Protocol for food allergy outcome assessment in the Barrier Enhancement for Eczema Prevention trial

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Summary

Growing evidence suggests that early-onset eczema may be an important cause of food allergy. Pilot studies have indicated that regular emollient use during early life may reduce clinical expression of eczema. The Barrier Enhancement for Eczema Prevention (BEEP) study is a larger, pragmatic, multicentre, randomised controlled trial of daily emollient for the first year of life for primary prevention of eczema, in infants with a family history of atopic disease (ISRCTN21528841). Food allergy outcomes using skin prick testing and oral food challenge were added to the protocol through separate funding.

Objective: To assess whether daily application of emollient from early life to one year of age can reduce reduce food allergy.

Methods: When participants are 2 years old they are offered skin prick testing, asked about frequency of allergenic food consumption and history of reactions. Participants with possible cow's milk, egg or peanut allergy are invited for oral food challenge. An algorithm modified from the European Integrated approaches to Food Allergen and Allergy risk Management (iFAAM) consensus guidance was developed for categorising participants' food allergy status in cases where oral food challenge was not possible. The algorithm was developed and applied by a panel of food allergy experts, blinded to treatment allocation, to categorise participants' food allergy status.

Methods

Formal evaluation for the point prevalence of IgE-mediated food allergy, using a combination of food allergy history, skin prick testing (SPT) and oral food challenges (OFC), is conducted at age two years. The SPT and potentially subsequent OFC were added to the trial protocol following approval by the research ethics committee and the BEEP trial funder. Food allergy evaluation was added to the study protocol after recruitment had commenced, but before any two year follow up visits were conducted once separate funding was secured for this additional aspect of the trial. Funding awards from Sheffield Children's Hospital Charity (grant CA15008 to Dr Jay) and Goldman Sachs Gives (grant 52869 to Dr Boyle) support this additional work of SPT and OFC for food allergy evaluation.

i. Skin Prick Test and Questionnaire at two year visit

All participants in the BEEP trial are offered SPT at the primary outcome assessment visit conducted when participants are two years. The two year visits are usually conducted in the participant's home, unless parents prefer a clinic visit. Included in the two year assessment is a questionnaire about food allergy, which includes questions about the child's consumption of milk, egg and peanut modified from those used in the Enquiring About Tolerance (EAT) trial, designed to detect frequent and recent ingestion of at least two grams protein from each of the commonest three food allergens. Any parent-reported reactions to a food within two hours of exposure during the course of the trial are recorded. The SPT is undertaken according to British Society for Allergy and Clinical Immunology guidance. The internal consistency of SPT is evaluated using histamine controls in an adult volunteer, in a procedure used previously in the International Study of Asthma and Allergies in Childhood survey and EAT trial. SPT reactions are measured after 15 minutes and the largest diameter of the wheal is recorded. Any result of 0mm is considered 'negative', or 'not sensitised', results ≥3mm are considered 'sensitised' and results ≥7mm are considered 'strongly sensitised'. The following food allergens are tested: peanut extract (Inmunotek, Spain), fresh whole cow's milk, and fresh raw hen's

egg white. Positive (1% histamine) and negative (0.9% saline) controls are also used (Allergopharma, Germany). Common inhalant allergens grass pollen, cat and dust mite are also tested.

ii. Oral Food Challenge

Participant who report frequent and recent consumption of milk, runny egg and peanut and no reported history of reactions within two hours of consumption are deemed tolerant of the food, regardless of SPT result. Participants who are not frequent and recent consumers of the allergenic foods and/or report a reaction within two hours of consumption are deemed to not have IgE-mediated allergy to the food if their SPT is negative. If they do not undergo a SPT or if they do not have a negative SPT, they are regarded as being possibly food allergic and invited for OFC. OFC are conducted by experienced allergy nurses following standard operating procedures modified from the European Academy of Asthma and Clinical Immunology PRACTicals of ALLergy (PRACTALL) consensus. All study staff remain blinded to treatment allocation. The presence of a clinical reaction is determined using modified PRACTALL criteria. Fresh whole cow's milk, raw hen's egg white (red lion stamped, salmonella free), and peanut butter (Sunpat, Histon Sweet Spreads Ltd, Leeds, UK) or ground peanut flour (Golden peanut company, Georgia, USA) are used for OFC. OFC use a five dose schedule with a cumulative dose of 4.43g protein, consistent with the doses used for children aged one and three years in the EAT trial. Study clinicians may modify the scheduling to more or less than five doses depending on individual circumstances, but always aim for a cumulative total dose of 4.43g protein.

