TEST (Trial of Eczema allergy Screening Tests): feasibility randomised controlled trial with economic scoping and nested qualitative study

Protocol (version 2.0 18 October 2018)

Research reference numbers
IRAS: 237046
NHS REC: 18/WM/0124
ISRCTN: 15397185
CPMS ID: 37831
Sponsor: University of Bristol (ref: 2832)
Funder: NIHR School for Primary Care Research (project no: 383)
Clinical trials unit: Bristol Randomised Trials Collaboration

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3 Study synopsis

Study title	Trial of Eczema allergy Screening Tests study
Short title	The TEST study
Clinical phase	IV
Study design	Feasibility randomised controlled trial with economic scoping and nested qualitative study
Setting	Primary care (GP practices)
Study participants	Children with mild, moderate or severe eczema
Aims	• To determine the feasibility of conducting a definitive randomised controlled trial to evaluate whether structured allergy history plus food allergy testing and advice can reduce the severity of eczema in children compared with usual care • To assess the feasibility of conducting an economic evaluation of the definitive RCT • To describe and explore GP and parent beliefs and practices regarding food allergy, food avoidance and allergy tests in children with eczema
Eligibility criteria	Inclusion: Children aged between 3 months and 5 years with mild, moderate or severe eczema (Patient-Oriented Eczema Measure (POEM), greater than 2) diagnosed by an appropriately qualified healthcare professional; parent able to give consent, willing for their child to have allergy skin prick tests (SPT) and oral food challenge(s), and complete outcome measures. Exclusion: medically-diagnosed food allergy or awaiting referral/investigations for possible food allergy; previous investigations for food allergy (does not include home tests).
Randomisation and blinding	Individual randomisation to the intervention or comparator group (1:1 ratio), stratified by age (less than 1 year, 1 year to less than 2 years, 2 years and above) and eczema severity (mild, moderate/severe). Eczema signs (Eczema and Area Severity Index, EASI) at 24 weeks will be assessed where possible by a researcher blinded to allocation.
Description of interventions	Structured allergy history plus skin prick tests from a standard panel of cow's milk, hen's egg, wheat, peanut, cashew and codfish. Some participants will also be offered an oral food challenge (hospital out-patient appointment) or advised a home dietary trial. Based on the findings, participants will be advised to either ingest or avoid these food(s) containing, with dietary advice. Children in comparator group will not receive any additional assessments or tests. Both groups will continue to receive treatment as usual, as described in the NICE eczema and allergy in children guidelines.
Primary outcome	Feasibility of a definitive trial with economic evaluation

Secondary outcomes	• Parent-reported eczema symptoms (POEM) every 4 weeks for 24 weeks • Eczema signs (EASI, by blinded assessor) at 24 weeks • Infant Dermatitis Quality of Life (IDQoL) at 8 and 24 weeks • Child quality of life (Child Health Utility 9D, CHU-9D) at 8 and 24 weeks • Atopic Dermatitis Quality of Life (ADQoL) at 24 weeks • Parental anxiety (Generalised Anxiety Disorder, GAD-7) at 24 weeks • Food ingestion every 4 weeks for 24 weeks • Adverse events related to food allergy or tests Data will also be collected every 4 weeks on personal costs, healthcare contacts and prescriptions (by parent-report and review of participant's electronic medical record (EMR) after 24 weeks); and acceptability of study interventions and procedures.
Number of participants	As this is a feasibility RCT, a formal sample size calculation is not appropriate. We have determined that 80 children (40 in each group) will be sufficient to provide estimates of recruitment, retention, adherence, assessment of contamination within practices and between groups.
Duration of study	Participants will be followed-up for 24 weeks. The total duration of the trial is 30 months, including 10 months set-up, 7 months participant recruitment and 6 months follow-up, and 5 months analysis and reporting.
Statistical methods	We will report our findings following the pilot and feasibility extension of the CONSORT guidance (2010), including a CONSORT diagram, descriptive and summary statistics, along with all important harms or unintended effects in each group.
Nested qualitative study	Around 20 parents and 10 GPs will be interviewed at varying time-points to capture issues related to different stages of trial participation. We will explore beliefs about food allergy and experiences/acceptability of the allergy tests as well as the conduct of the study and hence feasibility of the definitive trial itself. In addition, we will try and interview ~5-8 parents who decline to take part or withdrawal from the trial. Interviews will be recorded using an encrypted digital voice recorder, transcribed, anonymised and analysed thematically.
Keywords	Eczema, food allergy, allergy tests, RCT, children or paediatrics, primary care.

