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ORIGINAL ARTICLE

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An algorithm for diagnosing IgE-mediated food allergy in study participants who do not undergo food challenge

Maeve M. Kelleher[1] | Nicola Jay[2] | Michael R. Perkin[3] | Rachel H. Haines[4] | Rebecca Batt[5] | Lucy E. Bradshaw[4] | Alan A. Montgomery[4] | Joanne R. Chalmers[6] | Hywel C. Williams[6] | Robert J. Boyle[1,6]

[1]Section of Inflammation, Repair & Development, National Heart & Lung Institute, Imperial College London, London, UK

[2]Children's Allergy Dept., Sheffield Children's NHS Foundation Trust, Sheffield, UK

[3]Population Health Research Institute, St George's University of London, London, UK

[4]Nottingham Clinical Trials Unit, University of Nottingham, Nottingham, UK

[5]Children's Allergy Service, Evelina Children's Hospital London, London, UK

[6]Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK

Correspondence
Robert J. Boyle, Section of Inflammation, Repair & Development, National Heart & Lung Institute, Imperial College London, 2nd Floor Wright-Fleming Building, Norfolk Place, London W2 1PG, UK.
Email: r.boyle@imperial.ac.uk

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Abstract

Background: Food allergy diagnosis in clinical studies can be challenging. Oral food challenges (OFC) are time-consuming, carry some risk and may, therefore, not be acceptable to all study participants.

Objective: To design and evaluate an algorithm for detecting IgE-mediated food allergy in clinical study participants who do not undergo OFC.

Methods: An algorithm for trial participants in the Barrier Enhancement for Eczema Prevention (BEEP) study who were unwilling or unable to attend OFC was developed. BEEP is a pragmatic, multi-centre, randomized-controlled trial of daily emollient for the first year of life for primary prevention of eczema and food allergy in high-risk infants (ISRCTN21528841). We built on the European iFAAM consensus guidance to develop a novel food allergy diagnosis algorithm using available information on previous allergenic food ingestion, food reaction(s) and sensitization status. This was implemented by a panel of food allergy experts blind to treatment allocation and OFC outcome. We then evaluated the algorithm's performance in both BEEP and Enquiring About Tolerance (EAT) study participants who did undergo OFC.

Results: In 31/69 (45%) BEEP and 44/55 (80%) EAT study control group participants who had an OFC the panel felt confident enough to categorize children as "probable food allergy" or "probable no food allergy". Algorithm-derived panel decisions showed high sensitivity 94% (95%CI 68, 100) BEEP; 90% (95%CI 72, 97) EAT and moderate specificity 67% (95%CI 39, 87) BEEP; 67% (95%CI 39, 87) EAT. Sensitivity and specificity were similar when all BEEP and EAT participants with OFC outcome were included.

Conclusion: We describe a new algorithm with high sensitivity for IgE-mediated food allergy in clinical study participants who do not undergo OFC.

Clinical Relevance: This may be a useful tool for excluding food allergy in future clinical studies where OFC is not conducted.

KEYWORDS
atopic dermatitis, diagnosis, food allergy, oral food challenge, paediatrics

1 | INTRODUCTION

Food allergy affects approximately 5% of young children and has a significant quality of life and economic impact.[1-3] The gold standard for diagnosing food allergy in clinical studies is a double-blind, placebo-controlled oral food challenge (OFC).[4] However, open (non-blinded) OFC are widely used for detection of food allergy in young children, where placebo-controlled challenges may be impractical and the reporting of subjective symptoms less likely.[5] Recent guidance from the European iFAAM (Integrated approaches to Food Allergen and Allergy risk Management) project provides a framework for when to undertake OFC in clinical studies where food allergy is an end-point.[6] This guidance suggests that if a food has been eaten without symptoms of allergy, or if a food has not been eaten, but there is no evidence of allergic sensitization, then OFC is not required. However, the guidance does not specify more precisely the frequency, form and quantity of food ingestion that is sufficient to exclude allergy, or which symptoms related to ingestion indicate an allergic reaction. Importantly, the guidance does not address detection of food allergy where OFC is not completed. Hence, there is a need for a more detailed and complete algorithm to guide food allergy diagnosis within clinical studies, especially those where uptake of OFC by study participants is low.

