Boiled Oral Peanut Immunotherapy for the treatment of Peanut Allergy (The BOPI Study)

Version 2.6 dated 5 June 2018

SPONSOR: Imperial College London

FUNDING: Imperial/NIHR Biomedical Research Centre

STUDY CENTRE: Imperial College London

NRES reference: 15/LO/0287

Protocol authorised by:

Name & Role	Date	Signature

PROTOCOL SYNOPSIS

Title	Boiled Oral Peanut Immunotherapy for the treatment of Peanut Allergy
Abbreviated title	BOPI study
Clinical Trials.gov number	NCT02149719
NREC Number	London Central 15/LO/0287
Sponsor R&D Number	15SM2492
IRAS Number	158693
Primary objectives	To evaluate the effectiveness of Oral Immunotherapy (OIT) using boiled peanut to induce desensitization to roasted peanut in children with IgE-mediated peanut allergy
Intervention	Randomised open trial of 12 months of oral immunotherapy using a combination of boiled followed by roasted peanut. Control group receive standard clinical care, with option to undergo OIT after 12 months. Clinical reactivity to roasted peanut will be determined pre- and post-OIT using double-blind, placebo-controlled food challenge. Participants will be invited to return after 3 years for a set of assessments to determine longer-lasting tolerance to peanut.
Safety	Food challenges and updosing will take place in a dedicated hospital paediatric research unit, by personnel qualified in the recognition and treatment of anaphylaxis, and observed for at least 60 minutes following a dose. All families will be provided with an Allergy Management Plan, rescue medication including adrenaline autoinjector devices, and appropriate training in the recognition and management of allergic reactions.
Patient group	Children and young people with a diagnosis of IgE-mediated peanut allergy between 8 -16 years old. Target recruitment of 46 subjects
Sponsor	Imperial College London
Funding	NIHR Biomedical Research Centre at the Imperial Academic Health Sciences Centre (AHSC), a partnership between Imperial College Healthcare NHS Trust and Imperial College London.

Study Management

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Independent Data Monitoring Committee

Chair: Dr Mich Erlewyn-Lajeunesse, University of Southampton
Members: Dr Jonathan Cohen, University College London Hospitals
Mrs Karen Brunas, Parent of peanut-allergic child

Sponsor

Imperial College London is the research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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Funding

Funding has been obtained from the NIHR Biomedical Research Centre at the Imperial Academic Health Sciences Centre (AHSC), a partnership between Imperial College Healthcare NHS Trust and Imperial College London. Mechanistic investigations are co-funded through a Clinician Scientist award from the Medical Research Council to Dr Paul Turner (Imperial College London).

Clinical Queries

Clinical queries should be directed to Dr Paul Turner (Imperial College London) who will direct the query to the appropriate person

This protocol describes the BOPI study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	*Details of Changes made*
1	*2.1*	***26 Oct 2015*** ***approved 19.11.15***	*Paul Turner*	1) Change inclusion criteria [section 4.1] to: i. Allow for the assessment of potential participants who have never had an allergic reaction to peanut, but are highly likely to have peanut allergy given diagnostic testing. ii. Tolerance to ¼ boiled peanut at visit 3 (from 1 peanut) 2) Follow-up of participants excluded from the study due to failure to tolerate boiled peanut or significant reactions during updosing [section 5.7.2] 3) Changing some of the in-hospital updosing stages into a split-dose procedure where there had been a change in boiling time e.g. rather than give 4 peanuts as a single dose, to split this into 1 peanut followed by 3 peanuts 30 minutes later [section 5.3.4.1]
2	*2.2*	***9 Dec 2015*** ***approved 15.12.15***	*Paul Turner*	1. Assess a mobile 'app' as an alternative to the patient diaries currently being used [sections 5.3.3 and 5.3.4] 2. Extended laboratory work [section 5.7.3] 3. Recruit via PIC sites [section 5.1]
3	*2.3*	***28 Jan 2016*** ***Approved 16 Feb 2016***	*Paul Turner*	1. Extension of observation times following challenges to minimum 2 hours [sections 5.3/5.4] 2. Clarification of SPT at 6 month visit revised (non-substantial amendment) [section 5.7.1]
4	*2.4*	***8 April 2016*** ***Approved 24 Apr 2016***	*Paul Turner*	1. Inclusion of cardiac echocardiography as a non-invasive assessment [section 5.2.3] 2. Extend laboratory work on patient samples section 5.7.3]
5	*2.5*	***8 Feb 2017*** ***Approved 19 Apr 2017***	*Paul Turner*	1. Inclusion of DNA collection (opt-in) [section 5.2.3] 2. Increase in blood sample volume to max 75ml per visit (no change in per kg body weight volume) 3. Clarifications: i. Blood analyses at challenge (5.2.3) ii. Addition of blood sample at 13 months (5.7.3) iii. Correction of typo in 12mth challenge (5.4.1) iv. Updated co-investigators v. 24hr follow-up after challenges (5.2.2) vi. Use of peanut M&Ms instead of peanut (5.3.4.4)
6 *(minor)*	*2.5*	***22 Mar 2018*** ***Approved 19 Apr 2018***	*Paul Turner*	Extension to study end date (minor, no changes to protocol)
7	*2.6*	***5 June 2018*** ***Approved 21 Jun 2018***	*Paul Turner*	1. Addition of year 3 assessments with associated extension to study end date (section 5.7). 2. Change in maintenance dose beyond 1st year to thrice weekly dosing (section 5.4.2)

GLOSSARY OF ABBREVIATIONS

ABBREVIATION	TERM
AE	Adverse Event
BSACI	British Society for Allergy & Clinical Immunology
DBPCFC	Double blind, placebo-controlled food challenge
FAQL-Q	Food Allergy Quality of Life - Questionnaire
IDMC	Independent Data Monitoring Committee
LOAEL	Lowest observed adverse event level
NOAEL	No observed adverse event level
OIT	Oral Immunotherapy
PN	Peanut
PSS	Perceived Stress Scale
QoL	Quality of Life
SAE	Serious adverse event
SAR	Serious adverse reaction
SCORAD	SCORing Atopic Dermatitis tool
SPT	Skin Prick test

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1. INTRODUCTION

1.1 BACKGROUND

Peanut allergy is the most common cause of severe allergic reactions to food.[1] Onset is common in childhood, but in contrast to other food allergies such as cow's milk and egg, peanut allergy tends to persist into adulthood.[2] It is associated with a significant impact on quality of life, both for the affected individual and their family.

There is no current cure for peanut allergy. Oral peanut immunotherapy (OIT) using roasted allergen has been demonstrated to offer potential in this regard, but is associated with significant and frequent reactions and can cause life-threatening allergic symptoms.[3] Furthermore, although study regimes have been relatively successful in inducing transient desensitisation, most have not assessed for the induction of sustained unresponsiveness; where this has been investigated, OIT (typically under 6 months duration) has been largely unsuccessful in demonstrating when daily allergen is ceased.[4] A recent study involving peanut OIT for 12-18 months appears to be more successful in inducing sustained unresponsiveness,[5] which is consistent with the clinical data for immunotherapy to aeroallergens. Current protocols generally mandate increases in dose during induction to take place under medical supervision, due to the frequency and unpredictable nature of reactions experienced. This places a significant burden on families of children undergoing OIT, due to the need for frequent hospital visits along with observation after dosing at home.

We have previously demonstrated that the processing of peanuts through boiling results in a relatively hypoallergenic product due to the loss of key allergenic components from peanut into the water.[6] Our pilot has demonstrated that a desensitization protocol, using boiled peanut, can successfully result in desensitization to raw peanut; ongoing follow-up suggests these children also demonstrate desensitization to roasted peanut, but this has not been formally studied. The use of boiled peanut was well-tolerated with minimal symptoms at updosing, suggesting that this approach may well be appropriate as a safer, better tolerated approach to achieving successful OIT, with the possibility of improved sustained tolerance.

1.2 STUDY RATIONALE & JUSTIFICATION

We wish to formally assess, in a randomized controlled study, whether a modified approach using boiled peanut for peanut OIT can result in desensitisation and sustained unresponsiveness (i.e. tolerance) to roasted peanut. We will assess the safety of this approach, and study the immunological mechanisms involved, our secondary aim being to develop clinically-useful predictors for identifying individuals likely to undergo successful desensitization.

STUDY HYPOTHESIS:

A pragmatic protocol utilizing increasing doses of boiled peanut can induce desensitisation to roasted peanut, in peanut-allergic individuals, with an acceptable safety profile.

[1]Turner PJ, Gowland MH, Sharma V, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: An analysis of United Kingdom national anaphylaxis data, 1992-2012. JACI 2014; doi: 10.1016/j.jaci.2014.10.021.
[2]Bégin P, Paradis L, Paradis J, Picard M, Des Roches A. Natural resolution of peanut allergy: a 12-year longitudinal follow-up study. JACI In Practice 2013;1:528-30.e1-4.
[3]Wood RA, Sampson HA. Oral immunotherapy for the treatment of peanut allergy: is it ready for prime time? JACI In Practice 2014;2:97-8.
[4]Vickery BP, Scurlock AM, Kulis M, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. JACI 2014;133:468-75.
[5]Tang ML, Ponsonby AL, Orsini F, et al. Administration of a probiotic with peanut oral immunotherapy: A randomized trial. J Allergy Clin Immunol. 2015. doi: 10.1016/j.jaci.2014.11.034.
[6]Turner PJ, Mehr S, Sayers R, et al. Loss of allergenic proteins during boiling explains tolerance to boiled peanut in peanut allergy. JACI 2014;134:751-3.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

- To evaluate the effectiveness of OIT using boiled peanut to induce desensitization to roasted peanut in children with IgE-mediated peanut allergy.

2.2 SECONDARY OBJECTIVES

- To evaluate the safety of peanut OIT in children with IgE-mediated peanut allergy.
- To assess the rate of sustained unresponsiveness following peanut OIT
- To identify predictors which can identify individuals likely to undergo successful desensitization and sustained unresponsiveness using boiled peanut
- To assess the impact of peanut OIT on quality of life (QoL) measures, both from the child/young person's perspective as well as their parents'.
- To assess how duration of OIT impacts on sustained unresponsiveness

3. STUDY DESIGN

The study consists of 2 related work packages (see Figure 1):

WP1: A 52 week, phase 2 single centre open label interventional randomized controlled trial to assess the efficacy of OIT using boiled peanut to induce desensitization in children with IgE-mediated peanut allergy. Participants will be randomized 2:1 to active intervention or control (current best standard care, i.e. strict peanut avoidance plus provision of rescue medication and training) for 12 months.

WP2: Subjects in the active group will undergo a 4 week period OFF peanut intake, followed by an unblinded peanut challenge to assess for sustained unresponsiveness. Those who pass the challenge will continue weekly maintenance with roasted peanut, those who fail will resume daily peanut for a further year.

Subjects in the control group will be offered the option of receiving the active intervention following the 12 month control phase (boiled peanut immunotherapy). This will allow confirmation that the two groups are similar in response to OIT using boiled peanut, increasing the precision of the results.