4 Abbreviations

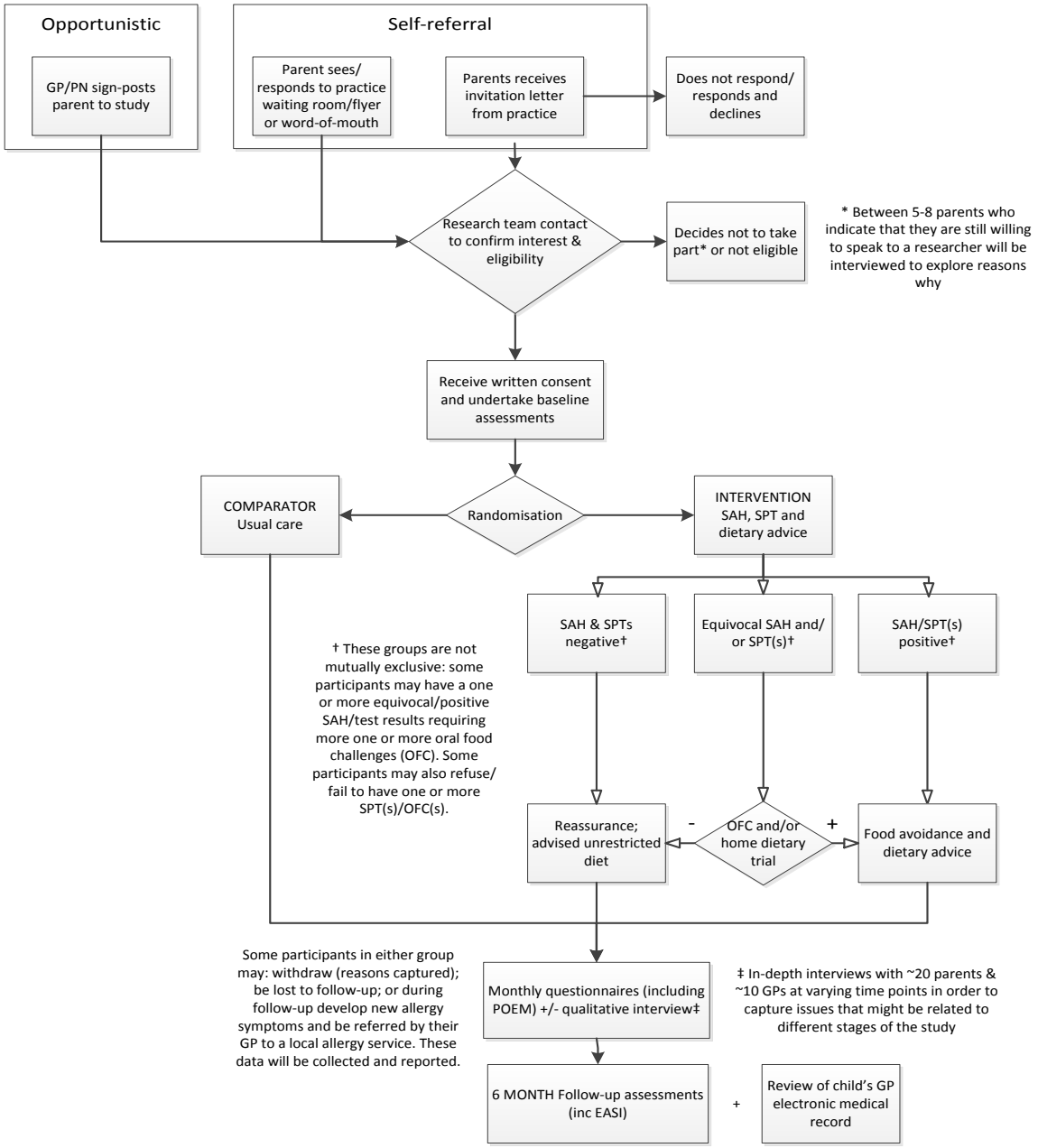
ADQoL	Atopic Dermatitis Quality of Life scale
AE	Adverse Event
AR	Adverse Reaction
BRTC	Bristol Randomised Trials Collaboration
CEBD	Centre for Evidence Based Dermatology
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRN	Clinical Research Network
CSO	Clinical Study Officer
CTA	Clinical Trial Authorisation
CHU-9D	Child Health Utility 9D scale
CTIMP	Clinical Trial of an Investigational Medicinal Product
DFI	Dermatitis Family Impact questionnaire
DSUR	Drug safety Update Report
EASI	Eczema Area and Severity Index
EMR	Electronic Medical Record
EudraCT	European Clinical Trials Database
FP10	Family Practice form 10 (for prescriptions)
GAD-7	Generalised Anxiety Disorder 7
GCP	Good Clinical Practice
GP	General Practitioner
HCP	Healthcare professional
HOME	Harmonising Outcome Measures in Eczema
HRA	Health Research Authority
ID	Identification number
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-To-Treat
MCID	Minimum Clinically Important Difference