The Barrier Enhancement for Eczema Prevention (BEEP) study is a pragmatic, multi-centre, randomized-controlled trial of daily emollient use for the first year of life for primary prevention of eczema, in infants with a family history of atopic disease (ISRCTN21528841). Evaluation of IgE-mediated food allergy was added to the initial study protocol after recruitment had commenced, but before any 2-year follow-up visits were conducted, once separate funding was secured.[7] It was anticipated that a significant number of participants might decline to attend for OFC in BEEP, as the food allergy testing was presented to parents at the 2-year visit as an optional sub-study in a pragmatic, low-contact trial with eczema prevention as its initial focus. Furthermore, the BEEP trial was a multi-centre trial run across a wide geographical area and study OFCs were limited to two UK centres, Sheffield and London (See map of geographical distribution of recruited individuals in Supinfo 2). In the EuroPrevall UK birth cohort study, based on a similar-aged population, over 30% of parents offered OFC to cow's milk declined attendance.[8] We, therefore, developed an algorithm for use in the BEEP study which aims to reliably diagnose IgE-mediated food allergy. We then validated the algorithm in BEEP study participants who had undergone OFC and separately in participants from the control group (standard introduction group) of another intervention trial, Enquiring About Tolerance (EAT; ISRCTN14254740), who had undergone OFC and had a similar set of information available about allergenic food exposure, reactions and sensitization status.

2 | METHODS

We evaluated food allergy outcomes in the BEEP study, which presented an opportunity to develop a new approach to food allergy diagnosis in clinical research studies with expected low uptake of OFC. We then validated our findings in BEEP study participants who had undergone OFC and in participants from the control group of the EAT study who had undergone OFC.

2.1 | BEEP study design

The BEEP study is a pragmatic, parallel-group, multi-centre, assessor-blind, randomized-controlled trial, details of which have been described elsewhere.[7] In brief, the BEEP study randomized 1395 participants between November 2014 and November 2016, recruited from 16 study centres across England. Participants were born at ≥37-week gestation and had a first-degree relative with parent-reported eczema, asthma or allergic rhinitis diagnosis. They were randomized within 3 weeks of birth to apply daily emollient for 12 months plus skin care advice, or skin care advice only. Written informed consent was obtained at screening, prior to randomization, either during pregnancy or within 21 days of birth. Separate written consent was obtained at the 2-year visit for skin prick testing (SPT) and additional consent was obtained if OFC was required.

2.2 | BEEP study food allergy evaluation

Formal evaluation for the point prevalence of IgE-mediated food allergy, using a combination of food allergy history, SPT and OFC, in accordance with iFAAM guidance, was conducted at the primary outcome assessment visit at age 2 years. All BEEP participants were offered SPT at these visits, usually conducted in the home unless parents preferred a clinic visit. Peanut extract (Inmunotek), fresh whole cow's milk, and fresh raw hen's egg white were tested, with positive (1% histamine) and negative (0.9% saline) controls (Allergopharma). OFC was offered if the participant had a positive SPT and was not a frequent consumer of relevant forms of milk, egg or peanut; or if they had a positive SPT and a reported reaction to one of the foods (Figure 1). Open OFCs were conducted by experienced allergy nurses in recognized paediatric allergy centres (Sheffield Children's Hospital and Imperial College London), following standard operating procedures modified from the European Academy of Asthma and Clinical Immunology PRACTicals of ALLergy (PRACTALL) consensus. Fresh whole cow's milk, raw hen's egg white (red lion stamped, salmonella free) and peanut butter (Sunpat, Histon Sweet Spreads Ltd) or ground