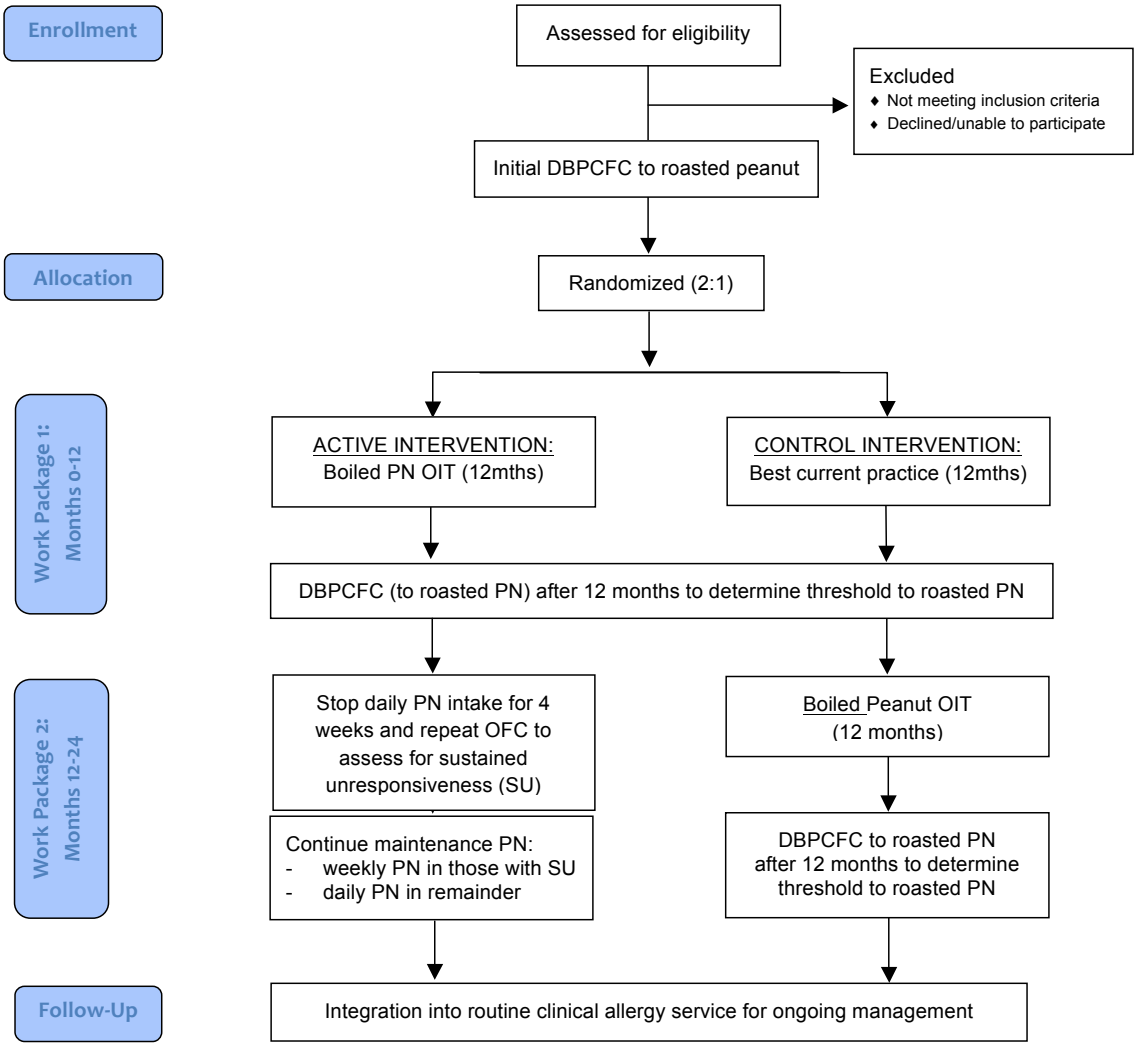


Figure 1: CONSORT diagram for the BOPI study.
[PN: Peanut; SU: Sustained unresponsiveness]

Summary of Study components:

1. **Recruitment and eligibility screen**: Peanut-allergic subjects will be recruited from both our local patient population and through our local paediatric allergy network in North West London.
2. **Initial double-blind, placebo-controlled food challenge** (DBPCFC) to roasted peanut. This will demonstrate true clinical reactivity to roasted peanut rather than sensitization alone, as it is unethical to undertake peanut OIT in children who are not clinically allergic to roasted peanut.
3. **Randomisation and WP1:** Peanut-allergic children will be randomized 2:1 to either active treatment (OIT using boiled PN) or control (current best practice, i.e. strict peanut avoidance plus provision of rescue medication and training) during months 0-12.
4. **1 year assessment:** At 12 months, all subjects will undergo a DBPCFC to roasted PN, to assess for ongoing clinical allergy (and determine threshold of reactivity) to roasted PN. Subjects in the active group will stop all peanut for 4 weeks and then undergo a further open challenge to assess for sustained unresponsiveness (ie. tolerance without the need for ongoing peanut exposure).
5. **WP2:** Those subjects in the control group will be offered OIT using boiled PN during months 12-24. Subjects in the active intervention groups will be offered ongoing maintenance therapy within the study protocol.
6. **2 year assessment** and option to determine longer-term tolerance to peanut.

Subjects will be invited to remain in the study for a 3rd year to allow longer-term evaluations to be performed.

The efficacy and impact of OIT on quality of life will be assessed at 6, 12, 24 and 36 months in all subjects (and their parents), using a validated questionnaire.

3.1 STUDY OUTCOMES MEASURES

3.1.1 PRIMARY STUDY OUTCOME

- The proportion of participants who tolerate 1.4g (or more) roasted peanut protein (equivalent to ≥ 6 roasted peanuts) after 12 months of OIT as assessed by DBPCFC, in the active vs control group.

3.1.2. SECONDARY STUDY OUTCOMES

- Relative change in clinical threshold (No observed adverse event level, NOAEL; Lowest observed adverse event level, LOAEL) to roasted peanut at 6 and 12 months.
- Rate of sustained unresponsiveness after 4 week cessation of maintenance OIT at 1 year and 3 years.
- Change in quality of life (QoL) assessments at 6 and 12 months after OIT, as assessed by FAQL-Questionnaire in children, teenagers and their parents – in the active vs control group.
- Safety of OIT using boiled peanut as defined by frequency and nature of allergic symptoms experienced.
- Compliance with study protocol
- Immunological outcome measures pre-, during and post-OIT

3.2 STUDY DESIGN RATIONALE

The is a **randomized controlled** study, utilizing a control group with a delayed start to control for the incidence of natural resolution of peanut allergy over 12 months. Natural resolution of peanut allergy occurs in 10%-20% of peanut allergic children over a longer time period. Inclusion of a control group also facilitates the assessment of the safety of OIT and QoL measures (by comparing active to control patients who may experience accidental allergic reactions despite best management).[7]

Controls will be offered a deferred start to OIT (using boiled peanut) after 12 months on current standard care (avoidance advice and provision of a rescue plan and medications in the event of an accidental allergic reaction). We consider it unethical not to offer control participants the opportunity to undergo active treatment having undertaken peanut challenges during the 12 months of non-intervention. We also expect that this design will encourage compliance with the study protocol.

To avoid selection bias, participants will be randomized to active or control groups. A level of stratification will be included to distinguish between those who are predominantly sensitized to a specific peanut protein epitope (Ara h 2). This is because pilot data indicates that the boiling process affects leaching of Ara h 2 from peanut more than other proteins. Patients who are predominantly sensitized to Ara h 2 may be more likely to have a successful outcome than those allergic to other peanut proteins. The stratification will reduce the risk of skewing the results through randomization.

As with most OIT studies, this study will be **open label**, as we wish to assess a pragmatic approach to dosing which would not be possible with blinding. Families will be provided with a specific peanut cultivar (Holt Runner, Peanut Company of Australia Ltd); families will be given specific instructions on preparing the peanut for OIT (through boiling) at home. The supply of raw peanuts direct from the wholesaler also reduces potential nut-contamination. We have chosen a specific cultivar with higher oleic oil content, resulting in a longer shelf-life (at least 18 months when vacuum packed and stored at 4°C). To perform OIT safely, supervision and frequent appointments to the research unit are required. A blinded study would increase the burden on families. Finally, the use of blinding might lead participants (and their families) to believe they are indeed tolerant to peanut and therefore result in less stringent allergen avoidance, putting them at increased risk of accidental reactions.

We have chosen a daily maintenance dose of 800mg roasted peanut protein, on the basis of previous reports that this amount is generally well-tolerated by subjects undergoing OIT on an daily basis, and is also associated with a suggestion of efficacy.[7] Our primary endpoint (able to tolerate 1.4mg roasted peanut protein, equivalent to ≥ 6 roasted peanuts) has been chosen on the basis of efficacy and ability to protect against accidental exposure to peanut in the community. This will be assessed using a blinded food challenge, an established research tool in food allergy.[8]

The inclusion of an assessment to determine tolerance (sustained unresponsiveness) to peanut in the absence of ongoing daily peanut exposure is essential. The realities of day-to-day life mean that outside the safety of a clinical trial, maintenance peanut doses are often omitted. It is therefore important to demonstrate ongoing tolerance to peanut in the absence of daily maintenance. Furthermore, the reassurance through the demonstrated tolerance in children with previous peanut allergy may well improve quality of life further. This outcome needs to be corrected for the possibility of natural resolution, thus a comparison to controls who have not undergone OIT is required.

The study has been designed as a **single centre** study: the procedures involved are complex and require intensive clinical assessment only available at a specialist allergy centre. The use of a single centre allows a more efficient use of resources and promotes consistency in clinical management. Our location (in central London) allows for the recruitment of patients from a diverse geographical area and ethnic background.

[7]Anagnostou K, Islam S, King Y, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet. 2014;383(9925):1297-304.
[8]Plaut M, Sawyer RT, Fenton MJ. Summary of the 2008 National Institute of Allergy and Infectious Diseases–US Food and Drug Administration Workshop on Food Allergy Clinical Trial Design. J Allergy Clin Immunol 2009;124:671-8.e1.

4. STUDY POPULATION

4.1. INCLUSION CRITERIA

1. Age 8-16 years.
2. Past history of peanut allergy, with:
   - Previous clinical reaction with ongoing sensitisation to peanut, OR positive allergy test to peanut (either skin prick test ≥8mm or serum specific IgE > 15kUA/l) to peanut consistent with >95% likelihood of clinical allergy[9], AND
   - further confirmation of clinical reactivity to roasted peanut at double-blind placebo-controlled food challenge at screening
3. Tolerates at least ¼ boiled peanut (boiled for 4 hours) at open food challenge at screening.
4. Full informed consent of parent/legal guardian and patient assent.

4.2. EXCLUSION CRITERIA

1. Required previous admission to an intensive care unit for management of an allergic reaction to peanut.
2. Clinically significant chronic illness (other than asthma, rhinitis or eczema).
3. Undergoing subcutaneous or sublingual immunotherapy and within the first year of therapy, for respiratory allergy.
4. Subjects receiving anti-IgE therapy, oral immunosupressants, beta-blocker or ACE inhibitor.
5. Clinical allergy to either soya or sunflower seed
6. Tolerance to ≥1.4 g peanut protein (approx. 6 peanuts) at initial DBPCFC during screening.
7. Subjects allergic to ¼ boiled peanut (boiled for 4 hours) at screening.
8. Poorly controlled asthma within the previous 3 months (as defined by clinician judgement with reference to the ICON consensus[10]), or asthma requiring oral corticosteroid therapy within the previous 3 months.
9. Pregnancy
10. Unwilling or unable to fulfil study requirements

4.3. WITHDRAWAL CRITERIA

Subjects will be free to withdraw from the study at any time without affecting their future medical care. Subjects who are withdrawn from active treatment will remain in the study for assessment of outcome relating to QoL measures.

The safety of the child is paramount in this study. Thus, children who experience anaphylaxis to an OIT dose at home, but who do not receive IM adrenaline as per the management plan, will have further updosing suspended until the family undergo retraining on the recognition and management of allergic symptoms.

A participant will be withdrawn from the study under the following circumstances:

- If, in the opinion of the study team, compliance with study procedures is suboptimal such that it compromises the patient's safety.
- If, in the opinion of the study team, further participation would adversely affect the participant's health.
- A child develops an exclusion criteria during the updosing phase of the study e.g. a new medication (which would normally be a contra-indication) is commenced.
- If consent is withdrawn or the subject fails to return for a study visit.

  In the event of a serious adverse reaction to OIT and/or if presenting with anaphylaxis requiring more than one IM adrenaline dose within 2 hours after an OIT dose.

Any subject excluded from further participation will not be replaced.

[9] Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. Clin Exp Allergy 2000; 30:1540–6.; AND Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol 2001;107: 891–6.

[10] Papadopoulos NG, Arakawa H, Carlsen KH, et al. International consensus on (ICON) pediatric asthma. Allergy. 2012;67:976-97.

