

FSA Science Council

Working Group 5

Review of the FSA's research programme on food hypersensitivity

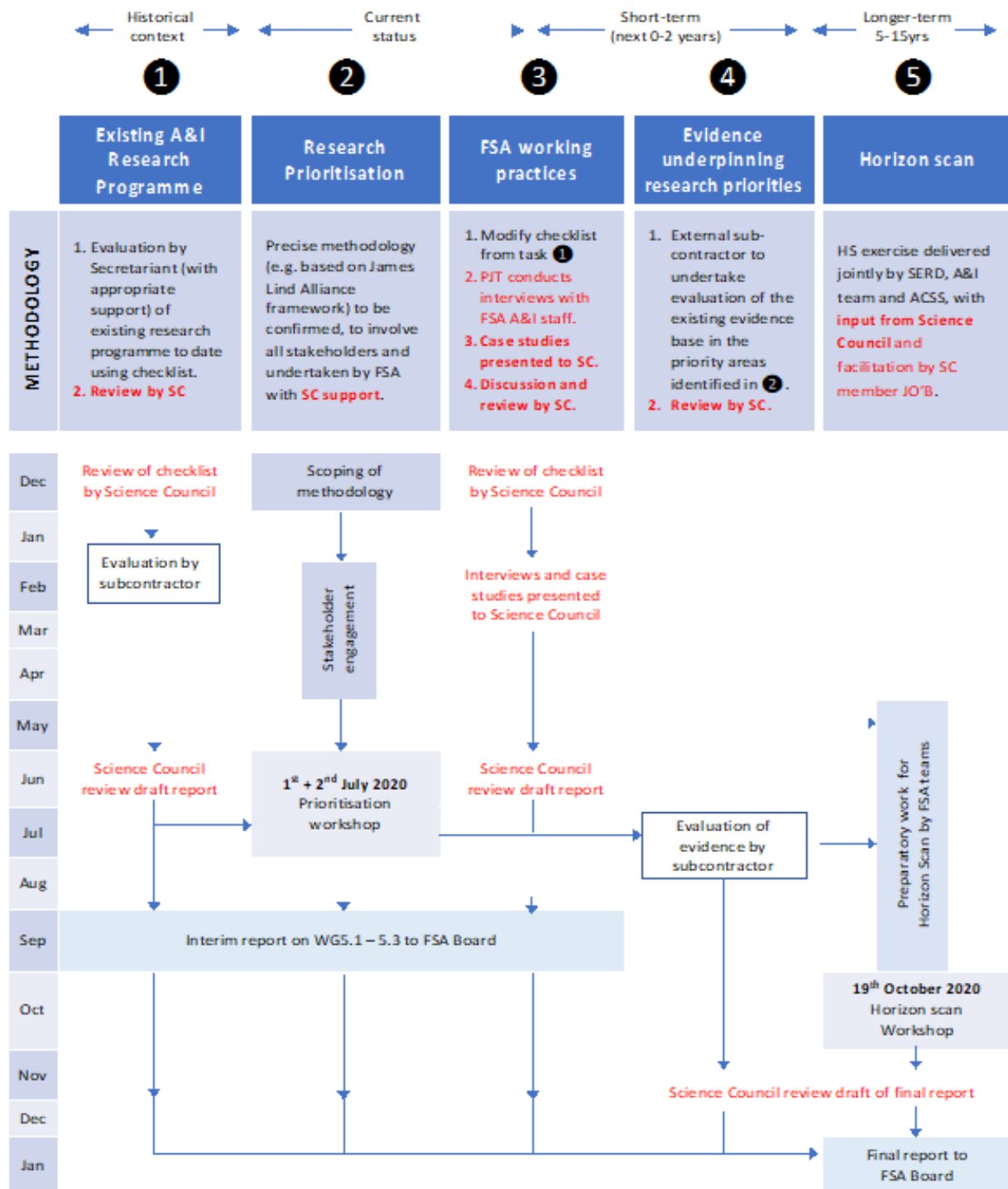
Interim Report – Annexes

August 2020

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ANNEX 1 - WG5 Overview



ANNEX 2 - Published projects under the FAIR research programme:

[Patterns and Prevalence of Adult Food Allergy \(PAFA\)](#)

This project has been set up to provide a step-change in our understanding of food allergy in adulthood by determining its prevalence in the adult population. It will provide data to allow the trajectories of the condition in relation to both persistent allergy from childhood and adult-onset food allergy to be described, together with adverse reactions to foods that are not mediated by IgE.

[Factors Influencing Adherence to Early Introduction of Allergenic Foods in the Enquiring About Tolerance \(EAT\) Study](#)

The EAT Data Analysis project was funded to further explore the EAT Study dataset. These analyses aimed to identify factors that were responsible for the relatively low adherence of approximately 43% to the study's early introduction regime and the reasons for this.

[Efficacy of the Enquiring About Tolerance \(EAT\) Study Among Infants at High Risk of Developing Food Allergy](#)

The EAT Data Analysis project was funded to further explore the EAT Study dataset. These analyses aimed to explore of the efficacy of the EAT Study amongst infants at high risk of developing food allergy.

[Young people and food allergies and intolerances](#)

An online survey of young people (16-24-year-olds) and their experiences of managing a food allergy/intolerance

[PIFA: Revisiting the UK EuroPrevall cohort](#)

This project is revisiting the UK EuroPrevall birth cohort which involves reassessing the same cohort at 8-9 years as part of the larger iFAAM (Integrated Approaches to Food Allergen & Allergy Risk Management) project.

[Further data analysis of the EAT study - Sleep](#)

The EAT data analysis project was funded to further explore the EAT study dataset, by investigating whether the introduction of solids has an impact on sleep behaviour of infants. It was also to further understand the factors that impact on the ability of infants' families to follow an early food introduction regime.

[Preferences for consumers with food allergies or intolerances when eating out](#)

The study aimed to develop an understanding of the choices and eating behaviours of food allergic and intolerant consumers when eating out. This included exploring the impact of the allergen labelling rules on consumers and gathering evidence to inform advice on the provision of allergen information.

[*The effect of extrinsic factors on food allergy \(TRACE\)*](#)

This was a randomised cross-over trial that investigated whether common extrinsic factors, such as exercise and sleep deprivation can modulate the threshold of responses to allergenic foods in a representative group of adults from the peanut allergic population.

[*Infant feeding and development of atopic and autoimmune disease - Review B - Timing of introduction of allergenic foods to the infant diet*](#)

This systematic review assesses the evidence available on the influence of the timing of introduction of allergenic foods into the infant diet on the development of atopic and autoimmune disease, such as eczema, asthma and food allergy.

[*Systematic review on infant feeding and development of atopic and autoimmune disease: Review A: Duration of total and exclusive breastfeeding, and timing of solid food introduction Review C: Maternal & Infant dietary exposures*](#)

Systematic Review C assesses the evidence available on the influence of dietary exposures during pregnancy, lactation and/or infancy.

[*Immune mechanisms involved in the induction of oral tolerance to peanuts in children*](#)

This study aims to find out the processes involved in the developing of an immune system that leads to the development of oral tolerance (as opposed to allergy) to peanuts.

[*EAT Study: early introduction of allergenic foods to induce tolerance*](#)

The EAT Study was funded to investigate whether the early introduction of six allergenic foods - milk, peanut, sesame, fish, egg, wheat - into the infant weaning diet, alongside continued breastfeeding, reduced the number of children developing food allergies and other allergic diseases, such as eczema, by the age of three.

[*Hydrolysed Formula and Risk of Allergic or Autoimmune Outcomes - a systematic review and meta-analysis*](#)

This systematic review assesses the evidence available on the influence of hydrolysed cows' milk formula and the development of atopic and autoimmune disease, such as eczema, asthma and food allergy.

[*Survey of allergen labelling and allergen content of processed foods*](#)

The survey examined the type of allergen advisory labelling present on pre-packed processed foods sold in the UK and aimed to quantify the level of allergens resulting from cross-contamination and establish whether the type of advisory labelling used related to the level of allergen present.

[Quantitative risk assessment of food products cross-contaminated with allergens](#)

This project aimed to investigate the public health risks posed by the levels of unintended allergens found to be present in foods sampled and tested as part of the FSA funded survey of allergen advisory labelling (project FS241038) using a quantitative risk assessment approach based on probabilistic principles.

[Data analysis of UK PIFA birth cohort to understand the incidence and risk factors for food allergy in children aged 0-2 years](#)

The main aim of this project is to undertake additional analyses using existing datasets generated from the FSA-funded Prevalence in Infant Food Allergy (PIFA) study. These analyses will then be used to produce a comprehensive peer reviewed publication on the incidence and risk factors associated with the development of food allergy in UK infants.

[Report of workshop on adult food allergy](#)

Over 60 leading research scientists and clinicians with expertise in food allergy and relevant areas participated in the Adult Food Allergy Workshop, which was held at the Royal Society, London.

[Baseline for evaluation of EU FIC \(Food Information to Consumers\) labelling](#)

The joint project with Defra is needed to provide baseline evidence on the current UK food labelling and consumer information requirements ahead of the introduction of the forthcoming EU Food Information to Consumers Regulation (EU) No 1169/2011.

[Baseline study to investigate the provision of allergy information for foods sold loose](#)

Stage I of the study (completed August 2013) aimed to assess the current baseline level of allergen information provided for loose (not pre-packed) foods. Stage II of the study (completed March 2014) further explored the levels of understanding of the new requirements and the challenges businesses anticipate in complying with these.

[Investigation of the association of skin barrier structure and function and the development of sensitisation to food allergens: a prospective birth cohort study](#)

This study aimed to find out whether abnormal skin barrier function predates and predicts food allergen sensitisation and whether the link between skin barrier function and food allergen sensitisation is driven by loss-of-function mutations in the FLG (Filaggrin) protein.

[Food allergy and intolerance research programme review 2012](#)

A review of the food allergy and intolerance research programme took place during 19-21 November 2012 at the De Vere hotel, Wokefield Park.

[Understanding the food choice of nut allergic consumers](#)

The research examines how people with nut allergies use food labels when choosing food to buy and eat. The results of the research will be used to help produce clearer allergy information for consumers.

[Understanding of labelling terms 'Lactose free', 'Milk free' or 'Dairy free'](#)

This project was carried out to explore understanding of the terms 'lactose free', 'milk free' and 'dairy free' among consumers with a sensitivity to milk or milk components, health professionals who advise such consumers and food businesses who provide products for these consumers.

[Evaluation of provision of allergen information for non-pre-packed foods guidance](#)

This research was commissioned to assess the awareness and uptake of the full guidance and gauge its impact on businesses.

[Prevalence of food allergy and weaning practices in a birth cohort of UK infants](#)

This project investigated the prevalence of food allergies and the current infant weaning practices adopted by mothers in the UK.

[Report of a joint FSA-MRC scientific Workshop](#)

Over 50 leading research scientists and clinicians with expertise in food allergy and relevant areas participated in the Workshop, which was held at the Royal Society of Medicine, London.

[Testing of government advice on peanut consumption during early life](#)

This research aimed to explore consumer, health professional and other relevant stakeholders' understanding of the draft revised Government advice on peanut consumption during early life.

[Consumer understanding of labelling terms for foods marketed for gluten-free diet](#)

Research was carried out to explore reactions towards new EU legislation relating to the labelling on products marketed to individuals who follow a gluten-free diet.

[Study of T cells in allergy and resolution](#)

A study of immunological mechanisms underlying the resolution of food allergy, specifically egg allergy, was undertaken to improve our understanding of the pathogenesis of food allergy. It also allows for more accurate and improved advice to be provided by healthcare professionals to individuals with an egg allergy.

[Evaluation of guidance on allergen management and consumer information](#)

In 2006, FSA published voluntary Guidance on Allergen Management and Consumer Information. This is best practice guidance on controlling food allergens in the factory setting, with particular reference to avoiding cross-contamination and using appropriate advisory labelling (e.g. 'may contain' labelling).

