

Project Title:	Study of Tolerance to Oral Peanut
Project Ref:	08-99-18
Cost:	£671,247
Lead Applicant & Institution:	Dr Pamela Ewan & Dr Andrew Clark University of Cambridge
Start Date:	1 January 2010
Plain English Summary:	<p>We propose to study a new treatment for peanut allergy with the potential for major improvement in patient care. Peanut allergy is the commonest cause of fatal food-allergic reactions, population studies show it affects 2% of children, meaning tens of thousands of UK children are at risk. Spontaneous resolution is rare and patients are at risk of anaphylaxis and death. The perpetual fear and inconvenience surrounding restricted food choices and the requirement to carry emergency adrenaline injections at all times causes a significant reduction in quality of life. There is no treatment for this condition except to advise patients to avoid peanuts. With current practice up to 55% of children have accidental reactions every year, a significant number are severe and deaths occur. There is a clear need to develop a novel disease-modifying treatment.</p> <p>This is a definitive study of a new treatment based on a successful pilot study. This treatment could be made widely available across the NHS with considerable benefit for patients. We will recruit 104 peanut allergic subjects and allocate them to treatment and control groups using methods to reduce bias. The control group will be advised to avoid peanuts during a 5 month waiting period (i.e. the current standard practice). For the treatment group we will carefully administer increasing amounts of peanut flour by mouth over 5 months. Doses are increased every 2 weeks in hospital and the same doses taken daily at home. Subjects then receive a period of maintenance treatment with the highest dose for six weeks (approx. 5 peanuts). The main outcome measure is the proportion of subjects in each group who do not react to a peanut challenge test (i.e. the proportion whose allergy is 'cured'). Afterwards, to maintain a high ethical standard and encourage good compliance, after the waiting period, subjects in the control arm will also be offered the treatment. Other outcomes will be the change in quality of life score before and after intervention. Blood laboratory tests will be analysed throughout to define the mechanism of intervention, identify biomarkers which predict successful treatment and identify individuals in whom treatment is likely to be successful.</p>

	<p>The pilot study demonstrated success in all 18 subjects who have completed the protocol to date. It also showed that the daily home treatment is well tolerated and no severe reactions occurred. The families involved say the therapy has transformed their lives, reflected by increased quality of life scores. Publication of the initial results last month attracted enormous positive media attention and the study was covered by over 600 television, radio and newspaper articles world wide. Ethical considerations include the risk that the initial oral challenge will induce a unpleasant allergic reaction. However, we have taken many precautions to ensure that this does not occur (confirmed in our pilot study). This risk is balanced by the likelihood that enrolment in the study will confer a significant benefit to subjects, who may be able to eat peanut after treatment.</p>
Abstract:	<p><u>Design:</u> This is a definitive efficacy study of peanut immunotherapy, with the potential to provide substantial health benefit in a common disease. It is a controlled study of efficacy and mechanism. The study design utilises double-blind placebo controlled food challenges to confirm the diagnosis of peanut allergy in 104 children, before allocating to active intervention or control groups using minimization (1:1 ratio). There are two work packages, in Package 1, the active group will undergo oral peanut immunotherapy (OIT- the intervention) and the control group will undergo a waiting list period of current standard management for 5 months. Both groups will then undergo double blind peanut challenge to determine tolerance. In Package 2, those subjects in the waiting list control group who are still allergic at the end of the period of standard management will undergo peanut immunotherapy. After active treatment the control group will undergo a final double blind peanut challenge.</p> <p><u>Setting:</u> The study will be performed in a single centre: Addenbrooke's Hospital, University of Cambridge Clinical School, by the Cambridge allergy research team as outlined in this proposal.</p> <p><u>Target population:</u> The target population will be subjects aged 7 to 18yrs with a history of peanut allergy, positive specific immunoglobulin E by skin prick test and/or serum assay and positive double blind oral challenge to peanut.</p> <p><u>Interventions being evaluated:</u> The intervention is peanut oral immunotherapy. Subjects will receive daily oral doses of roasted peanut flour starting with 1mg protein. Doses are increased at 2-weekly intervals (on the research ward) as follows: 1mg, 2mg, 5mg, 12mg, 25mg, 50mg, 100mg, 200mg, 400mg and 800mg. The median duration of up dosing in the pilot study (n=20) was 5 months. Daily doses are taken at home. The highest tolerated dose (up to 800mg protein) will be taken for six weeks following up dosing (maintenance period). This regime has been developed and refined in our pilot study and was well tolerated. The control group undergo a five month waiting period (with peanut avoidance advice and emergency treatment plan-current standard treatment) before undergoing a repeat peanut challenge.</p> <p><u>Measurement of outcomes and duration of follow up:</u> The primary outcome measure is the proportion of subjects in the active versus control groups who can tolerate a peanut challenge after six weeks of maintenance therapy at the highest tolerated dose, or avoidance respectively.</p>

	<p><u>Secondary outcome measures include:</u> 1. adverse reactions to OIT, 2. the proportion of control group subjects who have a negative peanut challenge after they undergo active treatment, 3. fold- and absolute-increase in tolerance for active and control groups after active intervention, 4. quality of life scores assessed by validated disease-specific quality of life questionnaires before and after intervention, 5. blood samples obtained in all subjects before and at 14, 75 and 150 days after starting OIT will be analysed for peanut specific IgE, IgG and peanut-specific lymphocyte proliferation and cytokine production (IL4, 13, and 10, IFN-gamma). Basophil activation markers CD63 and CD203c will be measured in older subjects by flow cytometry during peanut allergen stimulation and ratio of histamine HR1 to HR2 receptor mRNA on basophils by semi-quantitative polymerase chain reaction.</p> <p><u>Sample size:</u> 49 subjects in each group will provide 90% power to detect a 64% success rate in the active treatment group at 0.05% significance level (allowing for 30% success in the waiting list control group, which is higher than published natural resolution rates). We anticipate an approximate 5% drop out rate (as in pilot study) and we will therefore recruit 104 participants in total.</p> <p><u>Project timetables including recruitment rate:</u> We have a waiting list of 200 potential subjects for the study following the publicized release of our pilot results. We estimate that recruitment will take approximately 3 months.</p>
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