NHS	National Health System
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
OFC	Oral Food Challenge
PI	Principal Investigator
POEM	Patient-Oriented Eczema Measure
PPI	Patient and Public Involvement
PN	Practice Nurse
RA	Research Associate
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGF	Research Governance Framework
SAE	Serious Adverse Event
SAH	Structured Allergy History
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMS	Short Message Service (text)
SOP	Standard Operating Procedure
SPCR	School for Primary Care Research
SPT	Skin Prick Test
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TM	Trial Manager
TMG	Trial Management Group
TS-/DM-C	Trial Steering/Data Monitoring Committee
UH	University Hospitals (Bristol)
UK DCTN	UK Dermatology Controlled Trials Network
WHO	World Health Organisation

5 Overview of study

5.1 Participant flowchart

This diagram is designed to provide an overview of participants' pathway through the study only.



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5.2 Schedule of data collection

			Week						
		Expression of interest	00 - Baseline	04	08	12	16	20	24
Screening questionnaire		●							
Demographics and medical history			●						
Eczema diagnostic criteria			●						
EASI			●						●
POEM		●	●	●	●	●	●	●	●
Other eczema symptoms†			●	●	●	●	●	●	●
Other possible symptoms of food allergy			●		●				●
Diet of child (and breast-feeding mother)			●	●	●	●	●	●	●
Health service utilisation				●	●	●	●	●	●
Out-of-pocket expenses/time off work				●	●	●	●	●	●
ADQoL			●		●				●
CHU-9D			●		●				●
IDQoL			●		●				●
Parental anxiety (GAD-7)			●						●
Structured allergy history			○						
Skin Prick Test (SPT)			○						
Oral Food Challenge (OFC)			*						
Home dietary trial			*						
Exit questionnaire									●
EMR notes review									●