[Literature review of the nutritional adequacy of a typical gluten-free diet](#)

This research aimed to establish whether the diet of UK consumers with coeliac disease, is nutritionally adequate and whether there was a need for specific dietary advice or other strategies to ensure that these consumers can maintain a nutritionally adequate diet whilst avoiding gluten containing cereals

[Literature review early exposure to food allergens and development of food allergy](#)

This research reviewed all published scientific literature relevant to early life patterns of exposure or avoidance to major food allergens and the development of food allergy in children, since the COT advice was issued in 1998. The findings of this research assisted the Agency in reviewing this precautionary advice

[The role of peanut-specific T cell responses in children with and without peanut allergy](#)

This research furthers our understanding of T cell responses in tolerant individuals thereby devising immunomodulatory strategies to normalise T cell responses in future therapies.

[Characteristics of kiwi fruit allergy](#)

This project aims to fully characterise all of the clinical symptoms associated with allergy to kiwi fruit.

[Peri-natal egg and milk allergen exposure in relation to tolerance or allergic sensitisation to food in infancy](#)

This study investigated the hypothesis that high dose antenatal exposure to food proteins reduces the risk of subsequent allergy and atopic disease development in infants.

[Allergy Database Service: The FSA Nut Allergy Clinical Database and serum Bank](#)

This database was setup to gather retrospective clinical and laboratory information on all nut allergic patients attending allergy clinics at Manchester Royal Infirmary. Serum samples from patient were also banked.

[Systematic review on tolerable levels of gluten for people with coeliac disease](#)

This research reviewed all published scientific literature relevant to safe threshold amounts of gluten in foods in order to determine if it was possible to propose a threshold concentration of gluten in food products that would be tolerated by all people with coeliac disease.

[The role of IgG in allergy and tolerance to common food allergens](#)

This project aims to establish the role of IgG in the development of allergic sensitisation and reactions to foods.

[Prevalence and incidence of food allergies and food intolerance](#)

This research project aims to establish how common food allergy is among a group of children between birth and 15 years of age.

[*Influence of maternal experience of dietary antigen on the subsequent immune status of their offspring*](#)

The objective of this project was to identify in an animal model whether exposure to antigen, antibody or immune complex (where the antibody is bound to its antigen) at birth affected subsequent immune development. The pig was chosen as the animal model since pigs in contrast to the human, is born devoid of any maternal antibody or maternally derived dietary antigen

[*The immunomodulatory role of maternal IgG in infant atopic programming*](#)

This study was designed to investigate how maternal IgG antibody might regulate the developing foetal immune system in relation to the subsequent development of allergic problems

[*Trends of peanut allergy incidence in England using sequential childhood cohorts*](#)

This project aimed to establish whether the issuing of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) advice has resulted in a change in the incidence of peanut allergy.

[*Prevalence of peanut allergy in British children at school entry age in 2003*](#)

This project is evaluating the impact of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) report, that recommends atopic mothers avoid peanuts during pregnancy and breastfeeding, on the prevalence of peanut allergy.

[*Peanut allergy: routes of pre-natal and post-natal exposure*](#)

To quantify the exposure to environmental allergen during the allergic child's infancy. Environmental peanut exposure can occur through a variety of ways as well as the application of peanut-containing creams. Other important environmental components include the peanut consumption of all household members and the cutaneous contact and vapour inhalation that can result from this.

[*Qualitative Research into the Information Needs of Teenagers with Food Allergy and Intolerance*](#)

The piece of work involved qualitative research to establish the information needs of teenagers and young people with food allergies and intolerance, and to explore how best these needs can be met and how better to communicate with children and young people

[*Development, recognition and significance of IgG antibodies in allergic sensitisation and adverse reactions to peanut*](#)

This Study compared levels of peanut specific IgG and IgE in those reporting mild reactions vs those reporting severe reactions to investigate if the ratio of the antibodies had an effect on reaction severity.

[The Influence of dose and route of exposure on the early life origins of peanut allergy](#)

The aim of project T07028 was to investigate the effects of avoiding and/ or eating peanuts during pregnancy and lactation on the subsequent development of peanut allergy in children.

[Do protein structural features determine the allergenicity of the alpha-class family of plant proteins?](#)

Observations suggest that protein allergenic families might share common intrinsic attributes able to evoke an allergic response. This study focused on brazil nut to investigate these potential intrinsic attributes.

[Aberrant mast cell signalling as a cause for anaphylaxis](#)

The aim of this study was to determine if the same genetic alteration found in mastocytosis patients could be identified in blood cells taken from severely allergic individuals who had previously experienced an anaphylactic reaction

[The prevalence and natural history of peanut allergy and investigation into its genetic, environmental and immunological determinants](#)

The main objectives of this project were to define the risk factors for the development of peanut allergy, the burden of paediatric food allergy in 7-8 year old children in the UK, risk factors for sensitisation to food at age 7-8 years and immunological differences that underlie T cell function in children with peanut allergy as compared to tolerant children.

[Allergic cross-reactivity in peanut allergy](#)

This study investigated cellular reactivities in individuals reacting to peanut and other foods, compared with healthy control subjects. The study analysed effector T cells, antigen presenting cells, and IgG/IgE ratios

[Investigation of the immunological mechanism inducing cows' milk sensitive enteropathy](#)

The aim of this project was to see if there is an association between the behaviour of certain immune cells in children who are allergic to cows' milk and the general increase in development of allergies of all kinds among children.

[Immunochemical reactivity to peanuts and nuts in allergic individuals](#)

The aim of this three-year project was to establish whether there is a difference in allergic reactions to peanuts and other nuts between adults and young children, and if so, to determine the reason for this.

[Peanut allergens associated with provoking clinical symptoms](#)

The objectives of this study were to refine severity scoring methods for clinical reactivity and to also identify proteins in allergenic foods responsible for severe reactions vs those that aren't

[The effect of exposure to food proteins via maternal sources in the development of food allergy in infants](#)

This study investigated the hypothesis that maternal avoidance of dietary egg from early in the second trimester of pregnancy and throughout lactation would lead to a reduced incidence of egg allergy and associated allergic problems; in infants born to families where a first degree relative already had allergic disease (high risk)

[Investigation of Immune Responses to Food Allergens in Individuals with a Clinical Spectrum of Sensitivity to Different Foods](#)

This research project aimed to look at people with multiple allergies and examine why some foods cause serious symptoms in some people, while others will cause only mild or no symptoms at all.

[The development of PCR based method for the identification of peanut in commercial products](#)

The objective of this 1-year study was to develop a sensitive and robust assay for the identification of peanuts in commercial products

[Allergen specific antibody binding characteristics and longitudinal serological changes to purified peanut allergens](#)

Compared to other food allergies clinical sensitivity to peanut frequently continues into adulthood. This study was undertaken to investigate if one characteristic of antibodies “affinity” is different in those individuals with declining specific antibody responses to purified peanut allergens.

[Development of an in-vitro screening method for allergens in novel foods](#)

The ability to predict whether or not a novel protein has the potential to cause an allergic reaction in the human body has been hampered by the lack of suitable tests. The aim of this study was twofold, firstly, to examine the capacity of in vitro models to test the potential of an allergen to cause cross-linking of IgE bound to the surface of mast cells, and secondly, to test the model with potentially allergenic peptides generated in a related project

[Investigation of cross-reactivities toward peanut and other nuts in relation to the age of allergic individuals](#)

This research project endeavoured to confirm or refute the earlier observation in a 1996 study on cross-reactivity to peanut and other nuts by carrying out both clinical studies and laboratory studies using a group of over 700 nut allergic individuals

[Adverse reactions to food, in vivo & in vitro modelling](#)

The specific task of the BIBRA laboratory in this study was to utilize the BN rat strain model to study the allergenic potential of selected food extracts and specific food allergens, particularly with reference to sensitization potential

[A clinical trial to investigate potential allergic reaction from ingestion of storage mites](#)

Occupational allergy in workers involved in grain handling and associated industries is often caused by storage mite allergens. More recently non-occupational sensitisation to storage mites has been reported via ingestion of mites in flour and other foodstuffs containing flour. Sensitisation of this type can cause severe anaphylactic responses in individuals and may explain some cases of unknown food allergy.

[Development of food intolerance in atopic and non-atopic families: influence of maternal nutrition and infant feeding practices in preterm infants](#)

This project looked at a group of 257 infants born prematurely, some of whom came from families with a tendency to develop allergies and some who didn't. It compared the two to investigate whether particular factors influenced the development of food intolerances.

[Factors influencing the susceptibility to, and characteristics of kiwi fruit allergy](#)

This research project aims to describe the clinical characteristics of allergy to kiwi in adults and children

ANNEX 3 - WG5.1 and 5.3 Programme Review Checklist

The Science Council Working Group 5 (WG5) on food hypersensitivity was tasked with two core objectives:

- (1) To consider and advise on future research priorities and direction in respect to food hypersensitivity.
- (2) Conduct a review of the science and evidence base for addressing food hypersensitivity, and the part the FSA and others should play in enhancing knowledge.

To address each objective, WG5 outlined a number of work packages that seek to gather a historical context/review, review the current research programme and *modus operandi* within the FSA, and identify emerging priorities in the 5-to-15-year timeframe.¹

Relating specifically to objective (2) the Science Council agreed to:

- Evaluate the impact of science on FSA policy in the area of food hypersensitivity
- Advise as to the key issues in this area, to support the FSA's decision-making in the future
- Provide advice and challenge on how the FSA identifies, gathers and uses scientific evidence and advice in the area of food hypersensitivity

The FSA has defined science governance as *'the methods by which we assure and demonstrate that scientific evidence and analysis are sought, obtained, interpreted, used and communicated appropriately and effectively by the FSA'*. The FSA's approach to science assurance was set out in its response², the Science Checklist³, to the recommendations from Science Council Working Group 1 on science capability and Assurance, agreed by the FSA Board in December 2018.⁴

Inspired by The Methods Lab approach⁵ and the FSA Science Checklist, WG5 has developed a modified framework by which the FSA research programme surrounding food hypersensitivity will be reviewed for best practice surrounding the commissioning, management and utilisation of the research programme.

The checklist below was utilised to support desk studies, 1-to-1 interviews and group consultations on the FSA's internal organisation of a research programme. The questions were intended to gather understanding of the decision-making process in commissioning, project management and dissemination of outputs etc within the research programme.

¹ <https://science-council.food.gov.uk/science-council-subgroups/science-council-working-group-on-food-hypersensitivity> (Accessed 14/01/2020)

² https://www.food.gov.uk/sites/default/files/media/document/fsa-18-12-09-sc-wg1-capability-assurance-final_0.pdf (Accessed 14/01/2020)

³ <https://foodgov.sharepoint.com/sites/SCIChiefScientificAdviserTeam/Shared%20Documents/DWP%20Development/Updated%20Science%20Checklist%20Feb%202016%20-%20final.docx> (Accessed 14/01/2020 - Internal)

⁴ <https://science-council.food.gov.uk/science-council-subgroups/science-council-working-group-on-science-capability-and-assurance> (Accessed 14/01/2020)

⁵ Pasanen, T., and Shaxson, L. (2016) 'How to design a monitoring and evaluation framework for a policy research project'. A Methods Lab publication. London: Overseas Development Institute.