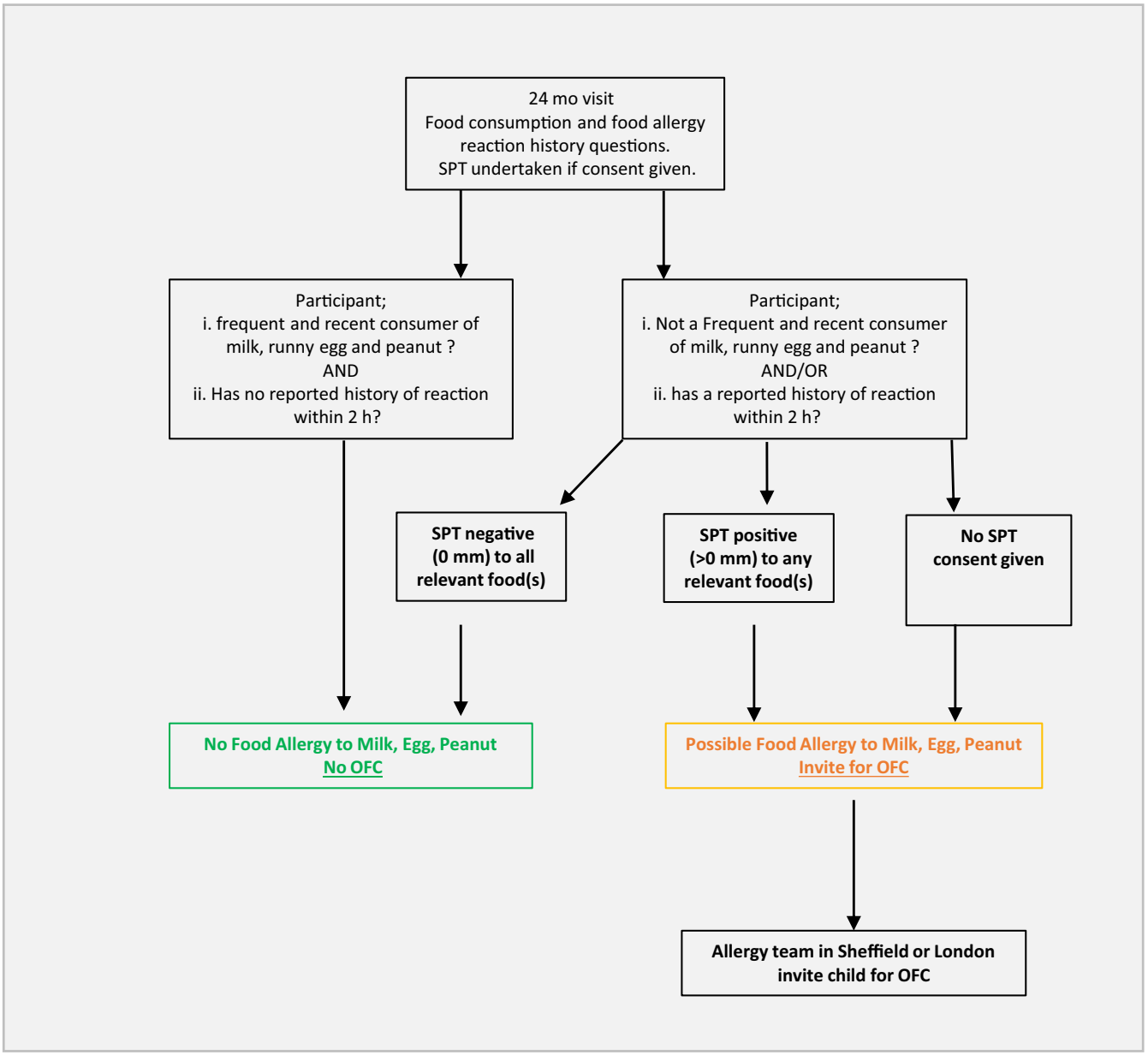

FIGURE 1 Selection of study participants for invitation to oral food challenge

peanut flour (Golden peanut company) were used for OFC.[9] All study staff remained blinded to treatment allocation. The presence of a clinical reaction during OFC was determined using modified PRACTALL criteria (See Supinfo 1).[4]

2.2.1 | Elaboration of iFAAM guidance

iFAAM guidance suggests OFC is not indicated in clinical trials if (A) the food is eaten without out symptoms or (B) the food has not been eaten but the participant is not sensitized. OFC is indicated if (C) the food is not eaten but the participant is sensitized or (D) the food is eaten and a reaction has occurred.[6] We first elaborated on these criteria in order to more precisely define "sensitized", "reaction", "food" and "eating without reaction".