5 STUDY PROCEDURES

The main study procedures are shown in Figure 2, and consist of the following stages:

1. **Recruitment and initial screening**
2. **Initial double-blind, placebo-controlled food challenge** (DBPCFC) to roasted peanut.
3. **Randomisation and WP1:** Following demonstration of tolerance to one boiled peanut, peanut-allergic children will be randomized 2:1 to either active treatment (OIT using boiled PN) or control (current best practice) during months 0-12.
4. **1 year assessment:** All subjects will undergo a DBPCFC to roasted PN, to assess for ongoing clinical reactivity (and determine threshold of reactivity) to roasted PN. Subjects in the active group (Group A) will stop all peanut for 4 weeks and then undergo a further open challenge to assess for tolerance (i.e. sustained unresponsiveness without the ongoing peanut exposure).
5. **WP2:** Children in the control group (Group B) will be offered OIT using boiled PN during months 12-24. Subjects in the active intervention groups will be offered ongoing maintenance therapy within the study protocol.
6. **2 year assessment** and option to determine longer-term tolerance to peanut.

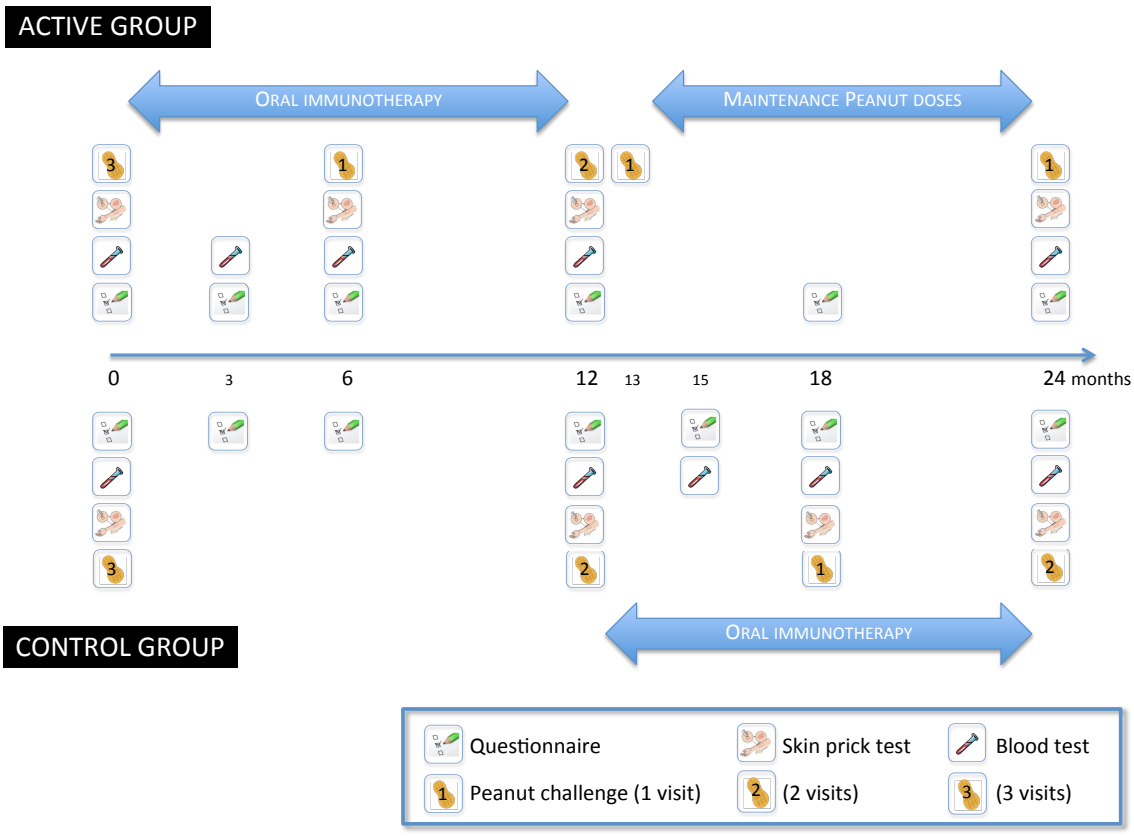


Figure 2: Study flowchart and interventions

5.1 RECRUITMENT AND SCREENING VISITS

Peanut-allergic children will be recruited through our clinical service at St Mary's Hospital (Imperial College Healthcare NHS Trust), one of the largest tertiary services in Europe providing specialist paediatric allergy services to the North Thames Region. We will also recruit through our local paediatric allergy network in North West London, including the use of PIC sites at the larger allergy centres. This study requires frequent visits (once every 2-4 weeks) to the Research Unit, thus it is important that participants live relatively local to the unit to minimize travel time and impact on other daily activities.

Potential participants will receive the Study Information either in person, by post or via email, following which the participants will be screened by telephone conversation with their parents, to determine likelihood of true peanut allergy and thus suitability for this study. Suitable participants will then have an appointment made for a screening visit.

The following will take place at the first screening visit:

- Informed consent
- Clinical history and physical examination
- Skin prick test (SPT) to commercial crude peanut extract and boiled peanut slurry according to national guidelines
- For children with asthma, current asthma status will be assessed by the clinician, with the help of lung function testing and completion of a validated asthma control test
- For children with eczema, eczema will be assessed using the SCORAD system[11] (which provides an objective measure of eczema severity) as well as completion of a POEM questionnaire, a validated patient-based symptom measure questionnaire

The first screening visit may take place on the same day as the first baseline food challenge, if requested by the family.

5.2 DOUBLE-BLIND, PLACEBO-CONTROLLED FOOD CHALLENGE (DBPCFC) TO ROASTED PEANUT

All participants who fulfil eligibility criteria for the study will undergo a baseline DBPCFC to roasted peanut at enrolment. The DBPCFC is established as the gold-standard test of diagnosis of food allergy by international consensus. The objectives are:

i. to confirm the diagnosis of IgE-mediated peanut allergy,
ii. to determine the threshold of clinical reactivity to peanut prior to OIT

The DBPCFC involves 2 half-day visits, at least one week apart. Participants are given incremental doses of peanut or placebo 30 minutes apart, and monitored for signs/symptoms of allergic reaction throughout. The challenge is halted once pre-determined stopping criteria have been reached. DBPCFC will be performed according to the international PRACTALL consensus for best practice.[12]

5.2.1 CLINICAL ASSESSMENT AND CHECKS PRIOR TO DBPCFC

All subjects will be assessed prior DBPCFC to determine suitability for a challenge, as follows:

- No intercurrent illness (viral or otherwise)
- No exacerbation in allergic symptoms (eczema, asthma, food allergy) in the preceding week.
- No short-acting β2 agonists used in the past 12 hours
- No short-acting antihistamine taken (e.g. cetirizine, loratadine) in the past 48 hours (72 hours for fexofenadine)
- No long-acting antihistamine (e.g. chlorphenamine, desloratadine) in the previous 5 days.
- No oral steroids have been taken in the past 2 weeks

[11] Kunz, B., Oranje, A.P., Labreze, L., Stalder, J.F., Ring, J., and Taieb, A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. Dermatology. 1997; 195: 10–19

[12] Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: AAAAI-EAACI PRACTALL consensus report. J Allergy Clin Immunol. 2012;130:1260-74.

- Baseline observations (temperature, blood pressure, heart and respiratory rate, oxygen saturation) within normal range.
- Baseline physical examination must not reveal any significant acute findings.

Challenges will occur on a Paediatric Allergy Research Unit (PRU) where food challenges are performed on a regular basis, and staff are familiar with the management of allergic reactions including anaphylaxis through clinical experience and regular training. Emergency equipment (including oxygen and suction) and medication will be checked beforehand, as per local protocol and international criteria for performance of DBPCFC.

5.2.2 DBPCFC

The challenge will consist of seven consecutive increasing doses of roasted peanut (or placebo) at 30 minutes intervals with an observation period of 2 hours after the final dose:

Protocol 1: DBPCFC to peanut	**Roasted peanut OFC (using defatted flour)**	
TIME POINT (mins)	Peanut flour (mg)	Peanut protein (mg)
0	6	3
30	20	10
60	60	30
90	200	100
120	600	300
150	2000	1000
180	6000	3000
Cumulative dose		**4443mg**
2 hours observation period following last dose to monitor for signs of reaction		

The food challenge doses will be prepared prior to challenge, in a matrix containing soya (soya-allergic children will be given a matrix based on sunflower seed instead). Tolerance to at least one of these will be established at enrolment. All doses (irrespective of active or placebo) will be double-checked prior to administration. The order of challenge days (active or placebo control) will be randomized by an independent research associate, according to a computer-generated randomization list (www.sealedenvelope.com). The randomization key will be recorded in a separate file and logged once both pair of challenges have taken place.

In brief, symptoms will be monitored during the challenge, with detailed assessment prior to each challenge dose, according to Figure 3.

- Green symptoms: Not generally sufficient to consider a challenge positive unless symptoms persist for at least 120 minutes.
- Orange symptoms: Symptoms that recur on 3 doses, or persist (e.g. 40 minutes) are more likely indicative of a reaction than when such symptoms are transient and not reproducible. - 3 or more scoring areas in orange more likely represent a true response, and if present the challenge should be halted.
- Red symptoms: A single red symptom is likely to indicate a true response, and if present the challenge should be halted.

The outcome of the challenge (positive or negative) and the apparent eliciting threshold dose will be recorded in the participant record.

Challenge outcome will be determined as per the PRACTALL Consensus criteria,[9] as shown in Figure 3:

I. SKIN
- A. Pruritus
  - 0 = Absent
  - 1 = Occasional scratching
  - 2 = Scratching continuously for >2 minutes at a time
  - 3 = Hard continuous scratching causing excoriations
- B. Urticaria/Angioedema
  - 0 = Absent
  - 1 = < 3 hives, or mild lip oedema
  - 2 = < 10 hives but >3, or significant lip, tongue or facial oedema
  - 3 = Generalized involvement
- C. Rash
  - 0 = Absent
  - 1 = Few areas of faint erythema
  - 2 = Areas of erythema
  - 3 = Generalized marked erythema (>50%)

II. UPPER RESPIRATORY
- A. Sneezing/Itching
  - 0 = Absent
  - 1 = Rare bursts, occasional sniffing
  - 2 = Bursts <10, intermittent rubbing of nose/eyes or frequent sniffing
  - 3 = Continuous nasal/eye itch, periocular swelling and/or long bursts of sneezing, persistent rhinorrhoea

III. LOWER RESPIRATORY
- A. Wheezing
  - 0= Absent
  - 1 = Expiratory wheeze on auscultation
  - 2 = Biphasic wheeze
  - 3 = Use of accessory muscles, audible wheezing
- B. Laryngeal
  - 0= Absent
  - 1 = >3 discrete episodes of throat clearing/cough, or persistent throat tightness/pain
  - 2 = Vocal hoarseness, frequent cough
  - 3 = Stridor

IV. GASTROINTESTINAL
- A. Subjective Complaints
  - 0 = Absent
  - 1 = Complaints of nausea or abdominal pain, itchy mouth/throat
  - 2 = Frequent c/o nausea or pain with normal activity
  - 3 = Notably distressed due to GI symptoms with decreased activity
- B. Objective Complaints
  - 0 = Absent
  - 1 = 1 episode of emesis
  - 2 = 2-3 episodes of emesis or diarrhoea or 1 of each
  - 3 = >3 episodes of emesis or diarrhoea or 2 of each

V. CARDIOVASCULAR/NEUROLOGIC
- 0 = normal heart rate or BP for age/baseline
- 1 = Subjective symptoms (weak, dizzy), or tachycardia
- 2 = Drop in mBP of >20% from baseline, or significant change in mental status.
- 3 = Cardiovascular collapse, signs of impaired circulation (unconscious)

Figure 3: PRACTALL consensus stopping criteria for food challenges.[9]

For safety reasons, families will be asked to provide their child with a snack one hour after the challenge has ceased i.e. prior to leaving the research unit. This is to avoid the possibility of further symptoms on feeding outside the medical unit, something which can occur if no food is eaten prior to discharge.

All families will be contacted by email or telephone the day following challenge to collect any data relating to the occurrence of delayed (late phase) symptoms.