Science Programme Checklist

1. Strategy and direction:

<p>1.1. How were individual research gaps identified, to inform the aims and objectives of the Research Programme?</p> <p>1.2. What measures were taken to ensure this process was transparent?</p>	<p><i>What inputs were obtained?</i> e.g. <i>comprehensive and structured literature review?</i> <i>Review of “grey” literature?</i> <i>Stakeholder engagement? External advisers?</i> <i>Other sources e.g. surveillance or enforcement, or unpublished data from government, industry?</i></p> <p><i>Were all key scientific uncertainties, including gaps in the analyses and strength of the evidence, highlighted and expressed clearly? What processes were followed to assess this? e.g. GRADE Evidence to Decision frameworks or equivalent.</i></p> <p><i>Relevant documentation: Programme reviews, Reports, other key documents, subsequent workshops and meetings with stakeholders, discussions on steering group or management meetings</i></p>
<p>1.3. Stakeholder engagement</p>	<p><i>Who was engaged, were they the right stakeholders?</i></p> <p><i>How was this reviewed on a regular basis, to capture new inputs (e.g. from early-career researchers; non-academic inputs)? e.g. Stakeholder analysis/social network analysis, stakeholder mapping</i></p> <p><i>What elements of the programme did stakeholders contribute to? e.g. identifying research gaps, methodology, communication of tender calls</i></p> <p><i>How and when were the identified stakeholders engaged in the decision-making process?</i></p> <p><i>Were iterative approaches (e.g. sandpits, validated frameworks) considered when commissioning work in new research areas? Please give details</i></p>
<p>1.4. Was there a strategic document which laid out the strategy and direction of the programme?</p>	<p><i>What did the document define with regard to research need, objectives, desired outcomes and policy change recorded to set / agreed?</i></p> <p><i>When was this reviewed? Was there a trigger for any review? How was it reviewed? Who reviewed this?</i></p> <p><i>How did this align the research programme to the FSA’s strategic objectives / priorities?</i></p>
<p>With respect to specific projects:</p> <p>1.5. What processes were followed by drafting research specifications and evaluating tender bids?</p>	<p><i>What guidance was followed for drafting research specifications and/or evaluating the research bids submitted?</i></p>

<p>1.6. How did the tender call evolve from the original research gap(s) identified?</p>	<p><i>How were these research questions/tender specifications informed by internal and external review?</i></p>
<p>1.7. Was there a clear rationale for the research commissioned, in terms of planned impact on FSA policy?</p>	<p><i>Did the commissioned research directly address the identified research gap in the most cost-effective way?</i></p>

2. Management and governance

	Programme	Projects
<p>2.1. Was the agreed programme realistic in terms of set-up, timing, staffing and resources?</p>	<ul style="list-style-type: none"> • <i>Were there internal FSA capacity issues, and how were these addressed? Issues with staff turnover?</i> • <i>To what extent were outputs from the overall programme completed on time and to budget?</i> • <i>How were risks of delivery identified (and managed)?</i> • <i>What was the effectiveness of countermeasures put in place? (To what extent did risks not materialise?)</i> 	<ul style="list-style-type: none"> • <i>From the perspective of contract managers working with the project delivery contractor:</i> • <i>To what extent were deliverables completed on time and to budget?</i> • <i>Were there capacity issues within contractors' teams, and how were these addressed? (Capacity relates to finance, human resources, expertise etc.)</i> • <i>Problems with staff turnover?</i> • <i>How were risks identified and managed?</i> • <i>What was the effectiveness of countermeasures put in place, and were these described upfront at tender?</i> • <i>To what extent did risks not materialise?</i>
<p>2.2. How was the relationship fostered between the FSA and interested stakeholders?</p>	<ul style="list-style-type: none"> • <i>How were stakeholders engaged?</i> • <i>How was insight and information shared to shape the programme?</i> • <i>Were their clear descriptions for different non-contractor roles within the programme?</i> 	<ul style="list-style-type: none"> • <i>How were tender partners engaging and sharing information among themselves?</i> • <i>Was there clarity over the roles of non-contractors in individual projects? e.g. independent Data Monitoring Committee (IDMC), Trial Steering Committee (TSC)</i> • <i>Did the scope and depth of collaboration with and between tender partners increase since the programme inception? If not, why?</i>

<p>2.3. How were decisions made, with what criteria, and how were they documented?</p>	<ul style="list-style-type: none"> • <i>Were any decisions made consistent, inclusive and transparent?</i> • <i>What processes were in place for documenting and learning from experiences and adjusting to changing context?</i> • <i>Frequency and nature of internal review and challenge of the programme objectives against FSA objectives and priorities?</i> • <i>What assurance and governance was completed during the decision making process and the resultant research outputs?</i> 	<ul style="list-style-type: none"> • <i>Were any decisions made consistent, inclusive and transparent?</i> • <i>What governance systems were in place, and were they as effective as they could be?</i> • <i>What processes were in place for documenting and learning from experiences and adjusting to changing context?</i> • <i>How often were project reviews undertaken by FSA, and what format did these take?</i> • <i>What assurance and governance was completed during the decision making process and the resultant research outputs?</i>
<p>2.4. Did the project compliment the aims of the wider research programme and FSA strategy?</p>	<ul style="list-style-type: none"> • <i>How were funded projects prioritised against other proposed projects that were not funded?</i> • <i>How was the research portfolio regularly review against FSA objectives?</i> 	<ul style="list-style-type: none"> • <i>Did the project compliment the aims of the wider research programme and FSA strategy?</i>

3. Outputs

<p>3.1. What review of the data was undertaken?</p>	<ul style="list-style-type: none"> • <i>Internal FSA review by specialists, External peer review</i> • <i>Was the scientific evidence base transparent to stakeholders?</i> • <i>Is the extent to which judgement has been used clear?</i> • <i>Are the conclusions consistent with the published evidence?</i> • <i>How were areas of uncertainty handled?</i> • <i>Are there alternative interpretations of the same evidence?</i>
<p>3.2. What outputs were generated?</p>	<ul style="list-style-type: none"> • <i>Was the output type appropriate?</i> • <i>e.g. Project reports, conference presentations, publications, blogs, infographics, films etc.</i>
<p>3.3. How does this compare to what was planned?</p>	<ul style="list-style-type: none"> • <i>What peer-reviewed journal articles (or similar) were published or directly generated by the research project in open access formats?</i> • <i>Are data available for sharing?</i>
<p>3.4. Were the outputs relevant to the context in which the research was originally commissioned?</p>	<ul style="list-style-type: none"> • <i>Do the outputs identify what the real issue is that end users face?</i> • <i>Are the outputs structured in a way that enhances the main messages?</i> • <i>Can target audiences access the outputs easily and engage with them?</i> • <i>To whom have outputs been sent, when and through which channels?</i>

4. Uptake and impact:

<p>4.1. What outputs have been used by stakeholders, and how?</p>	<ul style="list-style-type: none"> • <i>What metrics were collected to analyse the uptake of outputs? e.g. citations, downloads, altmetrics</i> • <i>Were data made accessible for FSA and non-FSA stakeholders?</i> • <i>Is there evidence of translation into policy: FSA (internal) / national / international?</i>
<p>4.2. To what extent has the research influenced policy?</p>	<ul style="list-style-type: none"> • <i>What impact did the research have on legislation, guidelines, advice, resource allocation etc. in the UK and internationally / plans in pipeline?</i> • <i>Any unintended impacts?</i> • <i>What was the strength of the commissioned evidence? How was this assessed?</i> • <i>Did any areas of uncertainty identified during this process match those identified in the original outputs?</i> • <i>To what extent was a need for further research identified?</i> • <i>Has the research led to capacity development/acted as a catalyst for further research?</i>
<p>4.3. To what extent has research shifted public agendas?</p>	<p><i>Did the research result in any of the following being generated?</i></p> <ul style="list-style-type: none"> - <i>Media items (traditional press media, radio, tv interviews / items etc)</i> - <i>Discussions on social media</i> - <i>Stories of change</i> - <i>Attitudinal / behavioural change?</i>
<p>4.4. What longer-term results have been achieved?</p>	<ul style="list-style-type: none"> • <i>Is there monitoring in place for longer term trends/surveillance data?</i> • <i>What type of changes have been observed in target groups behaviour?</i> • <i>How sustainable are observed changes likely to be?</i>

5. Review and learning mechanisms

<p>5.1. How has the success and impact of the research been reviewed?</p>	<ul style="list-style-type: none"> • <i>Did the Programme deliver as intended? Were the objectives addressed by the projects commissioned and the outcomes delivered?</i> • <i>How was success and impact measured? – was this an Internal and/or external review?</i>
<p>5.2. What would trigger a review of any decisions made?</p>	<ul style="list-style-type: none"> • <i>Who was involved in the review of the research programme, and when?</i> • <i>What points were assessed and discussed at the review?</i> • <i>How were the findings from the reviews recorded and shared?</i> • <i>Did this impact on further resource allocation?</i>
<p>5.3. What mechanisms have been put in place to ensure</p>	<ul style="list-style-type: none"> • <i>Was a plan put into place to implement recommendations coming out from review and learning mechanisms?</i>

changes are implemented in the future?	<ul style="list-style-type: none"> • <i>Who was involved in this?</i> • <i>Was a time line agreed?</i> • <i>When was a review of implemented change held?</i>
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ANNEX 4: List of interviewees and Acknowledgements

List of interviewees

Date of interview	Individual interviewed	FSA Role
05/02/2020	Peter Aggett	Chair, FAIR 2008 Review Panel
21/02/2020	Hannah Rose	Team leader for Allergy Policy (Policy)
21/02/2020	Joanne Edge	Allergy and Radiological Risk Assessment team leader (SERD)
21/02/2020	Ross Yarham	Food Allergy and Intolerance Research programme lead (SERD)
21/02/2020	Elsa Eugene	Food allergy and intolerance policy advisor (Policy)
21/02/2020	Katharine Porter	Social Researcher (Analytics SERD)
04/03/2020	Michelle Patel	Head of social science
05/03/2020	Michael Wight	Head of Food Policy
05/03/2020	Tina Potter	Head of Incidents
05/03/2020	Paul Tossell	Head of Radiological, GM, Novel Foods and Feed Additives Team
05/03/2020	Alison Asquith	Foodborne Disease Control Team in the FSA
18/05/2020	Rebecca Sudworth	Director of policy
12/05/2020	Ian Kimber	External Programme Adviser, FAIR
27/05/2020	Guy Poppy	FSA CSA
05/06/2020	Graham Roberts	External chair to 2 recent FSA-funded projects (EAT Study, TRACE Study)
05/06/2020	Michael Perkin	Lead co-contractor, EAT study; External advisor to FSA
11/06/2020	Charlotte Madum	FSA PMO

Working Group 5 Membership

Name	Role	Declaration of Interests
Dr Paul Turner	Working Group 5 Chair	
Professor John O'Brien	Working Group 5 Co-Chair	
Professor Sandy Thomas	Science Council Chair	
Professor Peter Gregory	Member	
Professor Patrick Wolfe	Member	
Professor Sarah O'Brien	Member	
Professor Jonathan Wastling	Member	
Ms. Claire Nicholson	Member	
Ms Alisha Barfield	Working Group 5 Lead Secretariat	
Dr Chun-Han Chan	SSAT Team Lead	
Dr Adam Cook	Head of SSCR	
Mr Paul Nunn	Science Council Lead Secretariat	
Dr Rachel Whiteside	Previous Working Group 5 Lead Secretariat	

ANNEX 5 – Case Studies

Enquiring About Tolerance (EAT) Study

1. Executive Summary

Food allergy is a significant public health problem affecting 5-8% of children in the UK. Previous official health advice was for women with atopic (allergic) background to avoid the consumption of peanuts during pregnancy and when breastfeeding; and for children to avoid peanut until after age 3 years. Subsequently, data emerged which called this advice into question. It became clear that children could become allergic following sensitisation (exposure) through the skin. This observation gave rise to the hypothesis that delaying oral exposure to allergens whilst cutaneous exposure was occurring might increase the risk of food allergy (and so not delaying oral exposure might induce oral tolerance).

Emerging data suggested that earlier introduction of peanut and egg (prior to age 12 months) might therefore reduce the incidence of food allergy. The FSA therefore put out a call in March 2006 for research to determine the factors, including weaning practices, that influence the development of clinical allergy or tolerance to food proteins in infants. The tender was awarded to Kings College London to undertake the Enquiring About Tolerance (EAT) Study.

The findings of the EAT study suggest that early introduction of allergenic food in sufficient quantities from 3 months of age, alongside conventional breastfeeding, may be able to help prevent food allergies developing in children. These data informed official UK Government guidance with respect to the introduction of potential food allergens in the first year of life.