For the definition of "sensitized", we considered a participant to be "sensitized" when the skin prick test was any response (>0 mm), in order to maximize the sensitivity of our procedure.[10] Though correlation between skin test response size and OFC outcome is dependent on the population studied, in general, SPT weal size correlates with probability of reacting at OFC, and in 2-year olds, a 7 mm response is considered strongly predictive for milk, egg or peanut allergy. Hence, we categorized ≥7 mm as "strongly sensitized".[11] Values between 1 and 6 mm were considered "intermediate sensitization". For those without SPT, we considered SpIgE to be negative if it had been done and <0.35 kUa/L.

For the definition of "reaction", we considered any parent-reported reactions to a food within 2 hours of exposure to be an "immediate" reaction.

For the definition of "food", we used the most allergenic form of food consumed in the local population. We considered milk and egg

allergy as allergy to any form of milk or egg, even if other forms such as baked or processed milk/egg were tolerated. We considered peanut ingestion in any form to be relevant. We used fresh milk, raw egg white and commercial peanut extract for SPT.

For the definition of "eating without reaction", we recorded parent-reported ingestion. We adapted food frequency questionnaires from the EAT study, to identify frequent and recent ingestion of each food allergen.[12] "Recent" ingestion was the food being ingested within 3 months of the 2-year interview for milk and egg; within 1 month for peanut. The shorter duration for peanut is due to the possibility of new-onset peanut allergy in the second year. "Frequent consumption" was defined as three or more separate reported ingestions of two or more grams of relevant food protein, at any age.

2.3 | Food allergy diagnosis algorithm

We expected some participants would decline to attend OFC, due to an established diagnosis or unwillingness to travel to an OFC centre. To establish accurate food allergy status for these participants we convened an expert panel of experienced paediatric allergists (MK, NJ, MRP, RJB) to determine food allergy status whilst remaining blinded to treatment allocation. We developed the algorithm using an iterative process of discussion and consensus-building, involving the panel and the wider trial management group and trial steering committee. We did not use a formal Delphi or nominal group process. We referred to relevant literature and recent cohort studies or food allergy prevention trials in developing the algorithm and modified some data collection materials and processes from the BASELINE cohort study and EAT prevention trial.[12,13] The panel used all available information from the study procedures to guide their decision-making (Table 1). Through repeated revisiting of all cases of possible food allergy within BEEP, we developed a consensus-based approach to diagnosing IgE-mediated food allergy to milk, egg or peanut in a setting where participants did not undergo OFC.

2.4 | Validation of food allergy diagnosis algorithm

Having developed the algorithm using information from BEEP study participants who did not have an OFC, we then compared algorithm-derived expert panel decision-making with OFC outcome in (i). BEEP study participants who underwent OFC; and (ii). EAT study, standard introduction group, participants who underwent OFC. Validation was conducted with panel blinding to food challenge outcomes and was conducted separately for each dataset.

EAT is a randomized trial of 1303 exclusively breastfed 3-month old infants that compared introduction of six allergenic foods from age 3 months with advice to continue exclusive breastfeeding to age 6 months.[12] The EAT data set (ITN900AD) is available through TrialShare, a public Web site managed by the Immune Tolerance Network (www.itntrialshare.org). Primary outcome of the trial was IgE-mediated food allergy evaluated by OFC. In the EAT study, at 36 months, all children in both standard and early introduction groups who had a positive SPT (≥1 mm) to a study food were offered OFC. "Frequent consumers" of the food underwent a challenge regimen with less doses.

We established algorithm-derived panel diagnoses for participants in both trials with an OFC outcome. Panel assessments were undertaken by the same four paediatric allergists, blind to OFC outcome. For EAT, we only used standard introduction group participants since the intervention involved a change to allergenic food exposure which is part of the algorithm and was associated with reduced food allergy in EAT. Sensitivities and specificities were calculated for the detection of IgE-mediated food allergy in BEEP and EAT separately.

