title	No.	Population	Type of graph	Horizontal Variables	Vertical Variables	Groupings
CONSORT diagram	1.1		Flow chart			
Peanut Threshold	2.1	Full analysis	Box plot	Peanut threshold (NOAEL) (mg)	NA	Treatment and time (Baseline, end of phase 1 and end of phase 2)
Peanut IgE	2.2	Full analysis	Box plot	Peanut IgE (kU/L); log	NA	Treatment and time (Baseline, end of phase 1 and end of phase 2)
Skin Prick Test	2.3	Full analysis	Box plot	Peanut SPT diameter (mm)	NA	Treatment and time (Baseline end of phase 1 and end of phase 2)
Basophil histamine release	2.4	Full analysis	Line	Peanut concentration	mean fluorescent intensity of CD63	Treatment and time (Baseline, end of phase 1 and end of phase 2)
Basophil histamine release	2.5	Full analysis	Line	Peanut concentration	%CD63 positive cells	Treatment and time (Baseline, end of phase 1 and end of phase 2)
Probability of desensitisation	2.6	Full analysis	Line	Baseline NOAEL	Probability	Treatment
Probability of treatment response	2.7	Full analysis	Line	Baseline NOAEL	Probability	Treatment

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DOI: 10.3310/eme01040

Appendix 2 Food allergy quality-of-life questionnaire – parent form (0–12 years)

FAQLQ-PF

Food Allergy Quality of Life Questionnaire – Parent Form (0-12 years)

Please return the completed questionnaire to:

Dr Andrew Clark
WTCRF
01223 762 603

This questionnaire is part of the EuroPrevall project, a European multidisciplinary study of the prevalence, costs and basis of food allergy in Europe.

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Food Allergy Quality of Life Questionnaire-Parent Form (FAQoL-PF) Children aged 0-12 years

Instructions to Parents

- The following are scenarios that parents have told us affect children's quality of life because of food allergy.

- Please indicate how much of an impact each scenario has on **your child's quality of life** by placing a tick or an x in one of the boxes numbered 0-6.

All information given is completely confidential.

This questionnaire will only be identified by a code number.

Response Options

0 = not at all

1= a little bit

2 = slightly

3 = moderately

4 = quite a bit

5 = very much

6 = extremely

There are 4 sections to this questionnaire : A, B, C, and D.

- If your child is aged 0 to 3 years, please answer Section A
- If your child is aged 4 to 6 years, please answer Section A and Section B
- If your child is aged 7 years and over, please answer Section A, Section B, and Section C.

Section D : For all age groups.

SECTION A : For all age groups

	Because of food allergy, my child feels……	Not at all 0	1	2	3	4	5	Extremely 6
1	Worried about food	☐	☐	☐	☐	☐	☐	☐
2	Different from other children	☐	☐	☐	☐	☐	☐	☐
3	Frustrated by dietary restrictions	☐	☐	☐	☐	☐	☐	☐
4	Afraid to try unfamiliar foods	☐	☐	☐	☐	☐	☐	☐
5	Concerned that I am worried that he/she will have a reaction to food	☐	☐	☐	☐	☐	☐	☐

	Because of food allergy, my child……	Not at all 0	1	2	3	4	5	Extremely 6
6	Experiences physical distress	☐	☐	☐	☐	☐	☐	☐
7	Experiences emotional distress	☐	☐	☐	☐	☐	☐	☐
8	Has a lack of variety in his her diet	☐	☐	☐	☐	☐	☐	☐

	Because of food allergy, my child has been negatively affected by…….	Not at all 0	1	2	3	4	5	Extremely 6
9	Receiving more attention more attention than other children of his/her age	☐	☐	☐	☐	☐	☐	☐
10	Having to grow up more quickly than other children of his/her age	☐	☐	☐	☐	☐	☐	☐
11	His/her environment being more restricted than other children of his/her age	☐	☐	☐	☐	☐	☐	☐

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	Not at all → Extremely						
Because of food allergy, my child's social environment is restricted because of limitations on……..	**0**	**1**	**2**	**3**	**4**	**5**	**6**
12 Restaurants we can safely go to as a family	☐	☐	☐	☐	☐	☐	☐
13 Holiday destinations we can safely go to as a family	☐	☐	☐	☐	☐	☐	☐

SECTION B : For children aged 4 to 12 years.