Key points	<p>FSA has had a key convenor role in facilitating discussions which led to global research efforts resulting in a reversal of prior advice to delay certain food allergens when introducing solids into the infant diet.</p> <p>The FSA has not fully capitalised on the public-facing visibility of communications around the outputs of the study, which would further enhance the reputation of the FSA both in the UK and at an international level.</p> <p>There was a lack of clarity over the different roles and responsibilities of the Independent Data Monitoring Committee (IDMC) which led to tensions during the study. Evidence of regular attendance by key members of the study team at project meetings was lacking.</p> <p>Recruitment and maintaining an adequate follow-up level was very challenging and depended on significant extra personal efforts of a limited number of key individuals in the study team.</p>
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	The study delivered excellent outcomes for a relatively modest budget; concerns were raised, however, that the study was significantly under-costed.
Project outputs	<ul style="list-style-type: none"> • Technical report • Multiple peer-reviewed publications (including main publication in NEJM) • Trial data available at Trialshare (www.itntrials.org) • Presentations at Scientific Meetings, and to the Scientific Advisory Committee on Nutrition (SACN) and COT
Impact	<p>The FSA commissioned a series of systematic reviews into the evidence base, including EAT, on the influence of maternal and infant diet on the development of food allergy, other allergic and autoimmune diseases. This resulted in joint recommendations by COT and SACN which have been incorporated into the SACN report on feeding in the first year of life (2018).</p> <p>EAT has added to the data underpinning changes to national and international guidelines on infant feeding.</p>
Recommendations	<p>FSA should endeavour to ensure costings are appropriate at the tender stage, to minimise risks of insufficient staffing to deliver projects according to the specified tender. This is an important part of project management.</p> <p>The FSA should address the quality of project management by contractors by developing an appropriate management dashboard</p> <p>Reinstitute regular stakeholder meetings to ensure FSA continues to facilitate state-of-the-art research in the area of FHS in the UK.</p> <p>There would be significant benefit to improving the internal and external visibility of outputs and telling a more complete story about how research has evolved from inception to outputs and impact. FSA should consider a public-facing communications strategy (similar to that used for the CSA report) published every 3-5 years.</p> <p>The FSA should consider ways of capturing best practice in terms of project management and governance, and the implementation of regular reviews of lessons learnt, as a continuous cycle.</p> <p>There may be future scenarios where there is a disagreement over the use of science and evidence which impact on project management to the extent that the tender could be terminated. In such circumstances, the FSA should have a clear process with which to obtain independent scientific review.</p>

	Importantly, these recommendations should be identified during project meetings and at project closure meetings, rather than reviews such as this Science Council-led exercise.
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2. Background

In 1998, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) (an independent scientific committee that provides advice to the Food Standards Agency, the Department of Health and other Government Departments and Agencies) recommended that women with an atopic (allergic) background avoid the consumption of peanuts during pregnancy and when breastfeeding; and for children to avoid peanut until after age 3 years. This was due to a concern that allergic sensitisation (which can lead to food allergy) may occur in utero, something driven by the observation that many children reacted to peanut upon apparent first exposure, and was also supported by the limited epidemiological data at the time.

Subsequently, higher quality epidemiological data did not show an association between early peanut exposure and the development of peanut allergy. In fact, data emerged indicating that infant consumption of peanut is higher in those countries with lower rates of peanut allergy (such as Israel). It also became apparent that children could become allergic following sensitisation (exposure) through the skin. Together, these observations gave rise to the hypothesis that delaying oral exposure to allergens whilst cutaneous exposure was occurring might increase the risk of food allergy (and vice versa, i.e. earlier solids introduction might induce oral tolerance, if there are critical windows during infancy where dietary exposure to food proteins will induce immunological unresponsiveness). This hypothesis was tested in the LEAP (Learning Early About Peanut Allergy) study, funded by the US NIH's Immune Tolerance Network (ITN), in which 640 atopic infants aged 4-10 months were randomly assigned to consume 6g peanut protein/week or avoid peanut until 60 months of age.

The FSA saw a unique opportunity to gain access to an important clinical trial in an area of direct relevance to the FSA's policy needs and research interests through providing co-funding. The FSA funded the immunological aspects of the LEAP study to identify potential preventative or immunomodulatory strategies regarding dietary exposure to food allergens in early childhood.

At the same time, the FSA noted that there was limited evidence in terms of the potential impact of earlier introduction of other key allergens into the infant diet. The EAT study was therefore commissioned to investigate whether early infant feeding practices with respect to other allergens can influence the development of clinical allergy or tolerance to food proteins in infants, including those at lower risk of developing food allergy.

The EAT study recruited, from the general population, 1303 exclusively breastfed infants aged 3 months and whom were randomly assigned to either the early introduction of six allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat; early-introduction group) or to the current UK practice of exclusive breastfeeding to approximately 6 months of age (standard introduction

group). The primary outcome was food allergy to one or more of the six foods between 1 year and 3 years of age. At 3 years, 7.1% (42/595) participants in the standard-introduction group developed an allergy to at least one allergen, compared to 5.6% (32/567) in the early-introduction group ($p=0.32$). In a per-protocol analysis, the prevalence of peanut and egg allergy were significantly lower in the early-introduction group than in the standard introduction group (peanut: 0% vs. 2.5%, $p=0.003$; egg: 1.4% vs. 5.5%, $p=0.009$). The early introduction of all six foods was not easily achieved but was safe.

Data from EAT were linked to another FSA-funded project, T07046 (EuroPrevall), part of an EU-funded study to determine the patterns and prevalence of food allergy across Europe and develop better food allergy management strategies. Following the end of EuroPrevall, a follow-on study also funded through the EU in which FSA was a partner (Integrated approaches to Food Allergy and Allergen Management, iFAAM) provided funding for the measurement of specific IgE antibody levels in sera collected in children at 3 years as part of the EAT study. Access to data generated by EAT was granted to enable further analysis. The specific IgE data generated as a result of the funding provided is jointly owned by the FSA, MRC and the European Commission.

More details about the EAT study are in Appendix A.

3. How was the research gap identified:

3.1. Evidence

- Whilst scientific evidence suggested that genetics played an important role in the development of food allergy, it is clear that there were other factors that influenced the allergic outcome of a child.
- Epidemiological data indicated that the timing, quantity and pattern of introduction of foods into the early infant diet, and especially of known food allergens, may influence the development of allergy or tolerance. Whilst the proportion of infants given solids by 8 weeks of age has decreased since 1975, there had been a proportional increase in the prevalence of food allergy in children.
- There was no international consensus regarding the timing and introduction of allergens into the infant diet and little published data that was based on prospective studies (retrospective studies can be influenced by recall bias).

3.2. Clear rationale for research in terms of impact on policy

- The Department of Health advice recommended that infants are exclusively breastfed until six months of age and that certain foods that are thought more likely to cause an allergic reaction should not be introduced before six months. However, this policy was developed primarily on nutritional grounds and not with a full understanding of the possible impact of early infant feeding practices on the development of clinical food allergy or tolerance.
- FSA had evidence that most mothers in the UK did not choose to exclusively breastfeed for the full 6 months, with many introducing solids prior to age 6 months. It was unclear what impact this behaviour may have been having on the allergic outcomes, compared to infants who were breastfed for longer or

had the introduction of solids (and thus common food allergens) delayed beyond 6 months. The EAT study would help provide scientific evidence to underpin Government advice on early infant feeding.

3.3. Stakeholder engagement

The 2003 FAIR programme review noted that the FSA (and previously MAFF) had sought to commission research that would address some of these areas of uncertainty to allow fully informed, evidence-based decisions to be taken to improve consumer health policies. Amongst the objectives identified since 1997 were:

- To investigate the impact of feeding practices in infancy on the development of food intolerance, and definition of the relevant mechanisms.
- The influence of maternal nutrition and neonatal feeding practices on the development of food intolerance in atopic and non-atopic children.

- 1.1 At the FSA's 2003 allergy research programme review, the panel discussed several suggestions for future research, however, feeding practices and the timing of introduction of allergens into the infant diet was not included. The commissioning of the EAT study followed encouraging evidence from the LEAP study, and galvanised the FSA's continued effort to address areas of uncertainty defined back in 1997 under the MAFF programme of work.

3.4. Development of tender call

A call was issued in March 2006 for research to determine the factors, including weaning practices, that influence the development of clinical allergy or tolerance to food proteins in infants.

3.5. Internal / external review

The original appraisal panel consisted of FSA officials and external experts, including Prof Christine Edwards (Head of Nutrition, Yorkhill Hospital), Dr Jane Lucas (University of Southampton) and Prof Judy Butriss from the British Nutrition Foundation.

4. Management and governance

4.1. Project Management structure

The Trial was co-coordinated by Dr M Perkin and Prof. G Lack. Prof. Lack was the designated co-ordinator for communication with the FSA and Prof Graham Roberts (Southampton University) chaired the Trial Steering Committee (TSC). Details of the management structure are in Appendix B.

4.2. Challenges during the project

4.2.1. Recruitment

- Recruitment projections to the EAT study were ambitious from the outset, something acknowledged by all involved but nonetheless thought to be feasible.
- Antenatal recruitment commenced on the 4th February 2009 and continued at both recruitment centres (St Thomas' Hospital and Kingston Hospital) until

15th April 2009, when recruitment at St Thomas' Hospital was suspended after 7 weeks due to a staff resignation (for personal reasons) and was not replaced due to insufficient interest among women who had been approached previously. It was already known that the demographic was less affluent at St Thomas' but it had been anticipated that the number of deliveries performed at the hospital (one of the largest delivery units in London) would mitigate for this.

- Antenatal recruitment continued in the sole recruiting centre (Kingston Hospital) until 5th September 2009 when it ceased following the resignation of the remaining recruiter.
- There were also unforeseen challenges in receiving support and endorsement for the study from colleagues within the Department of Health and the hospital representatives providing early infant feeding advice to new and expectant mothers e.g. National Childbirth Trust and breastfeeding coordinators. In addition, there were sensitivities over the level of publicity which was acceptable (the study intervention contradicted national infant feeding guidance at the time, and there was a concern that some families may not wait for the study findings before implementing earlier introduction of solids).
- The two resignations in conjunction with insufficient recruitment resulted in a decision, with agreement of the FSA, to switch to postnatal recruitment using the Bounty Parenting Club to achieve higher enrolment levels. This enabled:
 - Larger numbers of women to be targeted across a larger geographic area, allowing the overall study timescales to remain intact.
 - Targeting women with 2 month-old babies, which would reduce drop-outs with the original plan for antenatal screening (primarily due to non-sustained exclusive breastfeeding).

Some additional funding for recruitment was provided through the NIHR CLRN.

A pilot study of postnatal recruitment commenced on 5th October 2009 via a direct mailing of approx. 12,000 families. The results of the pilot were reviewed by the TSC and FSA on 22nd February 2010.

4.2.2. Revised power calculation and recruitment target

The original study protocol (submitted in 2008) included a power calculation, based on **90%** power and assuming a rate of **6%** and **3%** of food allergy in the control and intervention group respectively, allowing for **20%** loss-to-follow-up (LTF). This equated to an antenatal recruitment target of 3000 mothers, to ensure a minimum of 2500 infants enrolled and 2000 infants attending the final 3rd year assessment.

In February 2010, it became apparent that this level of recruitment would be extremely challenging. In addition, it was noted that a higher risk cohort was being recruited than originally anticipated, with over 30% of infants recruited up to that point having visible eczema at 3 month enrolment. This suggested that the rate of food allergy in the cohort at 3 years of age was likely to be much higher than the 6% originally predicted (upon which power calculations were based).

The power calculation was therefore revised, determining that a sample of 1302 infants would be required to detect, with **80%** power, a 50% relative

reduction in the absolute prevalence (from **8%** in the standard introduction arm to **4%** in the intervention arm) of food allergy by three years of age, assuming a **15%** drop out rate.

A concern was raised by the IDMC as to whether this revised power calculation was appropriate, and risked delivering an underpowered study. This was considered by the TSC and FSA. On the basis of the final study report, LTF was under **10%**; the rate of food allergy in the standard introduction group was **7.1%** and **5.6%** in the early introduction group respectively, by intention-to-treat analysis. This equates to a post-hoc power of **77%** to observe the 50% reduction in food allergy prevalence that the study team had predicted based on a rate of 7.1% food allergy in the standard introduction group.

4.2.3. Study Management

There was a lack of clarity over the different roles and responsibilities of internal and external committees, which led to tensions during the study. Evidence of regular attendance by all key members of the study team was lacking, although this was mitigated in part by a very effective Project Office (which appeared to be more due to individual efforts and good-will of key individuals), and Trial Steering Group who perhaps took a more involved role than initially expected.

An IDMC is important for ensuring safety of participants and ethical studies and together with a TSC provides a high level of governance to a project – this model should be used again for studies involving a non-typical intervention. IDMC are utilised where studies involved intervention trials.