TABLE 1 Study-specific information used in algorithm-derived panel decisions and OFC procedures

Source	BEEP study	EAT study
Study Questionnaires	Food ingestion–recentness and frequency	Food ingestion–form and frequency
	Reported reaction–age, form of food, symtoms, timing of symptoms	Reported reaction–age, form of food and symptoms
Study Investigations	Skin prick testing to fresh milk, raw egg and commercial peanut extract	Skin prick test to fresh milk, raw egg and commercial peanut extract
Other Health Care Provider Information	Correspondence from any assessments in a paediatric allergy clinic prior to BEEP study OFC	No
OFC Protocol	Fresh cow's milk	Semi skimmed milk powder.
	Raw egg white	Pasteurized raw egg powder (DBPCFC) or boiled egg (open challenges).
	Peanut butter or peanut flour	Peanut butter or Bamba
	Total 4.43 g food protein	Total 5.3 g food protein

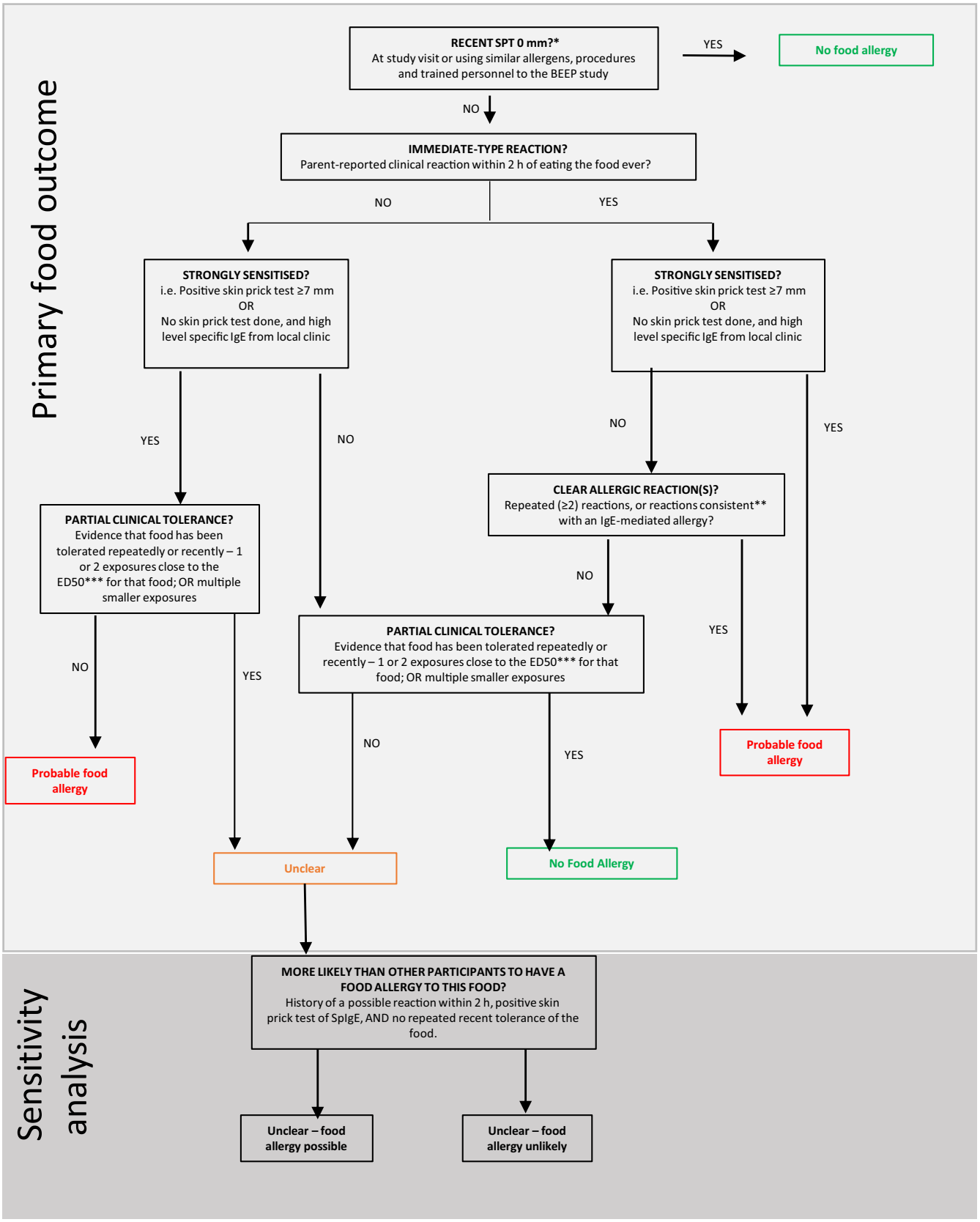

FIGURE 2 Algorithm for classifying food allergy where oral food challenge is requested but not conducted