5.2.3 ASSESSMENTS DURING FOOD CHALLENGES

The baseline food challenges are termed 'high-risk' on the basis that we expect the challenges to be positive. To minimize risk to the patient, all challenges will take place on a Paediatric Allergy Research Unit (PRU) where food challenges are performed on a regular basis, and staff are familiar with the management of allergic reactions including anaphylaxis through clinical experience and regular training. Since many of the study participants will be new to the research team, we propose additional safety precautions at the initial baseline challenge:

i. **Intravenous access**: Cannulation will be performed in order to secure intravenous access. This will allow treatment to be easily and rapidly administered in the event of a significant allergic reaction. In order to minimize discomfort to the child, we will offer local anaesthetic cream to be applied at least 30 minutes prior to cannulation, according to local practice.

   Blood will be collected prior to, during and after challenge via the cannula, in order to confirm a clinical reaction using objective laboratory assessments. This procedure will not cause discomfort to the child, as the cannula will already be in situ. Where the cannula does not bleed back, no further venepuncture will be attempted. If cannulation is not possible (for whatever reason), the challenge may proceed if authorised by the Chief Investigator, on the basis that emergency medicines can also be given by the intramuscular route.

   At the challenge visit, a maximum total volume of 2.5ml/kg (max 75ml) blood (up to 40ml prior to starting the challenge) will be collected for baseline laboratory assessments of immunological function relating to peanut allergy and assessment of tolerance (see section 5.7.2). These tests will include IgE antibodies to peanut (including peanut components); inflammatory mediators; inflammatory cell activation (by flow cytometry); and storage of RNA (using the PAXgene system) and DNA for latter analysis of protein signal transcription. We have elected to perform this test at this initial challenge, rather than at the screening visit, in order to reduce the number of blood tests required.

ii. **Non-invasive monitoring**: Children will be monitored during food challenges, using non-invasive monitoring. In addition to standard measurements of heart rate, blood pressure and oxygen saturations, we propose additional non-invasive measurements in order to gain as much information as possible about allergic reactions under controlled conditions, as follows:

   a. **Central blood pressure**: In addition to peripheral (brachial) BP, central BP will be measured using the Pulsecor BPplus non-invasive CardioScope II monitor (CE-marked) (Figure 4). Use is similar to a conventional BP cuff/monitor with measurements obtained within 60 seconds, and is very well tolerated by children.
   Rationale: The difference between central and peripheral systolic BP may be more representative of the effect of vasodilatation during a food allergic reaction. Furthermore, central diastolic BP correlates better with coronary perfusion than peripheral diastolic BP. There may be a difference between the ability of individuals to maintain central BP during a systemic allergic reaction, which could relate to the clinical symptoms observed.

Figure 4: Pulsecor II Central Blood Pressure monitor.

b. **Non-invasive hemodynamic monitoring**: In older children (above 12 years), continuous data will be obtained using non-invasive hemodynamic monitoring (Cheetah NICOM monitor); this type of monitoring is not validated in younger children, nor is practical due to the need to be inactive during measurements. The NICOM monitor has been extensively validated, has FDA approval and is CE marked. Data is collected through 4 ECG-type sensors (size 108 x 20 mm) placed on the front or back of the thorax, as shown in Figure 5. Measurements are not prone to movement artefact. The monitor allows for continuous cardiovascular monitoring (including cardiac output and peripheral resistance) during challenges.
Rationale: It is unknown as to how cardiac output varies during an allergic reaction. Some individuals may be able to compensate for capillary bed vasodilatation during a systemic allergic reaction by modulating cardiac output. The assessment of cardiac output will also facilitate the estimation of peripheral vasodilatation through measurement of total peripheral resistance.

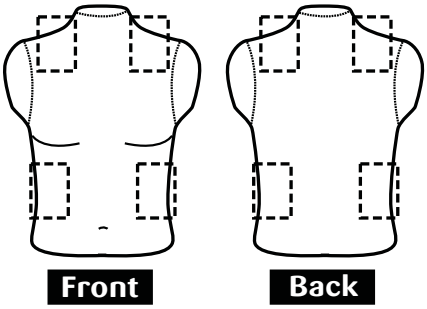


Figure 5: NICOM Sensor placement

To provide further validation of the measurements taken by the NICOM monitor, during some challenges participants will also be invited to undergo intermittent cardiac echocardiography (performed by a trained healthcare professional according to standard protocols in use at our hospital).

5.2.4 MANAGEMENT OF SYMPTOMS DURING PEANUT EXPOSURE

Any allergic reaction happening during the observation period following dose administration will be managed according to the British Society for Allergy and Clinical Immunology (BSACI) Allergy Action Plans for children (Figure 6).

Mild-moderate (non-anaphylactic) symptoms (as defined in Figure 6) will be treated with cetirizine as per local policy. Symptoms of anaphylaxis will be treated initially with IM adrenaline. Where feasible, the child or parent will use their adrenaline auto-injector device to administer the (first) dose of adrenaline in this event, as this can increase compliance with the Plan's recommendations outside the home environment and reduce anxiety relating to the use of auto-injector devices.

bsaci
British Society for Allergy and Clinical Immunology

Allergy Action Plan

Clinic details

THIS CHILD HAS THE FOLLOWING ALLERGIES:

Name:

DOB:

Photo

Parent / Carer details:

1) ☎

2) ☎

Child's Weight: Kg

Mild-moderate allergic reaction:

- Swollen lips, face or eyes
- Itchy / tingling mouth
- Hives or itchy skin rash
- Abdominal pain or vomiting
- Sudden change in behaviour

ACTION:

- Stay with the child, call for help if necessary
- Give antihistamine:
- Contact parent/carer (if vomited, can repeat dose)

Watch for signs of ANAPHYLAXIS
(life-threatening allergic reaction):

AIRWAY:	Persistent cough, hoarse voice, difficulty swallowing, swollen tongue
BREATHING:	Difficult or noisy breathing, wheeze or persistent cough
CONSCIOUSNESS:	Persistent dizziness / Pale or floppy Suddenly sleepy, collapse, unconscious

If ANY ONE of these signs are present:

1. **Lie child flat.** If breathing is difficult, allow to sit
2. **Give EpiPen® or EpiPen® Junior**
3. **Dial 999 for an ambulance*** and say ANAPHYLAXIS ("ANA-FIL-AX-IS")

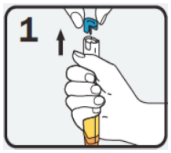
If in doubt, give EpiPen®

After giving Epipen:

1. Stay with child, contact parent/carer
2. Commence CPR if there are no signs of life
3. If no improvement **after 5 minutes, give a further EpiPen®** or alternative adrenaline autoinjector device, if available

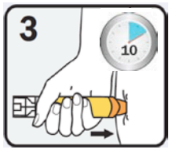
*You can dial 999 from any phone, even if there is no credit left on a mobile.
Medical observation in hospital is recommended after anaphylaxis.

How to give EpiPen®

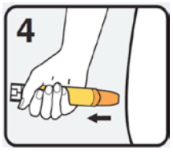


Form fist around EpiPen® and PULL OFF BLUE SAFETY CAP

SWING AND PUSH ORANGE TIP against outer thigh (with or without clothing) until a click is heard



HOLD FIRMLY in place for 10 seconds



REMOVE EpiPen®. Massage injection site for 10 seconds

Keep your EpiPen device(s) at room temperature, do not refrigerate.
For more information and to register for a free reminder alert service, go to www.epipen.co.uk

Patient support groups:
http://www.allergyuk.org or www.anaphylaxis.org.uk

Additional instructions:

This is a medical document that can only be completed by the patient's treating health professional and cannot be altered without their permission.

This plan has been prepared by: _____

Hospital/Clinic:

☎ Date:

Figure 6: BSACI Allergy Management Plan

5.3 TOLERANCE CHECK, RANDOMISATION AND WP1: ORAL IMMUNOTHERAPY

Eligible participants (who have a positive DBPCFC, confirming IgE-mediated peanut allergy) will then undergo a one-shot food challenge to confirm tolerance to at least ¼ boiled peanut to confirm eligibility. Children able to tolerate boiled peanut will then be randomized to either active treatment (OIT) or control, on a 2:1 basis.

Randomisation needs to occur after tolerance to ¼ boiled peanut has been demonstrated, and updosing commenced immediately on safety grounds. Were randomisation (and thus further daily dosing) to be delayed, there would be potential for priming which might result in subsequent reactivity to a previously tolerated dose of boiled peanut. Immediate randomisation and updosing thus ensures safety.

5.3.1 TOLERANCE CHALLENGE TO BOILED PEANUT

All children will undergo a single-dose OPEN (unblinded) food challenge to determine the starting dose of boiled peanut. Tolerance to at least ¼ boiled peanut is an eligibility criterion, and must be demonstrated prior to randomisation in all children. The open, single dose challenge will involve the consumption of ¼ boiled peanut (boiled for 4 hours) followed by a 2 hour observation period. The criteria listed in Section 5.2.2 will be used to determine outcome of this food challenge.

Children who are unable to tolerate ¼ boiled peanut will not be eligible for the study, and will be transferred back to routine clinical care.

5.3.2 RANDOMISATION

Once tolerance to ¼ boiled peanut has been demonstrated, the participant will be randomised using an online randomization tool (www.sealedenvelelope.com). Randomisation will be blocked (using random permuted blocks) to ensure that the groups are balanced, and include a level of stratification according to whether the child is predominantly sensitized to a specific peanut protein components (Ara h 2). Pilot data indicates that the boiling process affects Ara h 2 content more than other peanut proteins. Thus, patients who are predominantly sensitized to Ara h 2 may be more likely to have a successful outcome than those allergic to other peanut proteins.

The Ara h 2 predominant Phenotype is defined as:

- Specific IgE to Ara h 2 >1.0 kUA/l
- Specific IgE to Ara h 1 and Ara h 3 <1.0 kUA/l

5.3.3 CONTROL GROUP

Subjects randomized to the control group will receive current standard care according to best practice (as per British Society for Allergy and Clinical Immunology guidance). This includes:

- A **food allergy management plan** (Figure 5), with provision of rescue medication including an adrenaline auto-injector device. Families and participants will be instructed in the prompt recognition and treatment of allergic reactions.
- **Contact information** for the team, which will include telephone contact number for the team and an email address which will be checked daily by the research team from Monday to Friday for non-urgent queries.
- **Dietary advice on peanut avoidance**. Participants will not be allowed to ingest peanut for the whole study duration (52 weeks).
- A **home diary sheet**, on which parents will log all accidental reactions experienced. Participants will also be offered an opportunity to 'opt-in' to using an electronic 'mobile app' diary in parallel to the paper-based diary.

Children (and their parents) will undergo quality-of-life assessments at 0, 3, 6 and 12 months (see 5.7.1).

5.3.4 ACTIVE GROUP: ORAL IMMUNOTHERAPY

Subjects randomized to the active intervention arm will continue to undergo an OPEN (unblinded) food challenge at the same visit, to determine the starting dose of boiled peanut. This is because some children may exhibit a degree of *de novo* tolerance to boiled peanut, and thus demonstration of tolerance allows for individualization of the updosing protocol. The open challenge will utilize the following protocol:

Protocol 2: Open OFC to boiled PN	**Boiled peanuts (boiled for 4 hours)**		**If dose tolerated, commence updosing at STEP:**
TIME POINT (mins)	No. peanuts	Peanut protein (mg)*	
(Already given in 5.3.1)	¼ boiled peanut	30	pre-A
0	¾ boiled peanut	100	1
30	2 boiled peanuts	260	1
60	4 boiled peanuts	520	1
90	8 boiled peanuts	1040	5
Cumulative dose	**15 boiled peanuts**	**1950**	
2 hours observation period following last dose to monitor for signs of reaction			

**Boiled peanuts contain approximately half the amount of protein as roasted peanuts.*

The criteria listed in Section 5.2.2 will be used to determine outcome of this food challenge.

Children will receive daily doses of peanut at home, initially using boiled peanut. The updosing regime is shown in Table 1. Children who tolerate at least 1 boiled peanut will commence updosing at ½ boiled peanut, unless they have passed the challenge in its entirety (i.e. tolerates 15 boiled peanuts) in which case they will commence at STEP 5. Those who tolerate ¼ boiled peanut only will commence updosing at the pre-A step (Table 1).