There were a significant number of emails at the end of the study period between the IDMC, the secretariat, the study team, FSA and the Chair of the TSC. There was a lack of clarity on the remit of the IDMC, with significant and diverging views between the IDMC Chair and FSA. It is unclear as to whether agreed terms of reference were set at the outset, nor arguably were the perceived terms of reference consistent with MRC good practice at the time.

The IDMC raised a number of concerns that they did not have access to an appropriate level of statistical and data support, in part because this had not been included in the study costings. These concerns were communicated by the Chair of the IDMC to the highest level of FSA. Unfortunately, a successful resolution could not be negotiated, and the IDMC subsequently took a decision to stand down; the clinical aspects of the study had been completed by that stage).

4.2.4. Follow-up

As the study progressed, it became apparent that follow-up was sub-optimal. This was detected by the TSC and measures were instituted to address this by the Project team. Final LTF was <10%, which is a major achievement for a study of this nature.

4.3. Finance

Original timing and finance:

- FSA contribution of £1,726,260 (ex VAT) – Jan 2008 to Sept 2014
- Supplementary co-funding was obtained by the FSA from the Medical Research Council to the sum of £300,000 across the duration of the study.
- Additional funding from an NIHR Clinician Scientist award to Dr Carsten Flohr at Kings College.
- Significant additional funding was obtained from the NIHR CLRN.
- In-kind contributions to the project amounted to around £730k from Kings College London, St Thomas' Hospital and St George's Hospital

Variations to contract during life of EAT were as follows:

- 2009 – 4 month no-cost extension granted (new end date 31 January 2015).
- 2010 – time and cost extension to mitigate against recruitment issues, new end date May 2015. £365K.
- 2012 - Cost extension to further enhance recruitment. £48k.
- 2013 – Cost extension for an additional £37k to recruit an additional nurse required on the study to assist with the 1 and 3 year follow-up appointments, and allow flexibility in accommodating parent's preference for appointments.
- 2014 - No cost-extension to allow for addition time for reporting (last study visit March 2015, new project end date August 2015).

Therefore, costs for the FSA rose from £1,726,260 to £2,204,260 (£478,000 extra funding) and required an 11 month time extension.

It is noted that the LEAP study, which assessed the impact of earlier introduction of a single food (peanut) into the infant diet in an overall cohort 640 infants, and followed them through to age 5 years, received funding in excess of £8million.

5. Study Review and Outputs

A data analysis plan (DAP) was developed by the study team with support from the TSC and FSA in 2012, to provide a record of pre-planned analyses that would be included in the first and main outcome paper of the EAT study, and to outline the approach for further analyses that arise from the primary analyses. This was reviewed by the IDMC and their comments addressed.

Annual Research Workshops

- The EAT Study team presented their work to fellow FSA research contractors within the FAIR programme, FSA colleagues and key stakeholders throughout the life of the project, although this did not happen after 2012 as the annual workshops were halted.

Programme Reviews

- The EAT study was reviewed at the 2008 and 2012 Programme Reviews, but no external review subsequently occurred after 2012.
- The 2012 External review concluded that *“this is a well-designed study asking a very important policy and scientific question and is the only study of its kind being conducted worldwide. The project is currently on track, recruitment of subjects is complete and therefore it has a strong likelihood of success. Emerging data are showing that there is good definition between the*

comparator groups, and that breastfeeding rates in both study arms is high. Statistical design is good but it was highlighted that data analysis will be difficult and should be carefully considered.”

5.2 Peer Review of Study Outcomes

- **Review by TSC and FSA**

The final TSC meeting was held in May 2015, at which the study team presented initial findings on paper hard copy for discussion with TSC members. A draft final report was received from the contractor in July, and reviewed by: Professor Ian Kimber, Sarah Hardy, Liz Kendall, Shuhana Begum and Dr Cliff Gay from FSA Statistics team. Professors Christine Edwards and David Strachan from the TSC provided additional expert review.

Further peer-review occurred as a result of the submission of research papers to peer-reviewed journals and a number of further research papers are anticipated.

6. Outputs generated

- **Presentation to the Scientific Advisory Committee on Nutrition (SACN)** in 2009 to provide an update on the progress of the study.
- **Technical Report**
- **Data available via Trialshare website** (www.itntrialshare.org)
- **Peer reviewed journal papers**
 - Logan K, Perkin MR, Marris T, et al. Early Gluten Introduction and Celiac Disease in the EAT Study. *JAMA Pediatrics* (*in press*)
 - Marris T, Perkin MR, Logan K, et al. Bathing frequency is associated with skin barrier dysfunction and atopic dermatitis at three months of age. *J Allergy Clin Immunol Pract.* 2020; doi:10.1016/j.jaip.2020.04.043
 - Jabbar-Lopez ZK, Craven J, Logan K, et al. Longitudinal Analysis of the Effect of Water Hardness on Atopic Eczema: Evidence for Gene-Environment Interaction. *Br J Dermatol.* 2019; doi: 10.1111/bjd.18597
 - Voorheis P, Bell S, Cornelsen L, et al. Challenges experienced with early introduction and sustained consumption of allergenic foods in the Enquiring About Tolerance (EAT) study: A qualitative analysis. *J Allergy Clin Immunol.* 2019;144(6):1615-1623. doi:10.1016/j.jaci.2019.09.004
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 - Perkin MR, Bahnson HT, Logan K, et al. Factors influencing adherence in a trial of early introduction of allergenic food. *J Allergy Clin Immunol.* 2019;144(6):1595-1605. doi:10.1016/j.jaci.2019.06.046
 - Marris T, Logan K, Craven J, et al. Dog ownership at three months of age is associated with protection against food allergy. *Allergy.* 2019;74(11):2212-2219. doi:10.1111/all.13868

- Perkin MR, Bahnson HT, Logan K, et al. Association of Early Introduction of Solids With Infant Sleep: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Pediatr.* 2018;172(8):e180739.
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- Flohr C, England K, Radulovic S, McLean WH, Campbell LE, Barker J, et al. Filaggrin loss-of-function mutations are associated with early-onset eczema, eczema severity and transepidermal water loss at 3 months of age. *Br J Dermatol.* 2010;163(6):1333-6.

7. Uptake and Impact

7.1. On the back of the EAT study and in-line with the UK governments review of infant feeding at the time, the FSA commissioned a series of systematic reviews into the evidence base on the influence of maternal and infant diet on the development of food allergy, other allergic and autoimmune diseases. The EAT Study findings were a key component to the review and fed heavily into the outcomes of the findings.

7.2. A joint working group of COT and SACN published a statement in January 2018, which concluded that:

- *there were insufficient data to demonstrate that the introduction of peanut or hen's egg into the infant diet between 4-6 months of age reduced the risk of developing food allergy to any greater extent than introduction from around 6 months of age.*
- *there was reasonable data to demonstrate that the deliberate exclusion or delayed introduction of peanut or hen's egg beyond 6-12 months of age may increase the risk of allergy to these foods.*
- *the Government should continue to recommend exclusive breastfeeding for around the first 6 months of life. Advice on complementary feeding should state that foods containing peanut and hen's egg need not be differentiated from other complementary foods. Complementary foods should be introduced in an age-appropriate form from around 6 months of age, alongside continued breastfeeding, at a time and in a manner to suit both the family and individual child.*

7.3. SACN published their report on feeding in the first year of life in July 2018 (available from: <https://www.gov.uk/government/publications/feeding-in-the-first-year-of-life-sacn-report>). Their recommendations (adopted by the UK government) with respect to allergenic foods are as follows:

- *The available evidence indicates that allergenic foods such as peanut, hen's egg, gluten or fish can be introduced from around 6 months of age and need not be differentiated from other solid foods*
- *Advice on complementary feeding should state that foods containing peanut and hen's egg can be introduced from around 6 months of age and need not be differentiated from other solid foods*
- *The deliberate exclusion of peanut or hen's egg beyond 6 to 12 months of age may increase the risk of allergy to the same foods. Once introduced, and where tolerated, these foods should be part of the infant's usual diet, to suit both the individual child and family. If initial exposure is not continued as part of the infant's usual diet, then this may increase the risk of sensitisation and subsequent food allergy.*
- *Families of infants with a history of early-onset eczema or suspected food allergy may wish to seek medical advice before introducing these foods:*

7.4. The major change as a result of this work is the recommendation that advice on complementary feeding should state that 'foods containing peanut and hen's egg can be introduced from around 6 months of age and that deliberate exclusion of these foods may increase the risk of allergy to those foods.

7.5. EAT study findings were also crucial to advise to healthcare professionals issued by the British Society for Allergy & Clinical Immunology (BSACI) (<https://www.bsaci.org/pdf/Early-feeding-guidance-for-HCPs.pdf>) and other national societies.

7.6. The FSA have funded secondary analyses of the EAT study data, specifically:

- 7.6.1. exploring issues of non-adherence in the early introduction group
- 7.6.2. the influence of the introduction of solids (from age 3 months) on infant sleep patterns
- 7.6.3. an intention-to-treat analysis of earlier introduction of allergenic foods in specific subgroups of infants at higher risk of developing food allergies (those sensitised to foods at enrolment and those with significant eczema) – in which efficacy was demonstrated.

8. Review and learning

8.1. The EAT study is arguably the most ambitious project attempted within the FSA FAIR programme, and required more complex management than previously needed within the Programme.

- 8.2. Delivery of the study was under risk due to under-costing. FSA has since instituted processes to try and avoid this issue in the future.
- 8.3. The use of external, independent experts on a Trial Steering Committee has been adopted in contracted research since, where appropriate.

The FSA should be commended for commissioning an important piece of research with clear policy implications in a highly contentious area (in terms of balance between WHO recommendations for exclusive breastfeeding and timing of solids introduction).

Other areas for the FSA to consider:

- The FSA could monitor the effectiveness of project management by contractors by developing an appropriate management dashboard.
- There may be future scenarios where there is a disagreement over the use of science and evidence which impact on project management to the extent that the tender could be terminated. In such circumstances, the FSA should have a clear process with which to obtain independent scientific review.
- Reinstitute regular stakeholder meetings to ensure peer-review of ongoing work and to facilitate state-of-the-art research in the area of FHS in the UK.
- Improving the internal and external visibility of outputs and telling a more complete story how research has evolved from inception to outputs and impact.
- Ways of capturing best practice in terms of project management and governance.

Further Information

Full Report on the EAT Study

<https://www.food.gov.uk/sites/default/files/media/document/eat-study-full-report.pdf>

(Accessed 28/01/2020)

EAT Study website <http://www.eatstudy.co.uk/eat-study-info/> (Accessed 28/01/2020)

LEAP Study website <http://www.leapstudy.co.uk/>

Annex A. Study Details

Research Approach

The EAT Study enrolled exclusively breastfed infants from England and Wales. The study aimed to recruit infants who represented the general population. Infants were split randomly into two groups.

One group (the Standard Introduction Group) followed standard UK government advice and was asked to exclusively breastfeed for around 6 months, after which introduction of allergenic foods was a matter of parental choice.

The second group (the Early Introduction Group) was asked to introduce 6 allergenic foods from the age of 3 months. Parents were asked to introduce baby rice and/or pureed fruit or vegetables and then some cows' milk-based yoghurts whilst continuing to breastfeed. Then fish, egg, milk, sesame and peanut were introduced

sequentially in random order with 2 new foods per week. Wheat was always the last food given and not before 4 months. The aim was for babies to be consuming these foods twice weekly by five months of age in addition to still being breastfed. It was important that breast milk remained an important part of any babies' diet during the first year of life, so all mothers in the study were encouraged to breastfeed for at least six months regardless of study group.

For safety reasons, all infants in the intervention group were skin prick tested to the 6 foods to ensure they were not already showing signs of food allergy. If they were they had a food challenge to confirm whether the child had a food allergy.

Parents completed online questionnaires every month until their baby was 12 months, and then every 3 months up to 3 years of age. These questionnaires asked about consumption of allergenic foods, allergy symptoms and general health and behaviour. Both groups had a clinic visit at 12 months of age and at 3 years of age. They again had skin prick testing to the 6 foods, tree nuts and aero allergens e.g. dust, grass, pollen. They had an eczema examination, growth check and dietetic consultation. Those with positive skin-prick tests to one of the six foods or those with symptoms suspicious of food allergy underwent a food challenge to confirm.