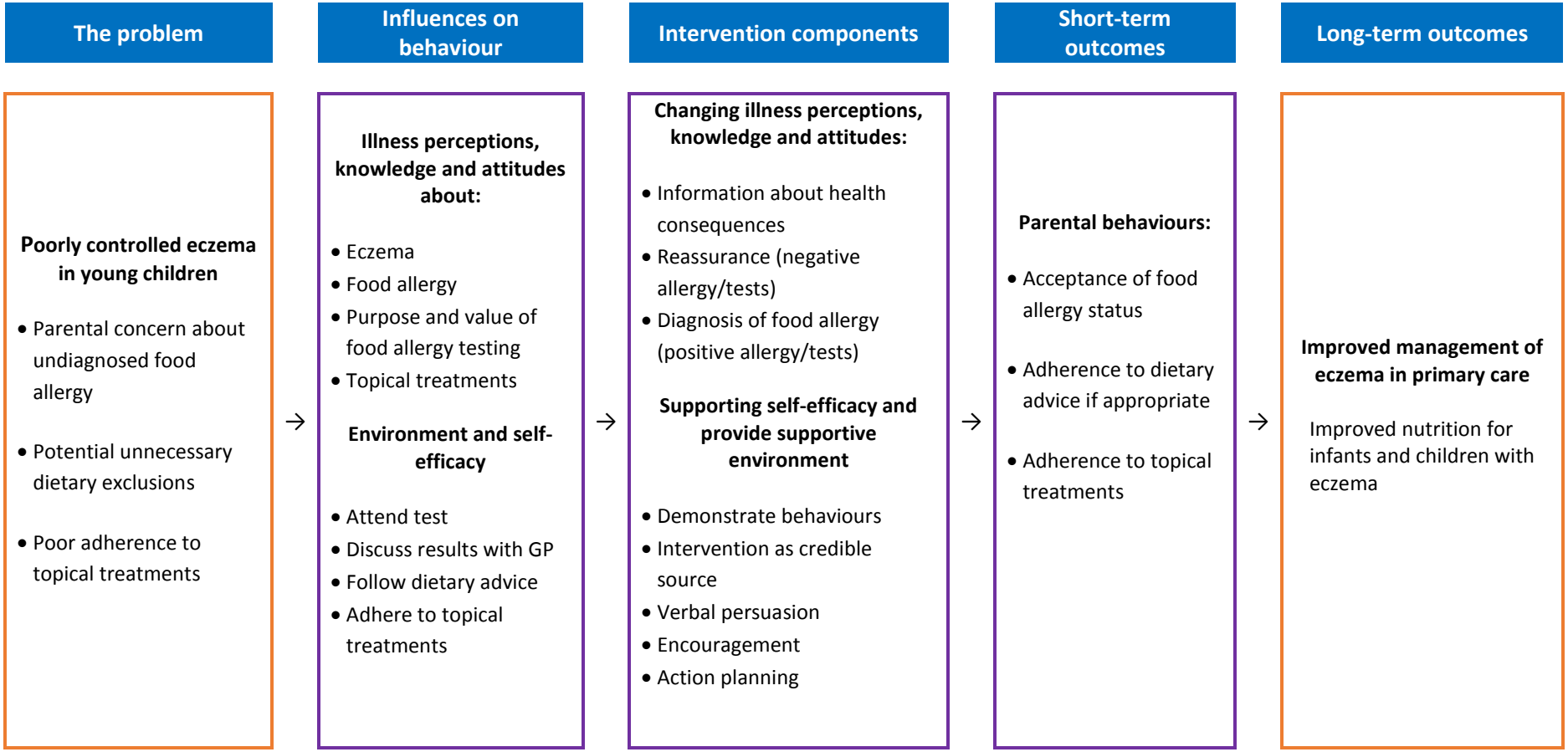
● All participants

○ participants in intervention group only

* participants in intervention group only with equivocal structured allergy history/SPT results

† bother score, itch intensity, parent global assessment

5.3 Logic model



6 Background

Childhood eczema is a common long-term condition characterised by dry and itchy skin. In accordance with the recommended nomenclature of the World Allergy Organisation, we use the label 'eczema' to refer to the clinical phenotype of atopic eczema/dermatitis.[1]

Eczema affects around 20% of pre-school age children in the United Kingdom (UK),[2] with 60% developing symptoms in the first year of life and 90% by five years of age.[2] Most children with eczema are diagnosed and managed in primary care with a combination of emollients and topical corticosteroids. It can have a significant impact on the quality of life of the affected child and their family. Treatment adherence can be problematic for numerous reasons, including parents/carers (hereafter, "parents") seeking a 'cure' through dietary exclusions for possible food allergy rather than 'control' through long-term use of topical treatments.[3-5]