Children in the ACTIVE group (and their parents) will undergo quality-of-life assessments at 0, 3, 6 and 12 and 24 months (see section 5.7.1).

Prior to discharge home, each family will be provided with:

- A **symptom advice sheet** (including advice on avoiding intense physical exercise up to 2 hours after the dose intake).
- A **food allergy management plan** (Figure 6), including an emergency medicine kit containing non-sedating oral antihistamine and two adrenaline auto-injectors. Where the child has a history of asthma or prior respiratory symptoms to a food allergen, the kit will also include a salbutamol inhaler and spacer device. Families and participants will be instructed in the prompt recognition and treatment of allergic reactions, including adrenaline auto-injectors.
- **Contact information** for the team, which will includes a dedicated mobile phone number with 24/7 access to a senior member of the medical team for urgent queries, and an email address which will be checked daily by the research team from Monday to Friday for non-urgent queries.
- **Dietary advice on peanut avoidance**. Participants receiving OIT will not be allowed to ingest peanut for the whole study duration (52 weeks) excluding the OIT doses.
- A **home diary and instruction sheet**, which will specify to parents what dose to give their child, and on to which they will log all doses taken at home and any resulting adverse events. Subjects will be asked to record any symptoms, duration, timing in relation to OIT dose and any exacerbating factors (e.g. exercise, excessive tiredness, viral illness). In the event of any symptoms, the family needs to contact the research team for advice. Participants will also be offered an opportunity to 'opt-in' to using an electronic 'mobile app' diary in parallel to the paper-based diary, the aim being to facilitate reporting by study participants and validate this approach for future OIT studies.

5.3.4.1 UPDOSING

At each step (i.e. all dose increases), the dose will first be given under medical supervision on the Research Unit, followed by observation for at least one hour (2 hours if participant has previously experienced a delayed reaction). Prior to a dose increase, the supervising clinician will assess the participant to ensure:

- No significant allergic reactions to doses given in previous 2 weeks.
- No acute exacerbation of asthma in the past week.
- No concurrent systemic illness.

The dose can be mixed into a carrier (such as low fat (rather than full fat) yoghurt, for example) if desired. Children will be monitored under medical supervision for one hour following dose administration. Following each dose increase, that dose will be given to participants at home daily for a minimum of 2 weeks until the next increase is performed.

STEP	PEANUT Boiling time	No. of peanuts / day	**No. weeks at this dose (minimum)**	**Cumulative No. of weeks (minimum)**	**Approximate Peanut protein (mg)**
pre-A	4 hours	1/8	2	-	15
pre-B	4 hours	¼	2	-	30
1	4 hours	½	2	2	65
2	4 hours	1	2	4	130
3	4 hours	2	2	6	260
4	4 hours	4	2	8	520
5	4 hours	8	2	10	1040
6	2 hours	4*	2	12	520
7	2 hours	8	2	14	1040
8	1 hour	2*	2	16	260
9	1 hour	4	2	18	520
10	1 hour	8	2	20	1040
11	1/2 hour	4*	2	22	520
12	1/2 hour	8	4	26	1040
	Open OFC to roasted peanut (to determine if updosing can be converted to roasted): • If reacts to ≤300mg dose, continue maintenance of 8 peanuts up to Wk 52 • If tolerates 300mg dose, continue updosing as follows:				
13	n/a	½ roasted PN	4	30	125
14	n/a	1 roasted PN	4	34	250
15	n/a	2 roasted PN	4	38	500
16	n/a	4 roasted PN	4	42	1000

Table 1: Updosing protocol for Peanut (PN) OIT using boiled and then roasted peanut.

*For initial (in-hospital) updosing at the time points marked, the dose to be administered will be split into 2 doses, given 30 minutes apart: Step 6: 1 + 3 peanuts; Step 8: 1 + 1 peanut; Step 11: 1 + 3 peanuts.

5.3.4.2 TRANSITION TO ROASTED PEANUT

After STEP 12 (approximately 4-7 months after commencement), the next updosing step involves a transition to roasted peanut. This will involve an OPEN (unblinded) abbreviated food challenge according to the following protocol:

Protocol 3: Open OFC to roasted PN	**Roasted peanut OFC (using defatted flour)**		**If dose tolerated, continue at STEP:**
TIME POINT (mins)	Peanut flour (mg)	Peanut protein (mg)	
0	20	10	Do not transition to roasted PN: continue at 8 boiled PN per day
30	60	30	
60	200	100	
90	600*	300*	13
150	2000	1000	13
180	6000#	3000#	16
Cumulative dose		**4440mg**	
2 hours observation period following last dose to monitor for signs of reaction			

*Dose to be given as 1 whole peanut (25% protein) + peanut flour to make a total dose of 300mg peanut protein
#Dose to be given as 4 whole peanuts + peanut flour to make a total dose of 3 gram peanut protein

The criteria listed in Section 5.2.2 will be used to determine outcome of this food challenge.

Children who tolerate at least 300mg peanut protein (i.e. a cumulative dose of 440mg) will continue updosing at STEP 13 using roasted peanut. Those who tolerate the entire dose (4440mg) will continue at STEP 16. This is equivalent to continuing OIT at a minimum of one half roasted peanut BELOW that tolerated at this open challenge. Children who are unable to tolerate the 300mg dose will continue maintenance at 8 boiled peanuts (boiled for 30mins) until the 1 year assessment.

All subjects will also undergo repeat skin prick testing to commercial crude peanut extract, and quality-of-life assessments as described in section 5.7.1.

5.3.4.3 CHANGES TO THE PROTOCOL DUE TO REACTIONS

In the event of an allergic reaction to a dose of OIT within 2 hours of a dose, either at updosing in hospital or after a dose given at home, the following measures will be taken:

- For a single reaction consisting of wheeze, persistent cough, difficulty breathing, stridor or marked swallowing difficulties, the family must not give further OIT doses without contacting the research team. The previous lower dose will be given the next possible day, ideally under medical observation on the Research Unit.
- For skin symptoms, itchy mouth, rhinoconjunctivitis or mild abdominal symptoms, reassurance to families will be provided and the current dose will be continued, with daily contact with the study team as needed.
- For persistent reactions for 5-7 days (within 2 hours of the OIT dose) consisting of abdominal pain, rhinoconjunctivitis or skin symptoms, the dose will be reduced to the previous dose.
- In the event of other symptoms that prove difficult to the child, the dose can be reduced at investigator's discretion.

Where a dose reduction is required, the subsequent dose increase will be performed at least 2 weeks later at the Research Unit in hospital under supervision.

In the event of omitted doses:

- If a single dose of OIT is missed, the subject can continue with the usual dose.
- If 2 - 4 days of OIT are missed, give the previous dose until the subject can attend the research unit for the next updosing.
- If more than 4 days are missed, daily doses should stop and the subject must attend the research unit.

In the event of an intercurrent illness, where symptoms occur but are not related temporally to dose administration, families should contact the research team to discuss reducing the dose depending on symptoms type and intensity.

5.3.4.4 PREPARATION OF BOILED AND ROASTED PEANUT FOR OIT

Families will be provided with blanched raw peanut at hospital visits, for preparation at home. Full instructions will be provided (as part of the **home diary and instruction sheet**). Peanuts (Holt Runner cultivar, supplied by the Peanut Company of Australia Ltd) will be supplied in 125g vacuum-packed batches to families on an as-needed basis, in order to monitor peanut consumption.

Families will be provided with instructions to boil the peanuts at home in batches, as follows:

- Boil 100g quantity of peanuts in a saucepan in ~600ml water for xx hours
- Drain and plunge peanuts into cold water, then drain in colander/sieve
- Lay peanuts in a single layer on a baking tray lined with baking paper
- Place tray in freezer until peanuts are 'snap frozen'
- Transfer peanuts into a plastic container and store in freezer until required.

The boiling time will be progressively reduced as depicted in Table 1 above.

In those children who tolerate roasted peanuts, families will be instructed to use commercial roasted peanuts (KP roasted peanuts) sourced from a UK supermarket. Alternatively, peanut M&Ms may be substituted for roasted peanut, where this is desired by the study participant: four roasted peanuts is equivalent to 6 peanut M&Ms.

5.4 1 YEAR ASSESSMENT

All subjects, in both the active (OIT) and control groups, will be invited to undergo a further DBPCFC to roasted PN at 12 months. Those who tolerate >1.4g of peanut protein at this challenge will be invited back for a further open challenge having stopped all peanut ingestion (including OIT doses) for 4 weeks. The challenges and outcomes are depicted in summary form in Figure 7.

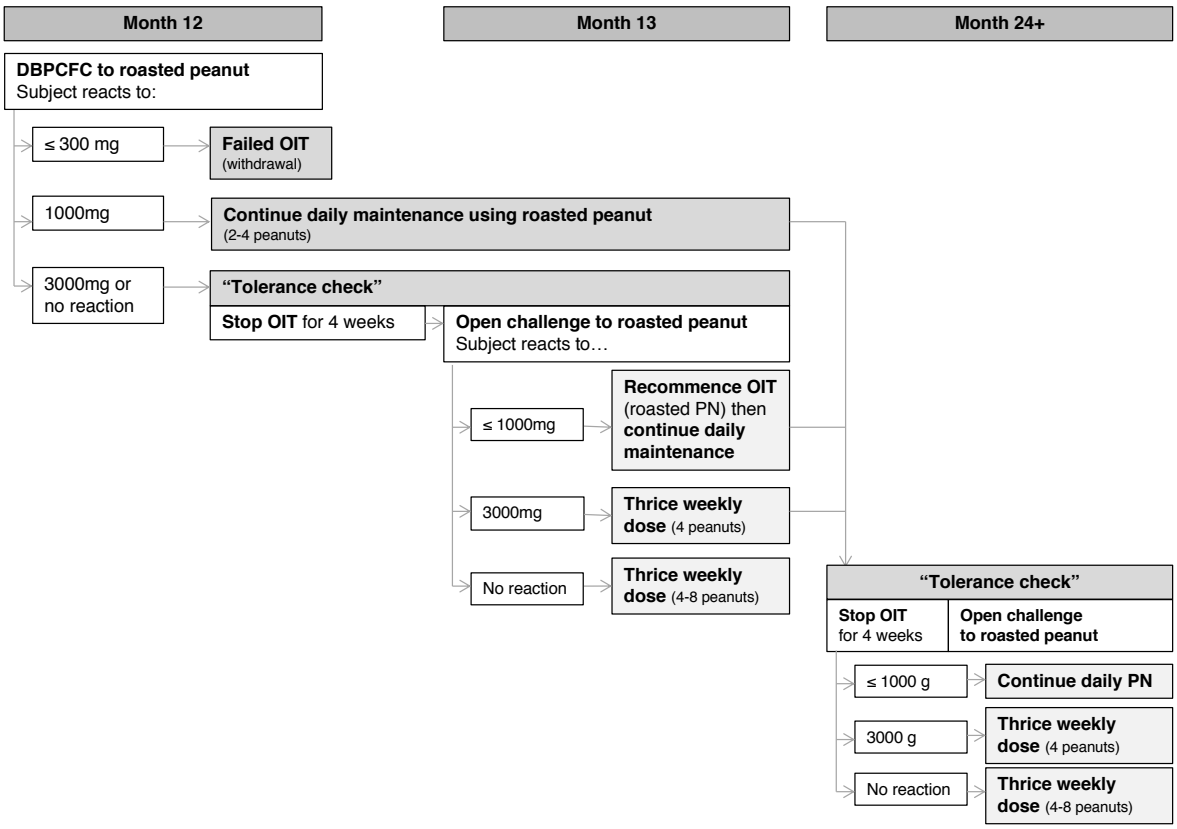


Figure 7: Challenges and outcomes, months 12-13

All subjects will also undergo repeat skin prick testing to commercial crude peanut extract, and quality-of-life assessments as described in section 5.7.1.

5.4.1 12 MONTH DBPCFC

The DBPCFC will be performed as per Protocol 1 in Section 5.2.2. The purpose of this challenge is:

- In those who have undergone OIT, to assess for desensitisation to roasted peanut and a resulting change in threshold of clinical reactivity (Primary and Secondary outcome measures).
- In the control group, to determine the rate of natural resolution of peanut allergy and for those continuing into WP2 (where they will undergo OIT), serve as the baseline threshold of clinical reactivity to roasted peanut.