	Not at all → Extremely						
Because of food allergy, my child's ability to take part has been limited……..	**0**	**1**	**2**	**3**	**4**	**5**	**6**
14 In social activities in other people's houses (*sleepovers, parties, playtime*)	☐	☐	☐	☐	☐	☐	☐

	Not at all → Extremely						
Because of food allergy, my child's ability to take part has been limited……..	**0**	**1**	**2**	**3**	**4**	**5**	**6**
15 In preschool/school events involving food (*class parties/treats/lunchtime*)	☐	☐	☐	☐	☐	☐	☐

	Not at all → Extremely						
Because of food allergy, my child feels……	**0**	**1**	**2**	**3**	**4**	**5**	**6**
16 Worried when going to unfamiliar places	☐	☐	☐	☐	☐	☐	☐
17 Concerned that he/she must always be cautious about food	☐	☐	☐	☐	☐	☐	☐
18 'Left out' in activities involving food	☐	☐	☐	☐	☐	☐	☐
19 Upset that family social outings have been restricted by the need to plan ahead.	☐	☐	☐	☐	☐	☐	☐
20 Concerned about accidentally eating an ingredient to which he/she is allergic	☐	☐	☐	☐	☐	☐	☐
21 Worried when eating with unfamiliar adults/children	☐	☐	☐	☐	☐	☐	☐
22 Frustrated by social restrictions	☐	☐	☐	☐	☐	☐	☐

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	Not at all						Extremely
	→						
Because of food allergy, my child……	**0**	**1**	**2**	**3**	**4**	**5**	**6**
23 Is more worried in general than other children of his/her age	☐	☐	☐	☐	☐	☐	☐
24 Is more cautious in general than other children of his/her age	☐	☐	☐	☐	☐	☐	☐
25 Is not as confident as other children of his/her age in social situations	☐	☐	☐	☐	☐	☐	☐
26 Wishes his/her food allergy would go away	☐	☐	☐	☐	☐	☐	☐

SECTION C : For children aged 7 to 12 years

	Not at all → Extremely						
Because of food allergy, my child feels……	**0**	**1**	**2**	**3**	**4**	**5**	**6**
27 Worried about his/her future(opportunities, relationships)	☐	☐	☐	☐	☐	☐	☐
28 Many people do not understand the serious nature of food allergy	☐	☐	☐	☐	☐	☐	☐
29 Concerned by poor labelling on food products	☐	☐	☐	☐	☐	☐	☐
30 Food allergy limits his/her life in general	☐	☐	☐	☐	☐	☐	☐

Thank you for completing the questionnaire. I would be grateful if you would now answer some questions on your child's food allergy.

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SECTION D: For all age groups

Part 1 : My child's food allergy.

Q1. What sex are you ? Male ☐ Female ☐

Q2. What sex is your child? Male ☐ Female ☐

Q3. What age is the child with food allergy? Years _____ Months _____

☐ ☐

Q4. What type of food(s) is your child allergic to? *Tick where applicable.*

Peanut	☐	Nut	☐	Milk	☐	Egg	☐
Wheat	☐	Soya	☐	Sesame	☐	Fish	☐
Shellfish	☐	Fruits	☐	Vegetables	☐	Other	☐

Please specify '**Other**'

Q5. After ingesting which food, did your child have his/her most severe reaction?

Q6. Has your child had an anaphylactic reaction? Yes ☐ No ☐

Q7. If 'Yes', how recent was the reaction? *Tick where applicable.*

Very recently ☐

6 to 12 months ago ☐

Approximately 1 yr ago ☐

Approximately 2yrs ago ☐

More than 2 years ago ☐

Q8(a). Has your child been issued with an anapen/epipen? Yes ☐ No ☐

Q8(b). Does the provision of an anapen/epipen cause?

(1) Reassurance ... For you ☐ For your child ☐

(2) Anxiety ... For you ☐ For your child ☐

Q9. Who diagnosed your child with food allergy? *Tick where applicable*

.