Study endpoints

Primary Endpoint: The period prevalence of IgE mediated food allergy to the six intervention foods between one and three years of age in both arms.

Secondary Endpoints: Period (one to three years of age) prevalence food outcomes.

- The period prevalence of all IgE mediated food allergy between one and three years of age in both arms.
- The period prevalence of all food allergy (IgE and non-IgE mediated) between one and three years of age in both arms.
- The period prevalence of sensitization to food between one and three years of age in both arms.
- The total number of foods (of the six intervention foods) to which IgE mediated food allergy has been diagnosed between one and three years of age in both arms amongst children with IgE mediated allergy to one or more of the six intervention foods.
- The total number of foods (any foods) to which IgE mediated food allergy has been diagnosed between one and three years of age in both arms amongst children with IgE mediated allergy to one or more foods.

Cumulative (by three years of age) prevalence food outcomes

- The cumulative prevalence of IgE mediated food allergy to the six intervention foods by three years of age.
- The cumulative prevalence of all IgE mediated food allergy by three years of age.
- The cumulative prevalence of all food allergy (IgE and non-IgE mediated) by three years of age.

- The cumulative prevalence of non-IgE mediated food allergy by three years of age.
- The cumulative prevalence of sensitization to the six foods by three years of age.
- The total number of foods (of the six intervention foods) to which IgE mediated food allergy has been diagnosed by three years of age amongst children with IgE mediated allergy to one or more of the six intervention foods.
- The total number of foods (any foods) to which IgE mediated food allergy has been diagnosed by three years of age amongst children with IgE mediated allergy to one or more foods.

Other allergic disease outcomes

- The point prevalence of eczema at one year and three years of age and cumulative prevalence of eczema by three years of age. The severity of eczema at one year and three years of age.
- The prevalence of allergic rhinitis at three years of age.
- The prevalence of inhalant allergen sensitization at one year and at three years of age by skin prick test
- The prevalence of inhalant allergen sensitization at one year and at three years of age by specific IgE measurement
- The prevalence of the atopic wheeze phenotype at three years of age

Composite allergy outcome

- The prevalence of combined allergic disease (a composite of cumulative IgE mediated food allergy to all foods, atopic wheeze phenotype, eczema and allergic rhinitis) at three years of age
- The prevalence of combined allergic disease (a composite of cumulative IgE and non-IgE mediated food allergy to all foods, atopic wheeze phenotype, eczema and allergic rhinitis) at three years of age

Safety outcome

Incidence of adverse events and laboratory abnormalities; nutritional evaluations.

Immunological outcomes

Results of cellular and humoral assessments of immune response related to the development of allergy or tolerance to specific allergens (*subject to additional funding*)

Genetic analyses

The association between skin barrier gene defects (such as carriage of the filaggrin skin barrier mutations) and other measures of skin barrier integrity (transepidermal water loss) with all the study outcomes will be assessed.

Results

The early introduction of allergenic foods alongside breastfeeding was both safe and demonstrated a significant reduction in food allergy prevalence in those that consumed sufficient amounts of allergenic foods from 3 months compared with those encouraged to follow the UK infant feeding advice of around six months exclusive breastfeeding.

However, when every participant was analysed regardless of whether they managed to follow their assigned protocol (referred to as intention-to-treat group) the reduced allergy rate of 21% seen was not statistically significant. For those who fed their infant the recommended amount of peanut (referred to as per-protocol) there was a statistically significant reduction in peanut allergy, 2.5% in the SIG compared with no cases in the EIG (0%). There was also a significant reduction for egg allergy- 5.5% in the standard introduction group compared to 1.4% in the EIG

The safety of participants was monitored very closely throughout the study. No cases of anaphylaxis (severe allergic reaction) were reported in the EIG during the key early introduction period. The EAT study suggests that cooked egg can be a safe way to introduce egg into infants' diets before 6 months of age which contrasts with previous studies which have used raw egg powder.

The study found that the prevention of food allergy could be achieved with weekly consumption of small amounts of allergenic food - about 1 ½ teaspoons of peanut butter and one small boiled egg. Breastfeeding rates were the same in both groups with over 96% of infants still being breastfed at 6 months of age and over 50% in both groups at one year of age.

There was no effect of the trial intervention on growth. In common with the UK population, ethnic participants were more likely to have food allergy and eczema than white participants.

Annex B: Management Structure

The overall management structure consisted of 3 decision making bodies:

1. The **General Assembly** ensured that the views of all the staff within the project were represented in the decision-making process.
2. The **Trial Steering Committee (TSC)** was the main decision-making body with overall responsibility for scientific strategy and direction.
3. The **Project (Trial) Management Group (TMG)**

Support by a Project Office and an external, Independent Data Monitoring Committee (IDMC).

	Members	Roles and responsibility
Project Office	<p>The Project Office was run by an experienced dedicated study data/ project manager.</p> <p>The study also benefited from a full-time project manager on another intervention study to provide extra cover e.g. whilst on annual leave.</p>	<p>Day-to-day running of the project in accordance with decisions taken by the TSC and TMG</p> <ul style="list-style-type: none"> • Recording project activity and ensure that milestones were met. • Financial monitoring and audit of spending • Preparing reports for TSC and FSA. • Organising meetings and providing administrative support to the chairpersons. • Implemented the study communication strategy.
Trial Management Group (TMG)	<p>The TMG was chaired by Dr M. Perkin (co-PI) and included Prof G. Lack (co-PI) and the study data manager.</p>	<ul style="list-style-type: none"> • Ensure that the goals set by the TSC and General Assembly were met. • Manage the day to day running of the project with the project office. <p>The TMG met weekly to discuss all operational business.</p>
TSC	<p>Independent members (voting)</p> <ul style="list-style-type: none"> • Dr G Roberts, U. Southampton (Chair) • Prof D Strachan, St George's (V/Chair) • Prof C Edwards, U. Glasgow • Mr D. Reading, Anaphylaxis Campaign • Dr M Fewtrell, UCL ICH <p>Dependent Members (voting)</p> <ul style="list-style-type: none"> • Prof G Lack, KCL • Dr M Perkin, KCL • Prof A Greenough, KCL • Prof J Peacock, KCL (Study Statistician) • Prof I Kimber (on behalf of FSA) <p>Observers (non-voting)</p> <ul style="list-style-type: none"> • Ms S Hardy, FSA • Ms S Begum, FSA • Dr C Flohr, KCL (non-voting) • Dr K Logan, Study Coordinator 	<ul style="list-style-type: none"> • To make decisions necessary to ensure successful delivery of the EAT Study. • To evaluate progress against the agreed timetable and deliverables. • To develop and implement successful communication between the study staff and external stakeholders (funders, sponsors and independent data monitoring committee). • To make decisions regarding the allocation and further analyses of biological samples. • To approve the use of EAT study data in all publications • In consultation with the FSA and MRC as funding bodies, to develop, implement and evaluate appropriate policies and procedures to facilitate the protection of knowledge and exploitation of results to appropriate stakeholders. <p>The TSC met as scheduled in the Scope of Work document.</p>

General Assembly	<p>All staff employed on the study and convened on a 3 monthly basis. If deemed appropriate by the TSC.</p> <p>An extraordinary meeting of the General Assembly could be called at any time with a week's notice.</p>	<ul style="list-style-type: none"> • Review the progress of the study. • Act as a forum in which staff can review the strategic direction of the project proposed by the Steering Committee and suggest amendments if appropriate. • Approve changes to the composition of the study staff proposed by the TSC.
IDMC	<p>An external IDMC was appointed to review decisions regarding the safety of the study.</p> <p>Independent members appointed to the IDMC were:</p> <ul style="list-style-type: none"> • Prof Peter Aggett • Dr Jane Lucas • Prof Tim Friede • Prof Ian Booth 	

FEMNAV

Patterns and Prevalence of Adult Food Allergy

1. Executive Summary

Around 1-2% of adults in the UK are estimated to have a food allergy, however the data underpinning this figure is limited. The FSA therefore commissioned the PAFA (Patterns and Prevalence of Adult Food Allergy) study to:

1. determine the prevalence of IgE antibody-mediated food allergy in adulthood in England
2. describe the different trajectories of food allergy across the life course
3. describe adverse reactions to foods that are not due to IgE-mediated food allergy in adults

Key events	<p>Clear benefit from the various stakeholder meetings held to tease out details of this difficult area of research.</p> <p>Challenges with new legislation such as GDPR and how this impacts on research data (particularly with FSA having ownership of data generated through contracted research), and associated lack of clarity over roles and responsibilities across study partners and FSA.</p> <p>Learning from previous studies in terms of independent oversight of the research project via a Steering Committee.</p>
Project outputs	Project ongoing
Impact	Project ongoing
Recommendations	<p>Reinstitute regular stakeholder meetings.</p> <p>The FSA should consider complementary methods to develop tender calls e.g. sandpits. This could be done at the same time as the regular stakeholder meetings.</p> <p>This tendering process should include a requirement for a data management plan, to incorporate details on data flow to facilitate compliance with GDPR and associated legislation.</p> <p>Ensure learning from the impact of GDPR on research activities and science is captured (perhaps centrally e.g. PMO)</p> <p>In conjunction with other Governmental Agencies, FSA should continue to request clarifications from the Information Commissioner's Office to clarify the application of GDPR and associated legislation on research activities.</p>

2. Background

In March 2017 a paper on the FSA's work in the area of FHS research was presented to the FSA Board. The Board were asked to consider the success of the programme to date (which had more recently focussed on primary prevention of food allergy) and instead agree to the shift in emphasis of the research programme to adult food allergy.

The Board agreed to the commissioning of research to better understand the prevalence and characteristics of allergy in adults, to further inform FSA as to future resourcing of FHS research areas, with the caveat that this should not be to the detriment of previous or future research on food allergy affecting other age groups (this latter point was made by a number of Board members and the CSA but not necessarily reflected in the written minutes).

A robust evidence base regarding the prevalence of adverse reactions, their patterns and risk factors for their development is required to underpin future research and policy in this area. Since adult food allergy has not been studied systematically in the UK, it is unknown whether the patterns, prevalence and phenotypes of adverse reactions to foods in adults have changed over the last 20 years, particularly in relation to IgE-mediated reactions. Studies in longitudinal cohorts can provide new knowledge on the trajectories of food allergies from childhood into adulthood which will help inform the likely impact of such strategies.

Following FSA and investment board approval a research call was published and following extensive discussions with lead researchers from the University of Manchester, Southampton, and the Isle of Wight, the project was commissioned in November 2018 with the intention to run and report at the end of 2021.

3. How was the research gap identified?

At the FSA's FAIR programme review in 2012⁶, meeting participants were invited to consider: "*What one thing would make a real difference to those with food allergy and/or food intolerance?*". Several recommendations were made, one of which was Adult Food Allergy.

The external review panel commented that while the FAIR Programme to date had focussed heavily on food allergy/intolerance in children, there would be merit in conducting a review of adult food allergy. The Panel strongly recommended that research should also be undertaken to understand why people develop food allergies later in life, what routes of exposure are relevant, and why it is that individuals acquire allergy to foods that they have previously eaten for long periods without ill effect. This would inform future FSA advice and policy with respect to consumers with food allergy.

⁶ <https://www.food.gov.uk/research/food-allergy-and-intolerance-research/food-allergy-and-intolerance-research-programme-review-2012>

3.1 Stakeholder engagement

The FSA convened a workshop in collaboration with British Society of Allergy and Clinical Immunology (BSACI) in 2014 to bring together researchers and clinicians working in the area to discuss the topic of allergy in adulthood. Key priority areas that emerged from this workshop included improving our knowledge of:

- the true prevalence of adult food allergy in the UK
- the characteristics of adult onset food allergy and factors affecting its development, and how this differs from unresolved childhood food allergy.

A subsequent Expert workshop was held in 2016 to build upon this, and ensure the knowledge requirements were still current, prioritise research questions and discuss potential methodologies and their limitations. Further scoping work was undertaken in-house to formulate a business case and secure the necessary funding. This included engaging with patient representative groups, which yielded further qualitative insights.