TABLE 2 Examples of case classification by algorithm-derived panel consensus

Food	SPT result	Comments	Panel decision
Milk	8.5 mm	More than two reactions in infancy within 30 min 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 min of milk exposure during infancy. Now tolerates at least 100 mL cow's milk (lactose free) daily, without symptoms.	No food allergy

Abbreviation: SPT, skin prick test.

3 | RESULTS

3.1 | Algorithm development

3.1.1 | Algorithm for diagnosis of food allergy where OFC cannot be completed

The final algorithm is shown in Figure 2. The algorithm was developed by an expert allergy panel blind to treatment allocation. Those with negative SPT are deemed not food allergic. If SPT was not completed in the trial but was completed in a local clinical service using the same form of allergen and standard procedures, the result is considered by the panel. If SPT is positive or missing the panel considers reaction history. Likelihood of allergy is considered lower for less consistent, less frequent reactions, or reactions without typical IgE-mediated features.[3,14] Where possible, grams of protein ingested can be calculated, based on review of ingredient lists of relevant foods, to identify whether relevant quantities have been ingested without reaction.

For participants not "eating without reaction", diet history is used to evaluate "probable tolerance" based on consumption of the ED 50 (eliciting dose at which 50% of allergic individuals react), or multiple exposures of lesser quantities, without reaction. Likelihood of allergy is lowest where parents reported larger, more unadulterated, frequent and recent asymptomatic food consumption. Presence of other doctor-diagnosed IgE-mediated food allergies is also be considered by the panel, where relevant, given the increased likelihood of a second food allergy.

Eczema history was not taken into consideration in developing this algorithm, since eczema prevalence may be modified by an emollient intervention such that use of eczema history to categorize food allergy could introduce a bias in food allergy outcome assessments in BEEP in favour of the study intervention. However, timing and severity of eczema could be used in other settings to inform algorithm-derived panel decision-making.[15]

For classification of overall food allergy status, the food with the highest hierarchical determined food allergy outcome is used; that is, if a participant has OFC confirmed egg allergy but has "probable" peanut allergy they are classed as having OFC confirmed food allergy.

We include a demographic table of those children who did not undergo oral food challenge and who had their food allergy status classified through this algorithm in the Supinfo 1.

3.1.2 | Algorithm approach for participants who are sensitized with immediate-type reaction

Reported immediate-type reaction and strong sensitization on SPT (≥7 mm) is "probable food allergy". If SPT data are missing, high-level SpIgE results in the same classification. For immediate-type reactions without strong sensitization, reaction symptoms are considered first. If the reaction is reproducible (occurred twice or more) and typical of an IgE-mediated reaction (eg acute urticaria, angioedema, vomiting, cough/wheeze settling within hours) participants have "probable food allergy". If reaction history is less clear, without strong sensitization, the precise quantity and frequency of allergen previously tolerated is considered. If the participant has evidence of subsequent sufficient exposure without reaction they are labelled "no food allergy", if there is no evidence of sufficient exposure they are labelled "unclear".

3.1.3 | Algorithm approach for participants who are sensitized with no immediate reaction

For participants with positive SPT who have not recently and frequently eaten the food allergen, the panel considers the SPT level. For those "strongly sensitized" (≥7 mm), the quantity and frequency of allergen previously tolerated are next considered, looking for evidence of partial clinical tolerance. Consumption at the ED50 or multiple exposures to smaller doses is evidence of clinical tolerance. Participants strongly sensitized by SPT with no evidence of partial clinical tolerance have "probable food allergy". Participants strongly sensitized by SPT with evidence of partial clinical tolerance are labelled "unclear". For participants who are not strongly sensitized (SPT < 7 mm), evidence of