G.P. ☐

Consultant Allergist ☐

Consultant Paediatrician ☐

Dermatologist ☐

Dietician ☐

Alternative Practitioner ☐

Q10. What Symptoms does your child have? *Tick where applicable.*

Itching in the mouth ☐	Throat tightening ☐	Urticaria/Hives ☐
Itching in the throat ☐	Difficulty swallowing ☐	Skin swelling ☐
Itching in the ears ☐	Hoarseness ☐	Nausea ☐
Itching of the lips ☐	Difficulty breathing ☐	Abdominal cramps ☐
Runny nose ☐	Shortness of breath ☐	Vomiting ☐
Stuffy nose ☐	Wheeze ☐	Diarrhoea ☐
Sneeze ☐	Cough ☐	Light-headedness ☐
Itchy eyes ☐	Itching of the skin ☐	Palpitations ☐
Tears ☐	Redness of the skin ☐	Inability to stand ☐
Red eyes ☐	Increase eczema ☐	Loss of consciousness ☐

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Q11. How often does your child meet another child with food allergy?

Never ☐

Rarely ☐

Sometimes ☐

Often ☐

SECTION E: For all age groups

Part 2 : You and your child's worries about food safety

0 = extremely unlikely
1 = very unlikely
2 = somewhat unlikely
3 = likely
4 = quite likely
5 = very likely
6 = extremely likely

Please answer the following questions with reference to the 6-point scale on the right

Q1. What chance **do you think** your child has of ….?

	Question	6-point Scale						
		0	1	2	3	4	5	6
1	……accidentally ingesting the food to which they are allergic ?							
2	……having a severe reaction if food is accidentally ingested ?							
3	……dying from his/her food allergy following ingestion in the future ?							
4	……effectively treating him/herself, or receiving effective treatment from others (including Epipen administration), if he/she accidentally ingests a food to which he/she is allergic ?							

Q2. What chance **does your child think** he/she has of ……?

	Question	6-point Scale						
		0	1	2	3	4	5	6
1	……accidentally ingesting the food to which they are allergic ?							
2	……having a severe reaction if food is accidentally ingested ?							
3	……dying from his/her food allergy following ingestion in the future ?							

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4	……effectively treating him/herself, or receiving effective treatment from others (including Epipen administration), if he/she accidentally ingests a food to which he/she is allergic ?							

Q3. How many foods **does your child** have to avoid ?

0-2	
3-6	
7-10	
10+	

SECTION F: For all age groups

Part 3: Your concerns as a parent

Q1. How would you describe ...

(A) *Your* general health?

Excellent	☐
Very Good	☐
Good	☐
Fairly Good	☐
Not So Good	☐
Poor	☐
Very Poor	☐

(B) *Your child's* general health?

Excellent	☐
Very Good	☐
Good	☐
Fairly Good	☐
Not So Good	☐
Poor	☐
Very Poor	☐

Q2. Because of food allergy, how much worry/concern does each of the following cause *you*?

(A) your child's physical health

None at all	☐
A little bit	☐
Some	☐
Quite a bit	☐
A lot	☐

(B) your child's emotional well-being

None at all	☐
A little bit	☐
Some	☐
Quite a bit	☐
A lot	☐

Q3. What level of stress does your child's food allergy cause ...

(A) You?

None at all	☐
A little bit	☐
Some	☐
Quite a bit	☐
A lot	☐

(B) Your Partner?

None at all	☐
A little bit	☐
Some	☐
Quite a bit	☐
A lot	☐

(C) Your Family?

None at all	☐
A little bit	☐
Some	☐
Quite a bit	☐
A lot	☐

Q4. How much has food allergy limited the type of activities ...

(A) you can do as a family ?

None at all	☐
A little bit	☐
Some	☐
Quite a bit	☐
A lot	☐

(B) your child can take part in ?

None at all	☐
A little bit	☐
Some	☐
Quite a bit	☐
A lot	☐

Thank you for taking the time to complete this questionnaire. Your participation is most appreciated.

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This report presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health

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