The FSA also explored whether existing surveys or cohorts would be a suitable platform to provide answers to these priority questions. The National Child Development Study, The UK Household Longitudinal Study (also known as NCDS), the EPIC-Norfolk cohort, The Health Survey for England (HSE), The 1970 British Cohort Study (BCS), The English Longitudinal Study of Aging (ELSA), and The Avon Longitudinal Study of Parents and Children (ALSPAC) were all investigated but were deemed unsuitable. Other complexities around integrating further questions into existing cohorts also presented an issue and did not appear good value for money. A solution to this was utilisation of the FSA's own Food and You survey, by adding questions on food allergy and in particular the age of onset. These results were presented in a [secondary analysis report](#) which showed that 43% reported their earliest allergy starting aged 18 or over.

Another approach to evidence collection the FSA utilised included social media listening, utilising the Pulsar tool which was established a scour for key words on adult food allergy in an effort to build a picture of the public's conversations on the topic. Over a 12-month period it found more than 300k relevant tweets. The analysis of these data demonstrated a growth in social media interest in adult food allergy with 35% of the discussions focusing on allergens other than of the 14 allergens that were traditionally believed to be the most prevalent.

4. Development of tender call

The detail of the tender was kept broad to enable applicants to utilise innovative methodology to address the call and to gain some insight from leading academics on appropriate approach. Within the specification, Tenders were invited to:

- i. Improve the understanding of the true prevalence of adult onset food allergy and adult food allergy persistent from childhood

- ii. Identify and understand important characteristics of adult onset compared to childhood food allergy and adult food allergy persistent from childhood
- iii. Identify factors that influence the development of food allergy in adulthood.
- iv. Applicants were encouraged to consider submitting project proposals which incorporate break-points to enable segmentation of the project during its lifetime. Project proposals with multiple segments/modules should have their costs laid out individually.

Specifically, tenders were asked to seek to consider:

- the use of social science research based on clinical data to evaluate the current evidence in late onset food allergy.
- collaboration with pre-existing cohort studies, allowing researchers to deliver outcomes to the FSA's priorities without the need to establish new cohort.

5. Management and governance

5.1 Project reporting structures

- **Executive Committee (ExComm)** – comprising the Module leaders meeting monthly, reflecting the multidisciplinary nature of the proposed project.
- **Project management team** – meeting 6-monthly, to ensure good connectivity between different module activities. This includes all ExComm members, representatives from partner organisations and FSA, to provide strategic oversight to ensure objectives are met and ensure it provides robust data to the FSA. It will prepare key data and inform decision making on breakpoints by the Steering Committee.
- **Project Steering Committee** - to provide a platform where independent experts and FSA representatives can engage directly with the project team to discuss and advise on technical and management aspects of the project, advise the FSA on decision making associated with critical assessment points, and assess the outputs from the project management meetings.

5.2 Data and GDPR

The contract and commencement of the project occurred prior to the introduction of the GDPR, meaning a new approach was required to ensure the handling of data from the project was compliant. The project experienced issues around role and responsibilities between project partners and the FSA regarding who were data controllers and/or data processors, with many aspects being unclear in the absence of specific guidance from the Information Commissioner's Office (ICO) in relation to research. The issue had been evolving since the introduction of the GDPR in the early stages of the project, where the FSA were initially identified as the only data controller. Subsequently University of Manchester, and Manchester University NHS Foundation Trust became joint data controllers with FSA.

An extensive Data Management Agreement had to be established between the contractors and FSA to meet the required of General Data Protection Regulation

(GDPR). Following extensive discussion, it was agreed that six of the seven project partners were to be identified as joint data controllers and one as a processor to enable appropriate sharing of data while complying to GDPR requirements.

These issues caused a knock-on delay in obtaining ethics approval and commencing recruitment. Unfortunately, the impact of GDPR could not be foreseen, given the project commenced prior to the legislation coming into force.

5.3 Delivery and cost

£1,837,782,52 Ex VAT (1 August 2018 – 31 December 2021). £1.9m approved by the investment board.

6. Outputs and Impact

****Project is still ongoing****

7. Further Information

PAFA Stage 1 on ISRCTN registry <https://doi.org/10.1186/ISRCTN72819770>

FSA webpage on the project <https://www.food.gov.uk/research/food-allergy-and-intolerance-research/patterns-and-prevalence-of-adult-food-allergy>

Report of FSA/BSACI workshop on adult food allergy
<https://www.food.gov.uk/research/food-allergy-and-intolerance-research/report-of-workshop-on-adult-food-allergy?navref=search-global-all-1>

Annex A. Study Details

Research Approach

The project will make use of two complementary epidemiological approaches. Firstly, a cross-sectional study will be used to assess the prevalence of food allergy across the adult population by utilising the diverse demographic of individuals from Manchester, Southampton and the Isle of Wight in urban and rural environments. This will provide a large group of participants, representative of the UK, who can be characterised with regards to adverse reactions to food including those which may not be mediated by IgE. A large community survey of adults aged 20-70 years will be carried out to identify the prevalence of food allergy in the general adult population.

Secondly, longitudinal cohorts that have now reached adulthood will be revisited. These contain high quality data including the factors that are likely to be associated with the development of food allergy in either childhood or adulthood. This will allow the study team to determine the trajectory of food allergy across the life course. Well characterised cohorts, including the Manchester Asthma and Allergy Study (MAAS), Isle of Wight 1989 and the Food Allergy & Intolerance Research (FAIR) population-based cohorts, will provide information on young adults aged between 20-32.

Clinical confirmation of food allergy (including using oral food challenge) will be undertaken in both study populations. The data from the different centres and study populations will be collected, curated and integrated within an innovative e-lab health informatics platform and analysed to provide a robust estimate of the prevalence of food allergy in UK adults, identify the major foods involved and assess the contribution made by persistent childhood food allergy and adult-onset food allergy.

The project builds on tried-and-tested inter-disciplinary partnership between the Universities of Manchester, Southampton and the Amsterdam Academic Medical Centre (involved in serological analyses). The partnership integrates clinical and epidemiological research with computer science and data analytics to provide a step change in our knowledge of the true prevalence of IgE mediated food allergy, in addition to prevalence of non-IgE mediated adverse reactions to food.

Survey of allergen labelling and allergen content of processed foods

1. Executive Summary

This summary report provides an overview of and how this was received by the public and academic community.

- 1.1. The regulatory framework set up in 2011 within the European Union mandates the declaration of 14 allergens as constituent ingredients in pre-packed foods. The legislation does not cover unintentional cross-contamination with allergens, nor the (voluntary) use of precautionary advisory labelling (PAL) which has increased.
- 1.2. The FSA introduced 'best practice' guidance on managing food allergens in 2006 to assist the food industry in the use of PAL.
- 1.3. The FSA commissioned a project ("**Survey of allergen labelling and allergen content of processed foods**") to assess the use of PAL in UK food products and whether presence/absence of PAL correlates with the actual detection of the relevant allergen (gluten, milk, hazelnut and peanut) in those same foods.
- 1.4. The survey found that:
 - i. undeclared allergen cross-contamination in the UK is lower than that previously reported in studies from other countries, notably Ireland and the USA.
 - ii. The wording used for specific PAL statements did not reflect the level of cross-contamination found.

Key events	<p>Unforeseen issue with commercial analytical method (resulting in false positives due to soya) – issue identified by study team and flagged to manufacturer.</p> <p>Provides key baseline data for future PAL surveillance, but no clear plans from either research or policy in terms of future work and follow-up</p>
Project outputs	<ul style="list-style-type: none"> • Evidence on the use of PAL on prepacked foods in UK, and how this relates to actual allergen presence: <ul style="list-style-type: none"> ○ Peer-reviewed publication ○ Presentations to scientific and industry conferences
Impact	<ul style="list-style-type: none"> • UK Industry guidelines developed for PAL and allergen in spices • Generated evidence to initiate discussion at European Commission Food Information Regulation working group to informally review precautionary allergen labelling across EU. • Informed actions for UK participation in CODEX Committee on Food Labelling and CODEX Committee on Food Hygiene working groups to consider precautionary allergen labelling.
Recommendations	<p>Need to capture future recommendations with respect to future research and policy.</p>

2. Background

- 2.1. The regulatory framework established in 2011 within the European Union mandates the declaration of 14 allergens (i.e. peanuts, tree nuts, soybeans, mustard, eggs, lupin, milk, fish, cereals containing gluten, sesame, celery, sulphur dioxide (added and present at >10mg/kg), molluscs and crustaceans) when present as an ingredient in pre-packed foods.
- 2.2. However, there is no defined requirement in labelling regulation which mandates for the declaration of allergens present due to unintentional cross-contact (PAL) or the absence of an allergen (free-from claim) with the exception of gluten-free claims.
- 2.3. Food businesses (FBOs) are not specifically required to provide labelling about the unintentional presence of or the absence of an allergen in a food. However, there is a requirement in legislation to ensure that food must not be unsafe when placed on the market.
- 2.4. The legislative landscape does not provide specific detail to define what is “unsafe” or “safe” for those with food allergy. The UK approached the EU Commission at working group level to propose discussions and amendments to EU Regulation No. 1169/2011 to consider inclusion of requirements in legislation to define “how much was too much” for allergen cross-contact for those with food hypersensitivity. However, other priorities at EU level prevented this piece of work from developing into a working group activity.
- 2.5. Due to the lack of established and internationally agreed reference doses to inform allergen management thresholds, FBOs need to demonstrate due diligence to maintain food safety. However, in the absence of agreed action levels with respect to allergen thresholds, combined with limitations in the lower limits of detection with allergen analytical methods, there has been over- application of PAL which adversely impacts on food choice for allergic consumers.
- 2.6. The FSA introduced ‘best practice’ guidance on managing food allergens in 2006 to assist the food industry in its use of advisory labelling. However, with the lack of standardisation in allergen risk assessment methodology and inconsistencies in allergen management practices, the application of advisory labelling varies in the way it is presented to consumers. Food Drink Europe refreshed the FSA’s guidance and published it in 2012.
- 2.7. These variations have led some allergic consumers to believe that different types of advisory statements convey different levels of risk (e.g. ‘made in a factory that also handles X’ might be considered to describe a lower risk scenario than ‘may contain X’).

3. How was the research gap identified:

- 3.1. Reports of incidents to FSA indicate that allergen management lacks consistency, for example, in cases where free from claims had been made the presence of an offending allergen in *free from* foods. Random sampling and surveillance demonstrated the presence of allergen at levels indicative of gross or low-level cross-contact, with the majority of incidents attributable to undeclared presence of gluten, milk, peanuts and tree nuts.

- 3.2. There has not been a UK wide survey of allergens in food. There have been surveys in other countries which suggested that allergens are present and not declared on the labelling.
- 3.3. Liaisons at industry expert committees and science committees suggested that this issue needed resolution. Thus, a need was identified to determine if food manufacturers managed allergens and labelled food to indicate unacceptable levels of risk to allergic consumers.

4. Development of tender call

- 4.1. A broad tender call was developed to identify the status regarding use of PAL on pre-packed processed foods sold in the UK
- 4.2. It also sought to quantify the levels of allergens present in foods as a result of cross contamination and assess the relationship between the use of different PAL and detectable allergen presence (for example, due to use of shared production equipment).
- 4.3. Specific objectives were to:
 - 4.3.1. investigate the frequency and level of allergen cross-contamination in a sample of pre-packed processed food products, with and without PAL, for the following four food allergens; milk, gluten, peanut and hazelnut.
 - 4.3.2. compare the level of food allergens in a sample of similar pre-packed processed food products with and without advisory labelling for milk, gluten, peanut and hazelnut.
 - 4.3.3. investigate the different types of PAL used in a sample of pre-packed processed food products purchased from UK retail outlets, and how these relate to the levels of allergen detected in the same foods.
 - 4.3.4. examine whether the suggested allergen advisory statements which are set out in the Best Practice Guidance (such as the FSA Guidance on Allergen Management) are being used by industry

5. Management and governance

- 5.1. Potential limitations in methodology were identified early in the development of the tender call:
 - 5.1.1. Snapshot survey – issues of representative sampling and any difficulties in extrapolating findings to the wider UK retail market.
 - 5.1.2. Heterogeneous vs homogenous contamination – as such, sampling would not necessarily be a true representation of the risk of unintentional allergen presence.
 - 5.1.3. Sampling methodology – introduced limitations in data interpretation, due to the choice of (4) allergens, the range of foods, choice of comparable samples and the numbers of samples across the broad range of product categories; this resulted in some limitations of the statistical significance of the data.
 - 5.1.4. Limitations in analytical techniques

5.2. In addition, during the validation work, the contractors discovered an issue resulting in false positives with the peanut test kit used. An investigation was initiated with the kit manufacturer, identifying an issue with the antibody used. An alternative kit was used, and samples retested in order to ensure the validity of results.