iii. Panel consensus procedure for participants who don't attend OFC

To establish food allergy status for participants who decline OFC, an expert allergy panel composed of three experienced paediatric allergists (NJ, MP, RJB) determine whether the participant is likely to be food allergic or not, whilst remaining blinded to treatment allocation. The panel use all available information to guide the decision, including local hospital or primary care records, telephone interviews with the family and any information recorded on BEEP trial questionnaires. In order to

guide panel decision making, and enhance consistency of decision making through the trial, the panel developed an algorithm to facilitate food allergy diagnosis (Figure 2). When using this algorithm, the following factors are also taken into consideration: (i). Presence of other doctor-diagnosed IgE-mediated food allergies, given the increased likelihood of a second food allergy in the case of one confirmed food allergy; (ii). Size of SPT and/or specific IgE readings; (iii). Precise quantity, form and timing of food previously tolerated in diet; (iv). Precise frequency and nature of any reported reactions. The likelihood of food allergy is decreased by lower level SPT and specific IgE readings; larger, more unadulterated, more frequent and more recent asymptomatic food consumption; and less consistent, frequent or typical IgE-mediated reactions. Family history of atopic disease is not taken into consideration, as this is an inclusion criterion for the study. Eczema history is not taken into consideration, since this may be modified by the intervention such that use of eczema history to categorise food allergy could introduce a bias into food allergy outcome assessments in favour of the study intervention. Anonymised examples of panel decisions about BEEP study participants are shown in Table 1. The primary food allergy outcome is point prevalence of IgE-mediated food allergy at the BEEP study two year visit, at least one of cow's milk, egg or peanut. The outcome is derived from a combination of parental report, allergic sensitisation and (if required) OFC. The food with the greatest likelihood of allergy is used for overall classification of the primary food allergy outcome i.e. if a participant has OFC confirmed egg allergy but peanut allergy "unclear - likely allergic" then they will be classed as overall OFC confirmed food allergy. The 'primary' food allergy outcome is classified as per Table 2. Food allergy outcomes will be analysed using the same method as for the BEEP primary outcome eczema, using a generalised linear model adjusting for the randomisation stratification variables of recruiting centre and number of immediate family members with atopic disease (one, two, or more than two). The effect of the intervention will be reported as a relative risk and absolute difference in risk with 95% confidence intervals. For the primary food allergy outcome, we will perform subgroup analysis according to whether the child has a FLG null mutation, the number of immediate family members with atopic

disease and number of immediate family members with eczema by including an interaction term in the analysis model.

In Figure 2 below we summarise the likely outcomes of BEEP eczema and food allergy assessments, and the implications that the different scenarios might have for our understanding of food allergy pathogenesis and the programming of skin health.

Tables

Table 1: Examples of case classification by expert allergy Panel consensus

Food	SPT result	Comments	Panel decision
Milk	8.5 mm	More than two reactions in infancy within 30 minutes of exposure, currently strictly avoiding all milk products.	Probable milk allergy
Peanut	5.5 mm	Confirmed egg allergy. Never ingested peanut.	Unclear – possible peanut allergy
Egg	No SPT	Never exposed to whole egg or runny egg. Tolerates baked egg in cakes.	Unclear – egg allergy unlikely
Milk	2 mm	Gastrointestinal symptoms within 30 mins of milk exposure during infancy. Now tolerates at least 100mls cow's milk (lactose free) daily, without symptoms.	No food allergy

Table 2: Classification of food allergy outcomes for milk, egg and peanut.