Protocol 1: DBPCFC to roasted PN	**Roasted peanut DBPCFC (using defatted flour)**		**OUTCOME if reacts**
TIME POINT (mins)	Peanut flour	Peanut protein	
0	6	3	OIT unsuccessful: withdrawn from study*
30	20	10	
60	60	30	
90	200	100	
120	600	300	
150	2000	1000	Continue daily PN at previous maintenance dose
180	6000	3000	STOP peanut for 4 weeks and proceed to open challenge
Cumulative dose		**4440mg**	**If no reaction:** STOP peanut for 4 weeks and proceed to open challenge
2 hour observation period following last dose			

*In the unlikely event that a child reacts to the 300mg dose during challenge but has previously tolerated ≥1 roasted PN, then they can continue daily peanut at the previous tolerated dose for a further 12 months, within this protocol.

5.4.2 TOLERANCE CHALLENGE AT 13 MONTHS

Children in the active group who meet the primary study outcome (desensitised to >1.4g peanut protein at DBPCFC) will then be instructed to stop all peanut exposure (including OIT doses). A further open challenge will be performed after 4 weeks, according to protocol 3, using criteria listed in Section 5.2.2 to determine outcome. Children who tolerate at least 1.4g peanut protein at this challenge will continue with thrice weekly maintenance peanut therapy (4-8 peanuts). Those who react will recommence updosing to the previously tolerated dose and then continue daily maintenance peanut until the 24 months time point.

Protocol 3: Open OFC to roasted PN	**Roasted peanut OFC (using defatted flour)**		**OUTCOME if reacts**
TIME POINT (mins)	Peanut flour	Peanut protein	
0	20	10	RECOMMENCE OIT and updose to previous tolerated dose. Then continue DAILY maintenance of up to 4 peanuts. Repeat tolerance OFC at 24 mths
30	60	30	
60	200	100	
90	600	300	
120	2000	1000	
150	6000	3000	Change to minimum thrice weekly maintenance dose of 4 peanuts.
Cumulative dose		**4440mg**	**If no reaction:** Change to thrice weekly maintenance dose of 4-8 peanuts
2 hour observation period following last dose			

5.5 WP2: YEAR 2 OF STUDY

Children in the control group will be offered OIT using boiled PN during months 12-24. An identical protocol to WP1 will be used (section 5.3.3).

Children in the active group (who underwent OIT during months 1-12) will be offered ongoing maintenance therapy, as described above in section 5.4.

5.6 2 YEAR ASSESSMENT

Children who were originally assigned to the control group and who have undertaken OIT during months 12-24 will undergo a further DBPCFC to roasted PN at 24 months. The DBPCFC will be performed as in Section 5.2.2. The purpose of this challenge is to assess for the development of sustained unresponsiveness to roasted peanut following OIT, and the resulting change in threshold of clinical reactivity.

All subjects will also undergo repeat skin prick testing to commercial crude peanut extract and boiled peanut slurry, and quality-of-life assessments as described in section 5.7.1.

All children (in both control and active groups), apart from those who passed the tolerance challenge at 13 months, will be offered a further tolerance challenge at 24 months, to be performed as in section 5.4.

5.7 YEAR 3/4 ASSESSMENTS

All children (in both active and control groups) will be invited to return at the 3 year timepoint for a further set of challenges, to define longer-term tolerance following 2-3 years of active immunotherapy. This is because there is data to suggest that longer duration of OIT is associated with immune memory and more sustained tolerance. These assessments will consist of:

i. A DBPCFC at the year 3 timepoint (3 years following randomisation) (conducted according to section 5.4.1)

ii. Open food challenge 4 weeks after stopping OIT (identical to tolerance challenge, section 5.4.2)

iii. In participants who exhibit sustained unresponsiveness at 4 weeks, a further DBPCFC (conducted according to section 5.4.1) after a further 8 weeks off OIT, to assess for sustained unresponsiveness at 12 weeks.

iv. In participants who exhibit sustained unresponsiveness at 12 weeks, a further DBPCFC (conducted according to section 5.4.1) after a total of 1 year off OIT, to assess for sustained unresponsiveness at 1 year.

These assessments are summarised in Figure 8.

All families will continue to receive access to the 24/7 helpline during this time. Any participant who reacts at challenge to a previously tolerated level will recommence updosing.

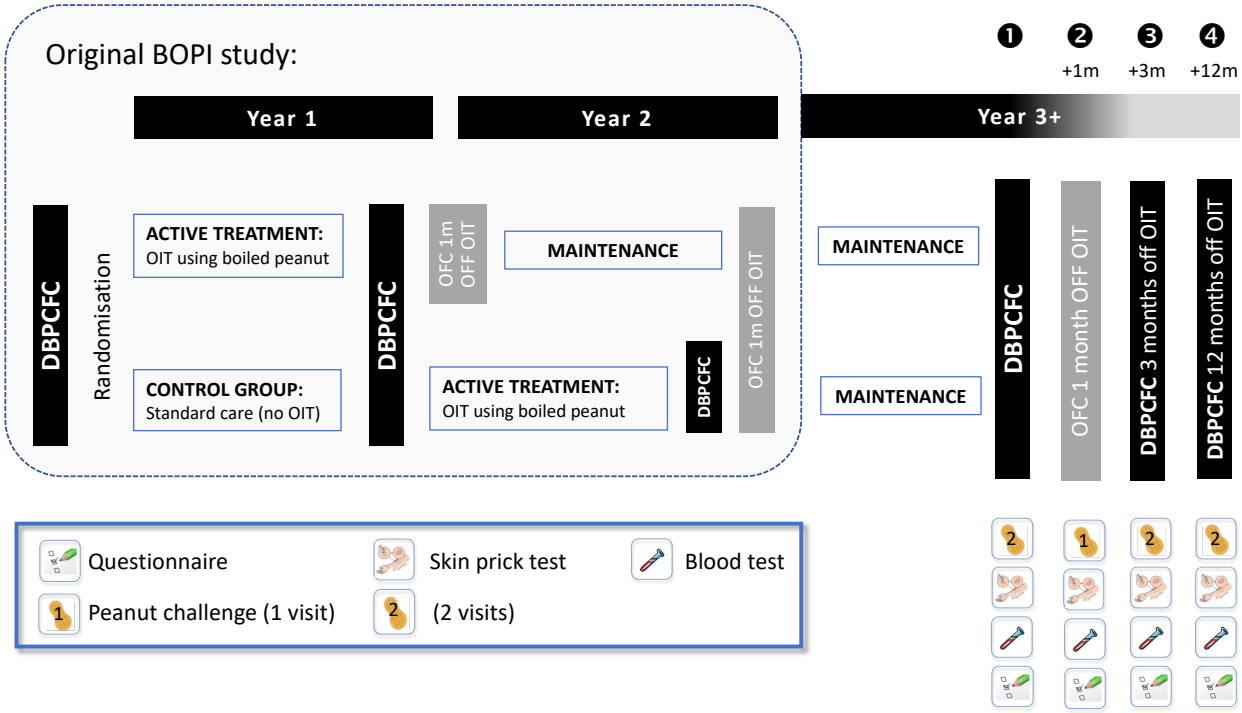


Figure 8: Year 3/4 Assessments

Participants who go on to stop all peanut for 12 months (i.e. who pass the 12-week DBPCFC without any loss of tolerance) will be asked to eat 8 roasted peanuts on a monthly basis as a safety measure, to ensure ongoing clinical non-reactivity during this time. Any participant who begins to exhibit symptoms during this 9 month period (prior to final DBPCFC) to the monthly dose of 8 peanuts will be reviewed by the study PI who may take the decision to recommence peanut and not to proceed to the 12 month challenge. This is in order to prevent any participant from reverting back to clinical reactivity that cannot be remedied easily.

5.8 OTHER ASSESSMENTS

5.8.1 ALLERGY SKIN PRICK TESTING

Skin prick testing (SPT) to commercial peanut extract, histamine positive and saline negative control will be performed at baseline, 6, 12, 24 months after starting OIT, and the year 3 assessments (see Fig 8), according to local standard operating procedures consistent with national guidelines.[13] The baseline SPT will include a modified SPT to boiled peanut.

At the open food challenges (e.g. 6 month challenge), SPT will be performed by an investigator independent to the challenge so as not to influence the interpretation of challenge outcome. Additional positive controls will be included as needed to ensure blinding of the participant.

[13] http://www.bsaci.org/Guidelines/Skin_Prick_Testing.pdf

5.8.2 QUALITY OF LIFE ASSESSMENTS

The impact of OIT on participants' quality of life (QoL) will be assessed both from parents' and participants' perspective using abbreviated versions of disease-specific validated "food-allergy quality of life questionnaire" (FAQL-Q) in its parental,[14] child[15] and teenage[16] forms at baseline, 3, 6, 12, 24 and 36 months in both the active and control groups. These new abbreviated versions have been validated (data submitted for publication). We will also assess the impact of the child's food allergy on parent QoL, using the FAQL-Parent Burden form (which has been validated in a UK population).[17] QoL assessments will be done both prior to and after oral challenges.

The FAQL-questionnaires are based on a 7-point Likert scale and changes greater than 0.5 points over time have been defined as clinically significant.[18] Previous studies have reported a positive effect on QoL following OIT to peanut from the parents' perspective,[7] however, there are no controlled studies which have addressed the impact on QoL as perceived by participants. This is a significant knowledge gap, since there is a concern that while parents report an improved QoL when their child undergoes OIT, the child themselves may experience a worsening of QoL due to frequent side effects and need to alter their activities following OIT doses.

In line with current expert opinion, and to ensure the ability to compare responses consistently during the first 12 months of OIT, children who are age 12 at study commencement will be asked to complete the Teenage versions of the QoL assessments, unless there are difficulties with comprehension which preclude this.

We will also assess parental anxiety before, and 12 and 24 months after their child commencing OIT, using the Perceived Stress Scale.[19]

In subjects who fail visit 3 (tolerance check to boiled peanut) or are withdrawn during the active OIT phase due to a significant allergic reaction, we will contact the family at 1 and 6 months after the event to repeat the QoL assessments. This will allow us to assess the impact of 'failing' OIT on the young person and their family. In addition, at both time points, we will ask the family if we can arrange a convenient time when we can undertake a limited structured telephone interview (10-15 minutes) with the parent/guardian(s) and their child, to explore any issues which might have been raised as a result of the reaction, following the outline in Appendix 3. The answers to these questions will be documented and analysed using the framework method.[20]

5.8.3 LABORATORY ASSESSMENTS

The development of tolerance in immunotherapy (whether to food or aeroallergens) is associated with several immunological changes, including decreases in peanut-specific IgE levels with concomitant increases in IgG4 levels, reduced basophil and TH2 cytokine responses to peanut stimulation and upregulation of IL-10-producing T-regulatory cells.[21] However, many of these appear to be transient, and there remain significant gaps in knowledge, particularly in understanding why many subjects require ongoing exposure to the allergen (i.e. maintenance dosing) to maintain sustained unresponsiveness.

[14]DunnGalvin A, Cullinane C, Daly DA, Flokstra-de Blok BM, Dubois AE, Hourihane JO. Longitudinal validity and responsiveness of the Food Allergy Quality of Life Questionnaire - Parent Form in children 0-12 years following positive and negative food challenges. Clin Exp Allergy. 2010;40:476-85.
[15]Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, et al. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. Clin Exp Allergy. 2009;39:127-37.
[16]Flokstra-de Blok B, DunnGalvin A, Vlieg-Boerstra BJ, et al. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. J Allergy Clin Immunol. 2008;122:139-44, 144.e1-2.
[17]Knibb RC, Stalker C. Validation of the Food Allergy Quality of Life-Parental Burden Questionnaire in the UK. Qual Life Res. 2013;22:1841-9.
[18]Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials 1989; 10:407–15.
[19] Cohen, S., Kamarck, T., and Mermelstein, R. (1983). A global measure of perceived stress. Journal of Health and Social Behavior, 24, 386-396.
[20] Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol. 2013 Sep 18;13:117.
[21]Gorelik M, Narisety SD, Guerrerio AL, et al. Suppression of the immunologic response to peanut during immunotherapy is often transient. J Allergy Clin Immunol. 2014; doi: 10.1016/j.jaci.2014.11.010.