5.3. Delivery and cost

5.3.1. The original cost for the survey at point of tender was £143,493, within the agreed internal budget of £145K. The estimated start date was 01/03/2012 and the study commenced July 2012.

5.3.2. A cost extension of £9,500 to pay for additional sample analysis due to the issue with the peanut analysis, however the actual cost of the project was less than anticipated (£5,666 less).

6. Outputs and Impact

- The survey found that undeclared allergen cross-contamination in the UK were lower than those found in previous studies in other countries, notably Ireland and the USA. A subsequent comparable study in the Netherlands showed similar results and referenced the FSA funded work⁷
- The technical report was peer reviewed by a panel comprising of FSA staff, FSA programme advisor and two external experts. This was published on FSA's website: <https://www.food.gov.uk/sites/default/files/media/document/survey-allergen-labelling-prepacked.pdf>
- Data were subsequently used by another study group to validate an allergen management tool with reference doses by a research group in the Netherlands and the USA (TNO in the Netherlands and Food Allergy Research and Resource Program (FARRP) at University of Nebraska). This work was funded by the FSA - Project FS241038 <https://www.food.gov.uk/research/food-allergy-and-intolerance-research/quantitative-risk-assessment-of-food-products-cross-contaminated-with-allergens>

6.1 Impact and Value for money

6.1.1 The project generated UK-specific data providing insight on the issue of PAL, in addition to work performed by Sweden and the Netherlands. This helped provide leverage to initiate discussions at an EU level to review use of PAL in 2015, to review the landscape and approaches adopted across EU Member States on how they dealt with allergen cross-contact and need for appropriate labelling to indicate this.

6.1.2 The survey complemented data from a previous consumer, industry and enforcement survey on the FSA 2006 guidance, and provided evidence to reinforce the need for the food industry and regulators to adopt a risk-

⁷ [https://www.jacionline.org/article/S0091-6749\(18\)30853-4/pdf](https://www.jacionline.org/article/S0091-6749(18)30853-4/pdf)

based approach for the risk assessment, management and communication with respect to unintended presence of allergens in food due to cross-contact.

- 6.1.3** The results from this survey formed the basis of engagement with industry and development of guidance⁸ in this area. One such example is the allergen risk assessment model⁹. This was done in collaboration with the Food and Drink Federation and the Seasoning and Spice Association and utilised the VITAL system. This is currently being adjusted in light of the new VITAL 3.0 levels with the FSA.
- 6.1.4** The results from this survey formed the basis of further engagement with industry and the development of guidance in this area. A joint EU DG SANTE and DG JRC workshop was convened in June 2017 and was attended by EU Member State representative and interested stakeholder. https://www.efanet.org/images/2017/Newsletter10_2017-10_DG_Sante_DG_JRC_Workshop_report_Geel_June_2016.pdf.
- 6.1.5** The survey was picked up by various media organisations and also reported on by the Allergen Bureau¹⁰. Following on from this work, many similar studies have been carried out across the world.
- 6.1.6** The impact of the new guidance was seen through the actions of one major retailer removing their three-tiered PAL (ingredients, recipe and factory) on prepacked food and reviewing and updating their allergen management to give more meaningful PAL.
- 6.1.7** Advice to consumers was reissued as to the importance of PAL and the need not to ignore such advisory warnings. This was highlighted in more general advice supporting the implementation of new allergen labelling rules being introduced by EU Regulation No.1169/2011 Food Information for Consumers Regulation.
- 6.1.8** In 2017, the FSA took the opportunity to develop Code of Practice on Allergen Management (Codex Committee on Food Hygiene CCFH) and to review the Codex Standard on Labelling of prepacked food with respect to allergen labelling (Codex Committee on Food Labelling CCFL). Initiatives led by Codex Committee will require the FAO/WHO to commission experts to review the evidential landscape on population reference doses to ascertain if these could help inform allergen management practices by the food industry and product food allergic consumers. Taking a global approach will mean the national legislation would have a defined global standard to be used as a basis which will lead to gaining greater international consistency and transparency on how allergens are managed, and risk assessed.
- 6.1.9** This study has also been used as an example for undergraduate students at the Manchester Metropolitan University to teach them about the importance of correct consideration of allergen management and communication of risk to consumers.

7. Review and recommendations for further work

⁸ <https://www.cieh.org/media/1234/Improving-the-use-of-may-contain-allergen-statements.pdf>

⁹ <https://www.fdf.org.uk/resources/allergen-risk-assessment.pdf>

¹⁰ <http://allergiebureau.net/uk-survey-precautionary-allergen-labelling/>

There has been no review to date. Agreeing approaches to allergen management requires an international consensus due to the nature of food trade. Agreeing on a national level will give consistency to the national industry and the market however other countries may have set different safety standards.

In the technical report, the authors suggested that further work could be divided into two areas; additional analysis on the data already collected (such as reproducibility, frequency of PAL across different retailers or between smaller and larger manufacturers), future data collection (with a wider range of food products and/or allergens) and a repeat survey following the introduction of the Food Information for Consumers Regulation to understand if the change in labelling has had any impact on the levels of allergen cross-contact and types of PAL applied.

Further Information

Final survey report (Accessed 29/01/2020)

<https://www.food.gov.uk/sites/default/files/media/document/survey-allergen-labelling-prepacked.pdf>

Food allergen labelling requirements, EU Food Information for Consumers Regulation, [https://eur-](https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:304:0018:0063:EN:PDF)

[lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:304:0018:0063:EN:PDF](https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:304:0018:0063:EN:PDF)
(Accessed 29/01/2020)

Publications

Remington BC, Baumert JL, Blom WM, Houben GF, Taylor SL, Kruizinga AG. Unintended allergens in precautionary labelled and unlabelled products pose significant risks to UK allergic consumers. *Allergy* 2015; 70: 813–819

<https://doi.org/10.1111/all.12625>

<https://www.food.gov.uk/sites/default/files/media/document/survey-allergen-labelling-prepacked.pdf>

Annex A. Survey Details

Research Approach

- The survey sampled 508 products with and without advisory labelling (254 of each), in duplicate (1,016 samples in total were sampled) across 12 different product categories from July 2012 – March 2013.
- The pre-packed processed food items were purchased in duplicate (two samples with identical batch/production codes giving a total of 1,016 products) from a range of retail outlets across the UK, including major and smaller national supermarkets as well as independent retailers.
- The wording of the advisory label did not reflect the level of cross contamination found (for any of the four allergens- gluten, milk, hazelnut and peanut across any product category).
- The survey found that undeclared allergen cross-contamination in the UK are lower than previously found studies in other countries, notably Ireland and the USA. A similar study in the Netherlands showed similar results and referenced the FSA funded work¹¹
- Five hundred and eight pre-packed processed foods were purchased in duplicate (two samples with identical batch/production codes giving a total of 1,016 products) from a range of retail outlets across the UK, including major and smaller national supermarkets as well as independent retailers. Products with allergen advisory statements and an equal number of comparable products without such statements were purchased.
- Samples were tested for the unintentional presence and quantity of one or more of the following four major food allergens: milk, gluten, peanut and hazelnut. These allergens were chosen due to the large number of incidents we received over the past few years and because of their importance to public health.
- The survey examined the different types of advisory statements used on pre-packed foods and compared the use of these phrases to the levels of allergens present. It was anticipated this may help to establish whether the use of certain advisory statements were linked to the level of allergen present and indicate whether different types of statements convey different levels of risk to the consumer. In addition, the survey examined whether the suggested advisory labelling statements set out in our Best Practice Guidance were being used by industry.

Results

- The snapshot nature of this survey and sampling methodology means that it may not be representative of the entire UK retail market; it was therefore difficult to extrapolate findings to the UK retail market as a whole. The main findings were as follows:
- Undeclared allergen cross-contamination in the UK was lower than previously found in studies in other countries, notably Ireland and the USA. The percentage of samples with detectable allergen (both with and without advisory labelling) and where that allergen was not present as an intentional ingredient, were as follows:

¹¹ [https://www.jacionline.org/article/S0091-6749\(18\)30853-4/pdf](https://www.jacionline.org/article/S0091-6749(18)30853-4/pdf)

gluten - 6.1% (33/542); milk - 8.2% (39/474); hazelnut - 2.9% (29/988); peanut - 0.21% (2/950).

- The percentage of samples with detectable allergen, where that allergen was not present as an intentional ingredient and which did not carry an advisory label were as follows: gluten 3.3% (18/542); milk - 2.1% (10/474); hazelnut - 0% (0/988); peanut - 0% (0/950). The percentage of samples in which no allergen was detected but carried an advisory label were as follows: gluten - 19% (97/509); milk - 18% (77/435); hazelnut - 44% (427/959); and peanut - 45% (430/948).
- The wording of the advisory label did not reflect the level of cross contamination found (for any of the four allergens across any product category).
- A wide variety of different statements were used across the product categories; the most frequently used was 'may contain traces' (38% (418/1106)). The second most frequently used was 'may contain' (20.6% (228/1106)).
- FSA guidance recommends the use of 'may contain X' or 'not suitable for someone with X allergy'. These two statements were found on 20.6% and 7.2% (80/1106) of products, respectively.

Annex B. Legislative & regulatory background

On 13 December 2014, the rules surrounding the provision of allergen ingredients information changed and new legislation was enforceable. The application of the new allergen rules under the EU Food Information for Consumers Regulation (EUFIC) No.1169/2011ⁱ introduced changes to rules on how allergen information is provided on prepacked foods and a new mandatory requirement for allergen ingredients information to be provided for non-prepacked foods. The latter requirement was for food businesses to declare the presence of allergenic foods when used as ingredients or processing aids in the non-prepacked foods they sell or provide.

The EUFIC rules are enforced in England through the Statutory Instrument Food Information Regulation (FIR) (SI 2014/1855).

Regulation (EC) No. 852/2004 on the hygiene of foodstuffs (R852) these rules were enforced from 1 January 2006. The purpose of this regulation is to lay out obligations of food business operators to ensure that all stages of production, processing and distribution of food under their control satisfy the relevant hygiene requirements.

Food hygiene requires the implementation measures and conditions necessary to control hazards and to ensure fitness for human consumption of a foodstuff taking into account of its intended use. Article 5 of R852 details Hazard Analysis and Critical Control Points to control risk where Article 5 2 (a) requires the identification of any hazards that must be prevented, eliminated or reduced to acceptable levels. In the context of allergens, risk of cross contamination should have been identified during storage, handling and preparation of food and appropriate controls put into place to reduce or remove that risk.

It should be noted that as well as FIR and R852, Article 14 of EU Regulation No.178/2002 on Food Lawⁱⁱ also details food safety requirements with respect to hygiene. It states that food should not be placed on the market if it is unsafe. Food shall be deemed unsafe if it is considered as injurious to health – this would include the lack of information around the deliberation inclusion of allergenic ingredients or from uncontrolled cross contamination.

With regard to overlap of the hygiene and information rules, if the critical controls are not in place for the allergens (hazard) to be identified, the food operator runs the risk of not complying with the requirements of the EUFIC, FIR and General Food Law. This will likely to result in the provision of incorrect allergen ingredients information, and undeclared allergens present due to cross contamination. Such foods would be considered to be unsafe for those with food allergies or intolerances.

ⁱ Official Journal of the European Union (2011). Regulation (EU) No.1169/2011 on the provision of food information to consumers. L304/18-63

ⁱⁱ Official Journal of the European Communities (2002) Regulation (EC) No.178/2002 laying down the principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety (L31/1-24)