TABLE 3 Validation of algorithm in BEEP and EAT cohorts where OFC was undertaken

	Positive OFC	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR
Cases with clear panel decision							
BEEP study (n = 31)	(16/31)	94% (CI 68%-100%)	67% (CI 39%-87%)	75% (CI 51%-90%)	91% (CI 57%-100%)	2.81 (CI 1.36-5.82)	0.09 (CI 0.01-0.67)
EAT study (n = 44)	(29/44)	90% (CI 72%-97%)	67% (CI 39%-87%)	84% (CI 66%-94%)	77% (CI 46%-94%)	2.69 (CI 1.3-5.6)	0.16 (CI 0.05-0.48)
Total Cases including "possible allergy"							
BEEP study (n = 69)	(23/69)	95% (CI 76%-100%)	52% (CI 37%-69%)	50% (CI 35%-65%)	97% (CI 78%-100%)	2 (CI 1.46-2.73)	0.08 (CI 0.01-0.59)
EAT study (n = 55)	(38/55)	87% (CI 71%-95%)	59% (CI 71%-95%)	83% (CI 67%-92%)	67% (CI 39%-87%)	2.11 (CI 1.18-3.77)	0.22 (CI 0.09-0.55)

Note: Panel diagnosis of food allergy was established by using the algorithm in Figure 2 by a panel of four allergists blind to result of OFC. Algorithm inputs were in brief; SPT results, ingestion history and reaction history. EAT and BEEP differed by (i). Reaction history, asked in a similar way but EAT did not determine the time course (ii). Food ingestion history was quite similar but somewhat more detail in the EAT questionnaires, (iii). Food used for OFC, EAT used milk and egg powder for DBPCFC. Numbers denote total individuals, not total number of OFCs, some children had more than one OFC.

Abbreviations: LR, likelihood ratio; NPV, negative predictive value; PPV, positive predicative value.

partial tolerance is again considered—there is "no food allergy", if partial tolerance criteria are met, and "unclear" food allergy status if not.

Examples of panel decision-making using anonymized BEEP study participants are shown in Table 2.

3.1.4 | Classification of participants with "unclear" food allergy status

Participants with "unclear" food allergy status cannot be reliably classified by the panel, but we undertook a sensitivity analysis where "unclear" participants were classified by the panel. They were categorized as "unclear–food allergy possible" where there was a history of reaction, a history of doctor-diagnosed food allergy to another food, or other features to suggest increased probability of food allergy compared with the rest of the study population. "Unclear–food allergy unlikely" status was given to participants where there was no information to suggest any increased risk of food allergy over the rest of the study population, including participants with significant missing data.

3.2 | Algorithm validation

3.2.1 | Comparison of algorithm-derived panel decisions with OFC outcomes from BEEP and EAT studies

In 31/69 (45%) BEEP and 44/55 (80%) EAT study control group participants who had an OFC the panel were able to classify participants as "probable food allergy" or "probable no food allergy". For these participants, algorithm-derived panel decisions showed high sensitivity 94% (95%CI 68, 100) in BEEP, 90% (95%CI 72, 97) in EAT; and moderate specificity 67% (95%CI 39, 87) in BEEP, 67% (95%CI 39, 87) in EAT. Other participants could not be confidently classified due to missing information about ingestion or reaction history or sensitization status. The available information was considered, and they were classified as "unclear–food allergy possible" and "unclear–food allergy unlikely" based on available information. Sensitivity and specificity were broadly similar when participants with "unclear" food allergy status were included in the analysis (Table 3).

4 | DISCUSSION

Making a robust food allergy diagnosis in clinical studies using the gold standard of OFC can be time-consuming, sometimes unpleasant and potentially risky for study participants.[16] Some studies are not resourced to undertake OFC to all potential food allergens and OFC may be declined by participants, carers or investigators or even considered unethical where participants are already known to have a firm diagnosis of IgE-mediated food allergy. While some studies have successfully confirmed the diagnosis of food allergy using OFC in up to 90% of cases[5,12,17] others have been less successful and

for pragmatic trials or those where food allergy is not the primary outcome measure then surrogates for OFC may be required. We, therefore, developed and evaluated a specific, algorithm-guided approach for detecting IgE-mediated food allergy as an outcome in clinical studies. We built on previous guidance for the diagnosis of food allergy using a combination of clinical information and, where available, specific allergy diagnostic.[6] Our algorithm-guided expert panel approach demonstrated high sensitivity, reliably detecting food allergy when present; but only moderate specificity, suggesting that our approach may misclassify some study participants without food allergy as "food allergic".