It is therefore important for this study to include mechanistic assessments to allow for markers of successful desensitisation to be assessed, in order to improve the efficacy of future OIT protocols. We will include a series of laboratory assessments in subjects undergoing OIT, allowing longitudinal comparisons to be made in those undergoing OIT (vs controls) to assess the following:

- Changes in serum specific antibodies pre- and post-OIT: Total IgE; specific IgE, IgG4 to whole peanut and peanut components (Ara h 1, 2, 3, 8 and 9) and their ability to cause an effector cell response will be measured
- IgE-immunoblot using patient sera to identify in vitro the binding of participants IgE to peanut proteins, and how this varies during OIT.
- Identification of serum factors associated with the development of oral tolerance during peanut OIT, by means of a validated IgE facilitated-binding assay.
- Changes in basophil responses (assessed by CD63 and CD203c expression by flow cytometry) following *in vivo* and *ex vivo* peanut stimulation, and how these vary during OIT. Confirmatory work will be performed in a subset of patients using purified basophils isolated from whole blood.
- Biomarkers that may identify successful tolerance induction to peanut
- Changes in T and B cell populations and their immune profile during OIT, including allergen-specific proliferation of T-cell subtypes (including T helper and regulatory T cells) and changes in immunoglobulin repertoire by peanut-specific B-cells.
- mRNA expression and methylation of proteins (such as forkhead box protein 3 (FOXP3) sites) on T cell subsets which may predict the presence of sustained unresponsiveness.

These assessments will be performed on blood samples taken at baseline, 3, 6, 12, 13 and 24 months, as well as at the 3 year assessments (outlined in Figure 8) after commencement of OIT. Laboratory work will be initially performed at the National Heart & Lung Institute, Imperial College London, although some assays may be performed elsewhere in the UK or abroad, where lack of local expertise necessitates this). Specimens may also be stored for future use in new assays to measure immune responses or biomarkers, as research tests are developed.

5.9 STUDY COMPLETION

The study duration is for up to 4 years following randomisation, as outlined in section 5.7. The study will be considered complete following enrolment of the last patient and completion of the study procedures in that patient.

At the end of the study, children will be re-integrated into the routine clinical allergy service for ongoing care.

5.9.1 EARLY STUDY TERMINATION

An Independent Data Monitoring Committee (IDMC) will assess study safety on a regular basis. The IDMC has the authority to suspend the study, or request withdrawal of a particular participant, at any stage if it concludes there are significant safety concerns affecting a single participant or the study as a whole.

Recruitment to the study, and further peanut challenges and updosing, will be suspended pending review by the IDMC in the event of:

- any death
- a participant being admitted to the intensive care unit for a study-related adverse event
- a participant experiencing a life-threatening anaphylactic reaction to an OIT dose.

The IDMC will consider the circumstances and make a recommendation as to whether to terminate the study, or continue with or without a protocol amendment.

6. ADVERSE EVENT REPORTING

6.1 DEFINITIONS

An **adverse event** is any occurrence or worsening of an undesirable or unintended sign, symptom, laboratory finding, or disease that occurs during participation, including occurrences that are not necessarily caused by or related to a study intervention. An adverse event will be followed until it resolves or until 30 days after a participant terminates from the study, whichever comes first.

A **serious adverse event** (SAE) is defined as any adverse event that suggests a significant hazard. This includes but is not limited to any of the following:

1. Death: Any death that occurs during the study must be reported whether considered treatment related or not.

2. A life-threatening event: Any adverse therapy experience that, in the view of the investigator, places the participant at immediate risk of death from the reaction as it occurred.

3. Inpatient hospitalization or prolongation of existing hospitalization.

4. Persistent or significant disability.

5. An event that requires intervention to prevent permanent impairment or damage. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

6. Important AEs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

The adverse event can be described as '**expected'** if it caused symptoms and/or signs that could be reasonably described as a consequence of an allergic reaction to peanut exposure within the protocol. Symptoms of an allergic reaction are defined as any described within this protocol.

An adverse event is considered "**unexpected**" when its nature or severity is not consistent with the investigator's protocol.

An adverse event is defined as "**related**" when it has resulted from the administration of any of the research procedures. Related adverse events are defined as "**adverse reactions"**.

Any symptoms requiring treatment for anaphylaxis (adrenaline, steroids, salbutamol) following an OIT dose **will be classified as a SERIOUS ADVERSE REACTION**.

6.2 DOCUMENTATION OF ADVERSE EVENTS

All adverse events will be recorded on a specifically designated case report form (CRF) from the time the participant provides consent until the time the event resolves or until 30 days after the participant completes study treatment. Adverse events may be discovered through observing and questioning the participant or receiving an unsolicited complaint and questioning the participant in an objective manner. All adverse events will be recorded, regardless of their severity or relation to study medication or procedures.

All serious adverse events (SAEs) will be reported on a SAE report form in addition to CRFs. Safety data will be reviewed at least every four months by the Independent Data Monitoring Committee (IDMC). The IDMC has the authority to recommend withdrawal of a study participant or termination of the trial because of safety findings.

All SAEs should be reported to the Research Ethics Committee, where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

6.3 GRADING AND ATTRIBUTION OF ADVERSE EVENTS

The study site will grade the severity of adverse events experienced by study participants according to the criteria set forth in the NCI-CTCAE Version 3.0.[22] This document provides a common language to describe levels of severity, to analyse and interpret data, and to articulate the clinical significance of all adverse events.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event.

Grade 2 = moderate adverse event.

Grade 3 = severe and undesirable adverse event.

Grade 4 = life-threatening or disabling adverse event.

Grade 5 = death.

All adverse events will be recorded and graded whether they are or are not related to disease progression or treatment. The NCI-CTCAE grades will be the primary source for scoring.

Allergic reactions will be graded according to World Allergy Organisation (WAO) criteria for allergic reactions to immunotherapy, modified for use with food-triggered allergic reactions. These can be used to inform as to the appropriate NTI-CTCAE grade (Table 2).

The relation, or attribution, of an adverse event to study participation will be determined by the investigator and recorded on CRF and/or SAE reporting form. The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below (Table 3). If any doubt about the causality exists the investigator will discuss with the Chief Investigator. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case.

[22] http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom(s)/sign(s) of GI and/or 1 organ system present **Cutaneous** Generalized pruritus, urticaria, flushing, or sensation of heat or warmth **or** Angioedema (not laryngeal) **or** **Gastrointestinal** Abdominal cramps, vomiting, or diarrhoea **or** **Upper respiratory** Rhinitis - (eg, sneezing, rhinorrhoea, nasal pruritus and/or nasal congestion) **or** Throat-clearing (itchy throat) **or** Cough perceived to originate in the upper airway, not the lung, larynx, or trachea **or** **Conjunctival** Erythema, pruritus or tearing **Other** Nausea, metallic taste, or headache	***Symptom(s)/sign(s) of 2 or more (not including GI) organ system present*** **or** **Lower respiratory** Asthma: cough, wheezing, shortness of breath (e.g. fall in PEF or FEV_1 <40%, salbutamol-responsive wheeze) **or** **Other** Uterine cramps	**Lower respiratory** Asthma (e.g. fall in PEF or FEV_1 >40%, wheeze not responsive to salbutamol) **or** **Laryngeal oedema** with or without stridor	**Lower or upper respiratory** Respiratory failure with or without loss of consciousness **or** **Cardiovascular** Hypotension with or without loss of consciousness	Death

Table 2: World Allergy Organisation (WAO) Grading System for allergic reactions (modified for applicability for food-triggered reactions) adapted from J Allergy Clin Immunol 2010; 125:569-74**.**

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Table 3: Assignment of causality for adverse event

7. STATISTICS AND DATA ANALYSIS

7.1 SAMPLE SIZE ESTIMATION

Current data from Europe and North America indicates that at least 80-85% of peanut-allergic children will react to 1.4g peanut protein. The incidence of natural resolution of peanut allergy over a 12 month period is typically <10%, on the basis of data arising from our clinical service.

For the purpose of this study, we have assumed a conservative estimate of 10% for natural resolution, and a 20% drop-out rate. We note that such is the demand for OIT that in the published studies, drop-out rates have been consistently <10%.

We propose to recruit 46 peanut-allergic children to the study, who will be randomized 2:1 to active (n=30) or control (n=16) groups. This will allow us to detect a rate of successful desensitisation of 60% in participants undergoing OIT, with 80% power using a two-sided significance level of 0.05 and with continuity correction, whilst allowing for a 20% loss-to-follow-up.

These figures for desensitisation rate and resolution are based on published data relating to the UK.[7]

7.2 STATISTICAL ANALYSIS PLAN

Data will be collected on paper CRFs which include the patients name, DOB and hospital number. Participants will be assigned a study number, which will be noted on the paper record. Data will then be entered on to a password-protected computer database on the secure hospital IT system; only the study number will be used to identify the patient data.

De-identified data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

The primary analysis will be performed on an intention to treat basis: all subjects allocated to each arm will be analysed together as representing that treatment arm, irrespective of compliance and whether or not they have completed the prescribed regimen. A secondary analysis will also be performed on a per protocol basis.

Subjects who are withdrawn from active treatment will remain in the study for assessment of outcome relating to QoL measures.

7.2.1 ANALYSIS OF PRIMARY ENDPOINT

The primary analysis will compare the proportion of subjects who tolerate 1.4g (or more) roasted peanut protein in the active and control groups, 12 months after randomization, using a two-sided Fisher's exact test at a $p<0.05$ level of significance.

7.2.2 ANALYSIS OF SECONDARY ENDPOINTS

The following secondary analyses will be performed, using two-sided testing for non-parametric data at a $p<0.05$ level of significance:

- Relative change in clinical threshold (NOAEL, LOAEL) to roasted peanut at 6 and 12 months in active vs control, using Mann-Whitney U test.
- Proportion of subjects who tolerate 1.4g (or more) roasted peanut protein in the active and control groups, 12 months after randomization and following cessation of all peanut intake for 4 weeks after 1 and 3 years of OIT, using a two-sided Fisher's exact test at a $p<0.05$ level of significance.
- Change in quality of life assessments before, and at 6 and 12 months after OIT, as assessed by FAQL-Questionnaire in children, teenagers and their parents – in the active vs control groups – using paired and group comparisons by non-parametric testing.
- The incidence of adverse events experienced between active and control groups. Statistical differences will be determined using Fisher's exact test for proportions or using non-parametric tests for graded reactions. Logistic regression will be used to assess the influence of age, gender, asthma status and prior history of anaphylaxis on incidence of adverse events.
- Immunological outcome measures pre-, during and post- 12 months of OIT, using Mann-Whitney U test (for paired comparisons) or Friedman's test (for trends over time).

7.2.3 INTERIM ANALYSIS

There will be no formal interim analysis, however the IDMC will review safety data at least every 4 months.

8. ADMINISTRATIVE AND REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Chief Investigator will obtain the required approvals from the relevant Research Ethics Committee. The study will be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 INFORMED CONSENT AND PARTICIPANT ASSENT

Consent to enter the study must be sought for each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed consent from the parent/legal guardian should be obtained. Participant assent will also be sought. The right of the parent/guardian to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 MHRA EXEMPTION

Following discussions with MHRA, it has been confirmed that this study is not a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC, thus no submission to the Clinical Trials Unit at the MHRA is required. The peanuts are a food product and are not presented as a medicine (eg in a pharmaceutical form). The study is therefore exempt from MHRA requirements for a clinical trial. This confirmation is reproduced in Appendix 4.

8.4 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study under the Data Protection Act.

8.5 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.6 SPONSOR

Imperial College London will act as the main Sponsor for this study.

8.7 FUNDING

Funding has been secured from the NIHR Biomedical Research Centre at the Imperial Academic Health Sciences Centre (AHSC), a partnership between Imperial College Healthcare NHS Trust and Imperial College London.