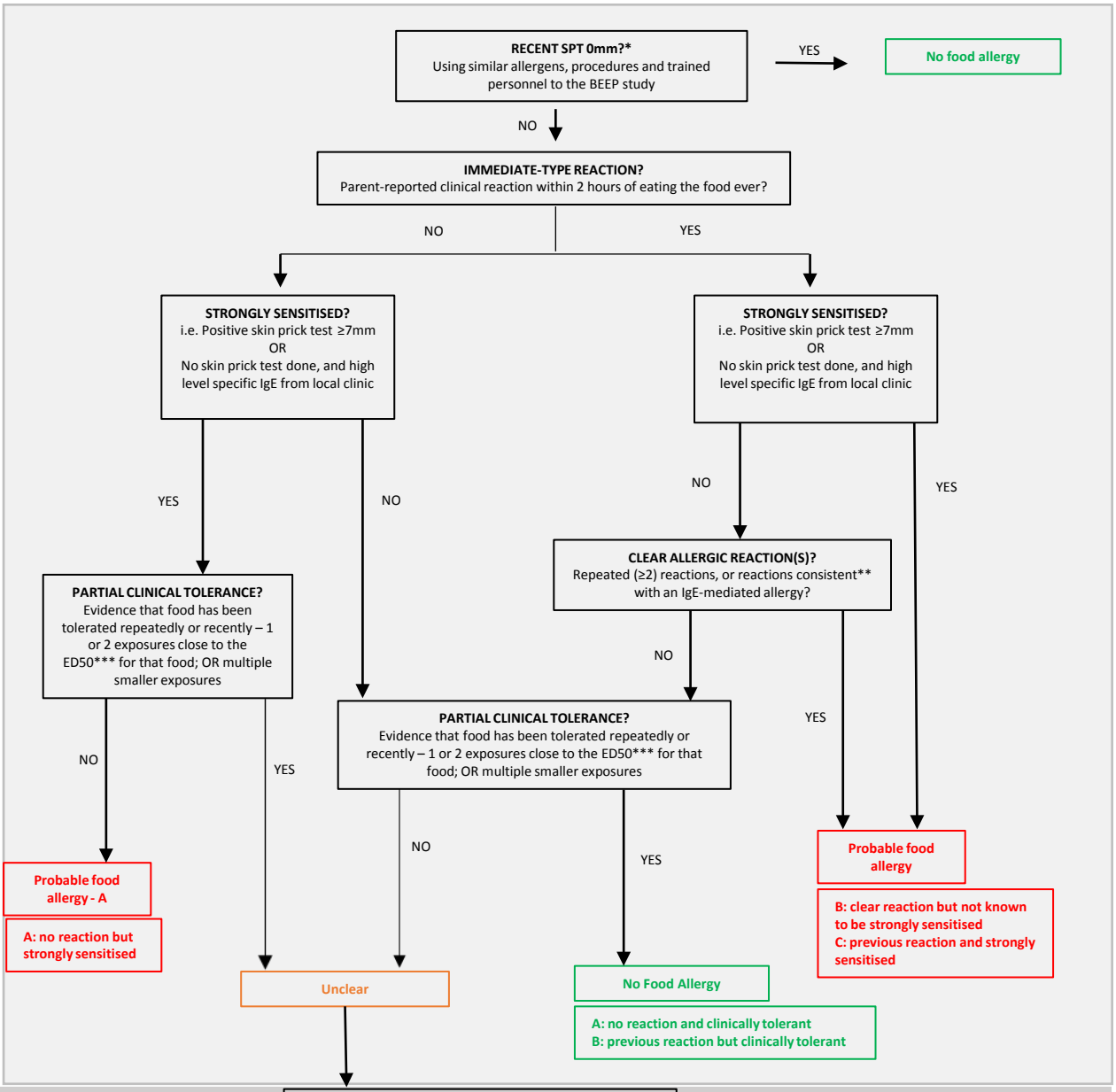
	FOOD ALLERGY	NO FOOD ALLERGY
PRIMARY FOOD ALLERGY OUTCOME	1. confirmed by OFC OR 2. panel "probable food allergy"	1. frequent and recent consumption of relevant food, and no reported history of reactions within 2 hours of consumption OR 2. negative SPT OR 3. Passed OFC OR 4. Panel diagnosis of 'no food allergy'.

Figure Legends

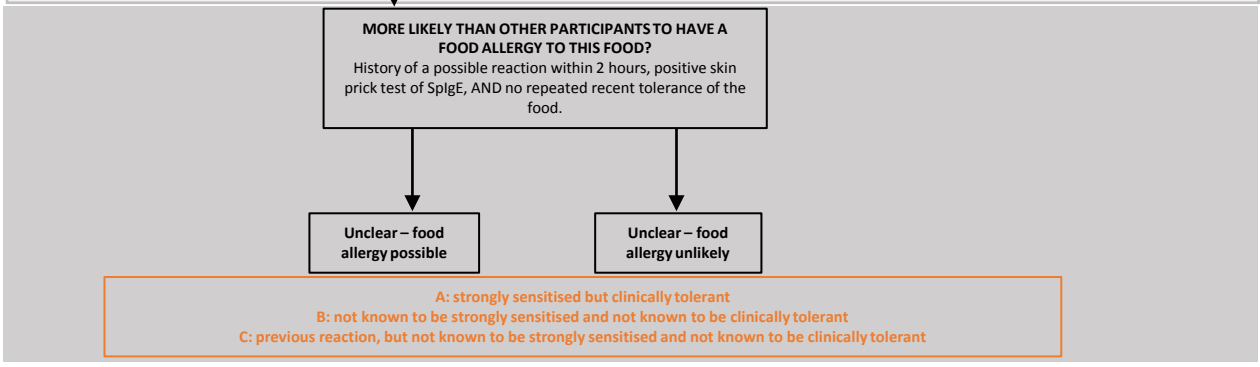
Figure 1. Algorithm for classifying food allergy where oral food challenge is requested but not conducted

Figure 2. Likely outcomes for participants in intervention arm compared to control arm.

Primary Outcome



Sensitivity Analysis



* Recent is defined as within the year prior to the 2 year visit for milk or egg, and within 3 months prior to the 2 year visit for peanut.
Symptoms include urticaria, angioedema, vomiting/diarrhoea, sneezing, coughing, wheezing, stridor. Age at reaction and natural history of relevant food allergy are taken into consideration when assessing whether reaction is consistent with ongoing IgE-mediated allergy at age 2. * ED50 = eliciting dose at which 50% of people allergic to that food will react, estimated as 0.2g protein i.e. 5mls milk, 1.5g egg white, 0.7g peanut butter.

Risk of developing	Eczema	Eczema	Food Allergy	*Interpretation*
	During intervention (1st year)	During second year	At 2 years	

Reduced	No change	No change	Emollients transiently reduce eczema, no effect on FA
Reduced	No change	Reduced	Emollients transiently reduce eczema and reduce FA
Reduced	Reduced	No change	Emollients reduce eczema beyond the treatment period, but have no effect on FA
Reduced	Reduced	Reduced	Emollients reduce eczema beyond the treatment period and reduce FA