In both BEEP and EAT, there was often a time-lag between questionnaire responses at 24 and 36 months, and subsequent OFC. For egg and milk allergy which are in the process of resolving over the first couple of years, this could account for some cases where algorithm-derived panel diagnosis based on information from the 24 or 36 month visit suggested "food allergy", but OFC found no food allergy. Variations in allergen formulation in SPT and OFC could also impact on accuracy of the algorithm. For example, in EAT raw egg white was used for SPT but a mixture of both whole egg powder (for the double-blind component) and boiled egg (for the open component) was used for OFC. Although the panel took this information into consideration when making algorithm-derived decisions, the discrepancy between materials used in SPT and OFC may introduce some inaccuracy.

Algorithm-based diagnosis has been used by others in a clinical context for food allergy diagnosis, both with and without comprehensive information on sensitization status.[18,19] Our findings in a clinical research setting at a homogenous, defined age, complement this prior work and build on the guidance from the iFAAM project, but would need separate validation before use in a clinical context.

This algorithm was also developed in the context of an eczema prevention trial, so that eczema could not be used within the algorithm, despite being a major predictor of food allergy risk. Future iterations of this algorithm may consider including timing of eczema onset and eczema severity as variables to be considered by the panel in their decision-making. Algorithm development using formal Delphi consensus or nominal group techniques may also have higher validity.

Finally, aside from our algorithm development, in BEEP we have confirmed in a clinical trial of 1395 infants that SPT can be safely conducted at home, by appropriately trained and equipped personnel. We favoured SPT over SpIgE for detection of sensitization, due to the better sensitivity and specificity of SPT for food allergy diagnosis in young children.[20] This approach, therefore, remains to be validated in clinical studies which rely on SpIgE without SPT testing for foods.

In conclusion, we have described the development and evaluation of a new algorithm for the diagnosis of IgE-mediated food allergy in clinical studies of young children. This may be a useful tool for excluding food allergy in study participants who do not attend an OFC. We cannot recommend our algorithm in replacement of OFC since it only has moderate specificity, but the algorithm reliably excludes food allergy and is, therefore, likely to be a useful supplement to OFC in future clinical studies.

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CONFLICTS OF INTEREST

HW is chief investigator of the BEEP study–an independent study that was funded by the NIHR Health Technology Assessment Programme.

AUTHOR CONTRIBUTIONS

MK contributed to protocol development, drafted the manuscript and coordinated edits on the protocol. NJ contributed to grant applications for the project, to protocol and standard operating procedure development and reviewed drafts of the manuscript. MP contributed to protocol and standard operating procedure development and reviewed drafts of the manuscript. RH contributed to protocol and standard operating procedure development and reviewed drafts of the manuscript. RB contributed to standard operating procedure development, implementation of the protocol and reviewed drafts of the manuscript. LB contributed to data analysis plan development and reviewed drafts of the manuscript. AM contributed to protocol development and reviewed drafts of the manuscript. JC contributed to protocol and standard operating procedure development and reviewed drafts of the manuscript. HW is chief investigator for the BEEP trial, contributed to grant applications for the project, to protocol and standard operating procedure development and reviewed drafts of the manuscript. RJB led grant applications for the project, protocol and standard operating procedure development and reviewed drafts of the manuscript.

ETHICAL APPROVAL

The trial was approved by the NRES Committee West Midlands (REC reference 14/WM/0162) on 9 June 2014 prior to the start of recruitment. Ethics approval for the food allergy work was introduced as a part of Protocol Version 4.0 20 May 2016, Substantial Amendment 06 20 May 2016. This was given REC approval on 15 June 2016.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Maeve M. Kelleher https://orcid.org/0000-0002-3764-0461

Michael R. Perkin https://orcid.org/0000-0001-9272-2585
Robert J. Boyle https://orcid.org/0000-0002-4913-7580

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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