8.8 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9 STUDY MANAGEMENT

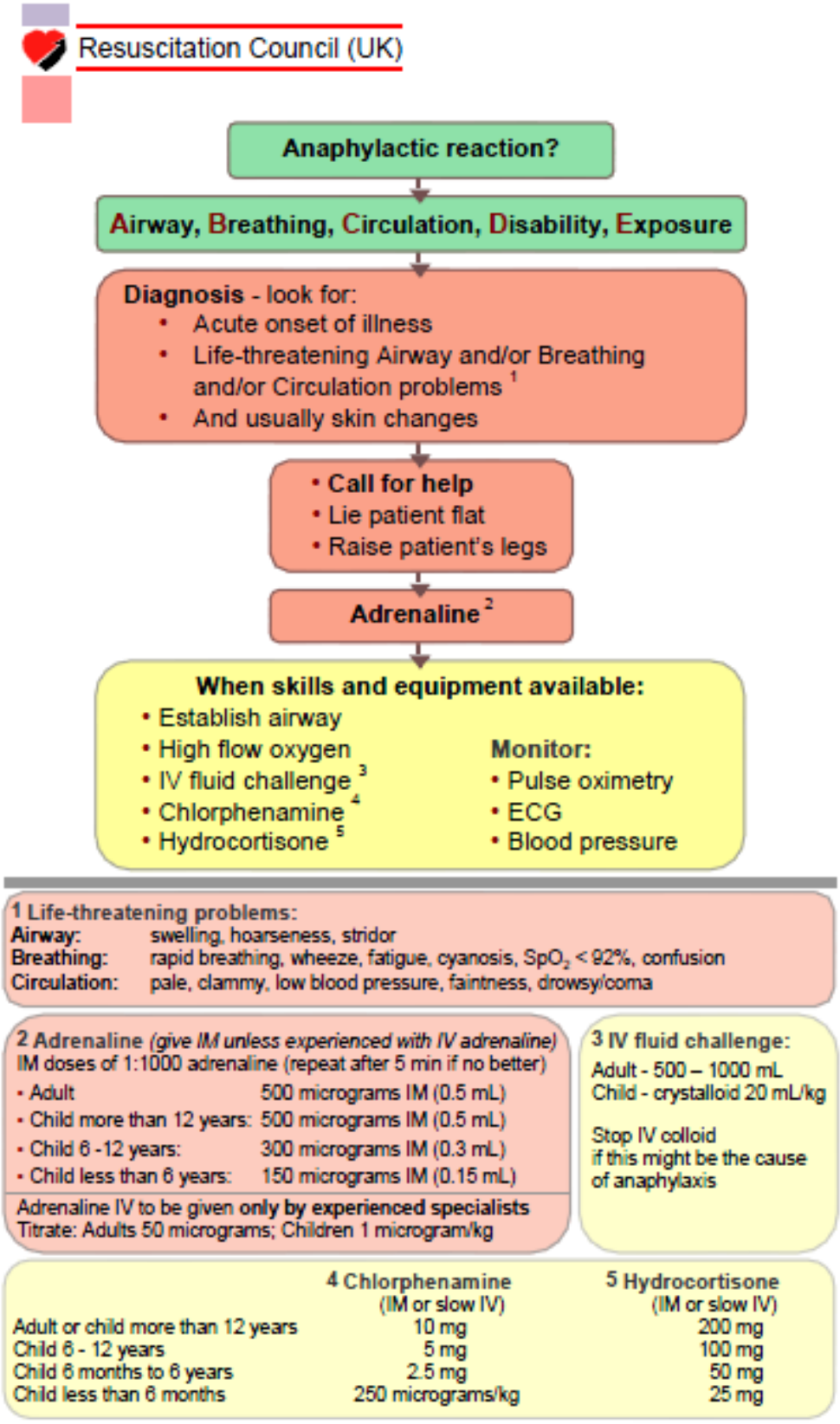
The day-to-day management of the study will be co-ordinated through Dr Paul Turner (CI).

10 PUBLICATION POLICY

Results of this study will be published in scientific peer-reviewed literature relevant to allergic disease. Members of the Trial Management Group and the Data Monitoring Committee will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy.

APPENDIX 1: MANAGEMENT OF ANAPHYLAXIS

In the unlikely event of a participant requiring treatment for anaphylaxis beyond an initial dose of IM adrenaline, the UK Resuscitation Council guidelines for anaphylaxis will be followed:



In the event of refractory anaphylaxis (requiring over 2 doses of IM adrenaline or at investigator initiation), consideration will be given to initiate an adrenaline infusion according to a published protocol (reproduced below). This will be initiated ONLY under the direct supervision of a consultant experienced in the management of anaphylaxis.

The adrenaline infusion should be delivered by a syringe pump and not via a volumetric pump. The infusion can be administered through a dedicated peripheral line (to avoid inadvertent bolus dosing with other drugs/fluids), but the cannula should be sited in a large vein.

ADRENALINE INFUSION GUIDELINE FOR ANAPHYLAXIS

1 PREPARATION

- Requires continuous physiological monitoring **(ECG, SpO2, BP 3-5 minutely)**
- Give via an **infusion pump** through a **dedicated line**, or piggybacked with **anti-reflux valves on all other lines** to prevent the adrenaline going back up into another fluid bag instead of into the patient
- BEWARE infusions on the same side as a BP cuff; frequent BP measurements may interfere with the infusion
- FIRST BAG: **1mg adrenaline in 100 mL saline = 0.01mg/mL (1:100,000)**
  i.e. 1 ml/kg/Hr gives the equivalent of a 0.01 mg/kg dose over 1 hour (0.17 ug/kg/min)

2 INITIATION & ADJUSTMENT

- **Start at 0.5-1 mL/kg/Hr** (30-100 mL/Hr in adults) depending on reaction severity:
  Moderate severity: 0.5 mL/kg/Hr Severe (hypotensive or hypoxic): 1 mL/kg/Hr
- **Titrate** up or down according to response, aiming for the lowest effective infusion rate
  Allow for a short elimination half-life; steady state is reached 5-10 minutes after a change in the infusion rate
- **Tachycardia, tremor, and pallor with a normal or raised blood pressure are signs of adrenaline toxicity:**
  Reduce the infusion rate (if toxicity is severe, stop the infusion briefly before recommencing at a lower rate)
- **The safe maximum rate of adrenaline infusion** is unknown, but is probably <1 ug/kg/min (6mL/kg/Hr of the above solution of 1mg in 100 mL).

3 DE-ESCALATION AND CESSATION

- **As the reaction resolves, an infusion that was previously therapeutic can start to have toxic effects:** Therefore, when features resolve begin reducing the infusion, aiming for around half the starting rate if possible
- 60 minutes after the resolution of all symptoms and signs, wean the infusion over another 30 minutes and stop; watch closely for reaction recurrence

APPENDIX 2 MHRA EXEMPTION

From O'Kane, Martin **Date** 29/05/2014 22:08:21
To Turner, Paul J
Cc
Subject RE: SCOPE - Food allergy study

Dear Paul,
Following our 'scope' meeting today I can confirm that your study would not be considered as a CTIMP under the Clinical Trials Directive 2001/20 EC. The peanuts are a food product and are not presented as a medicine (eg in a pharmaceutical form).

Best regards,
Martin

Dr E Martin O'Kane
Pharmaceutical Assessor & Acting Manager
Clinical Trials Unit
MHRA
Buckingham Palace Road, London, SW1W 9SZ, UK
Telephone: 020 3080 6659

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MHRA is a centre of the Medicines and Healthcare Products Regulatory Agency

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From: Turner, Paul J [mailto:p.turner@imperial.ac.uk]
Sent: 22 May 2014 23:19
To: O'Kane, Martin
Subject: RE: SCOPE - Food allergy study

Dear Martin,

I hope you are keeping well. You may recall that back in January, we had a conversation about the need for a CTA for various discussions regarding food allergy studies. Given those discussions (see your email below), I was hoping to pick your brain again on a closely-related matter.

We wish to conduct a clinical trial to desensitise patients with peanut allergy. This approach is standard practice in some European countries, and involves giving small amounts of the food to which the person is allergic to build up a level of tolerance (in much the same way that someone planning to run a marathon needs to train to get fit).

A recent study (in Cambridge, which made BBC news etc) used powered peanut flour to acheive this end, and I understand from colleagues that this would be considered as medicinal product as the flour was not presented as food and was used to treat a medical condition (ie food allergy).

In our proposal, we wish to use peanuts (out of a packet, like you might purchase in any shop) for desensitisation. The novel aspect is that we have data from Australia that cooking the peanut (something which is routine in Asian cuisine) results in many peanut-allergic people tolerating the peanut (interesting!).

We want to provide peanuts (from a packet purchased in a supermarket) for families to boil at home and then use as part of a desensitisation protocol, under strict medical supervision. I am unclear as to whether such a study would qualify as a CTIMP; it is a clinical trial, but the product (peanut) is presented as exactly that - a whole peanut, without any form of modification or processing at our end. In fact, the only reason we are providing the peanuts (rather than the patients purchasing them direct) is to reduce cost to participants, ensure that we are using a similar 'cultivar' of peanut throughout, and help us monitor patient compliance (from how long the packet lasts).

Given this, would the product be classified as a "food product not presented as a medicine" and thus not be subject to MHRA oversight? Or, if it is considered to be an IMP, what information would you need in our CTA application, given that we are providing subjects with packets of peanut purchased from a supermarket? Would the MHRA adopt the same 'pragmatic' approach as you outlined below "accept a bare minimum package (<1 page) essentially saying how the product is made" - as this product would not have been 'made' as such, it is peanut!

Just in case you need, here are further details of what we are planning:

Trial Design: An open, randomised 2 phase cross-over study in subjects with peanut allergy. During the first phase, subjects in the active group will be provided with peanuts (commercial source, from supermarket, in sealed packets as purchased) to use as part of a protocol. The protocol will provide instructions to the subjects to boil the peanuts at home (in water) for set amounts of time, and then consume the peanut under medical oversight. Subjects in the control group will undergo no intervention other than routine care, until 12 months when they will be offered to receive peanut desensitisation as per the active group.

Purpose of Trial: To investigate whether low dose exposure to boiled peanuts results in tolerance to roasted peanut after 12 months of treatment.

Products Administered: Supermarket-sourced peanuts, in original (unopened) packaging as purchased.

Key Parameters: Amount of peanut tolerated pre- and post-protocol, as determined at formal food challenge (as per routine clinical practice)

Many thanks for your help and advice.

With kind regards,

Paul

Dr Paul Turner
MRC Clinician Scientist, Senior Lecturer and Honorary Consultant in Paediatric Allergy & Immunology
Imperial College London / Imperial College Healthcare NHS Trust
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F: +44 (0) 20 3312 7571

APPENDIX 3 STRUCTURED TELEPHONE INTERVIEW FOR STUDY PARTICIPANTS WHO FAIL THE OIT PROTOCOL

In participants who fail the OIT protocol (either due to allergy to ¼ boiled peanut, or who are withdrawn due to adverse events during updosing), we will contact the family at 1 and 6 months after the event, to ask if we can arrange a mutually convenient time to undertake a limited structured telephone interview (10-15 minutes) with the parent/ guardian(s) and their child. The aim is to explore any issues which might have been raised as a result of the reaction, following the following outline:

Guide to telephone interview:

1. Confirm interviewee's identity

2. Introduce yourself:

   "I am <name>, from the BOPI Study. We arranged to speak briefly today to discuss any issues or questions you may have, following your <participant's name> involvement in the BOPI study.

3. *"First, do you have any questions about the study or your allergy?"*

4. *"Has your understanding of food allergy, and peanut allergy in particular, changed as a result of the study?"*

   [In what ways? Explore views on significance / perceived severity / future care]

5. *"Has taking part in the study changed how you feel about your peanut allergy? Is there anything that now worries you or bothers you?"*

6. "*How do you feel about taking part in the study? Did it help you?"*

   [Do you think it was good / bad / waste of time / unsure?]

7. *"If you were taking part in the study again, is there anything you would suggest that we do differently?"*

8. *"Thank you for taking part in the study, please do let us know if there is anything else you would like to ask us."*