The World Allergy Organisation defines food allergy as an immune-mediated hypersensitivity reaction to food[1] and may be divided into Immunoglobulin E (IgE) mediated and non-IgE mediated reactions.[1] IgE-mediated food allergy involves immediate hypersensitivity through the action of mast cells, whereas non-IgE mediated food allergy is delayed and thought to be caused by an aberrant T-cell response. While immediate-type, multi-system reactions to allergens can be diagnosed relatively easily by a detailed history (respiratory, gastrointestinal and skin symptoms) and demonstration of specific IgE (on blood or skin prick allergy tests) towards the suspected food, it is more difficult to determine that specific foods cause delayed, eczematous reactions.[6]

Compared with objective assessments, parents' suspicions of food allergies in general and especially with respect to eczema have low specificity. Depending on the specific population studied and how researchers have chosen to apply definitions, between 15-36% of children with eczema compared to about 6% of the general population have a food sensitivity (a 'positive' test result, without clinical symptoms) or allergy.[7] To date, most allergy research relevant to eczema has been observational and focused on immediate, 'anaphylactic' reactions; as opposed to examining the role (if any) of food allergy in long-term eczema severity.

A Cochrane review[8] of dietary exclusions for adults and children with eczema published in 2008 did not find any evidence of benefit for exclusion diets in unselected populations (i.e. those without clinically suspected food allergies), but did identify one trial which suggested that infants with suspected egg allergy who have positive specific IgE to eggs may benefit from an egg-free diet.[9] While this suggests allergy testing may be worthwhile, both this and the two other subsequently published systematic reviews[10 11] have called for better-designed and well conducted trials.

The James Lind Alliance eczema research priority setting partnership (2013) identified the following questions: "What role might food allergy tests play in treating eczema?" and "What is the role of [exclusion] diets in treating eczema?"[12] We have not identified any economic evaluations in this area and while concerns about food allergy have been raised during in-depth interviews of parents' general experiences of looking after children with eczema,[3-5] and have arisen as an important concern for parents in online discussion forums,[13] we are not aware of any qualitative work specifically exploring this issue.

There are wide variations in provision of allergy testing for children with eczema, depending on several factors. In surveys, GPs report a lack of confidence in diagnosing food allergy,[14 15] and in recent qualitative work with GPs,[16] parental concern and clinician uncertainty about the role of food allergy in eczema has been highlighted as a barrier to effective treatment. Most GPs do not undertake allergy tests in primary care and if a referral is made, the chance of a child receiving an

allergy test depends on which specialist they see. In general, paediatricians and allergists support the role of food allergy in eczema, whereas dermatologists are largely unconvinced.[17] In the UK, food allergy and eczema are the two most common reasons for GP referral to an allergy clinic,[18] but access to allergists is poor.[15] Consequently, some parents circumvent professional advice altogether and purchase self-test allergy kits on the high street or through the Internet, which are not validated and not recommended.[19] Up to 70% of parents make significant modifications to their child's diet, usually without professional advice,[20] even if the child has only mild eczema. Consequently, not only is medical management suboptimal in these children, but they are also at increased risk of food faddism or malnutrition.

Arguments in support of a link between food allergy and eczema severity are based on observations that food allergy tests are more likely to be positive in children with eczema, and that for some children their eczema appears to improve on an elimination diet. Therefore, potential advantages of undertaking allergy tests include detection of children with associated food allergy prior to serious or prolonged allergic reactions, and possible identification of foods causing eczema flares. Avoidance of these foods in the diet could reduce the frequency of flares and possibly overall severity and duration of eczema.

Arguments against food allergy testing in this population are that exacerbations of eczema provoked by food may not be due to immunological mechanisms, positive tests to food allergens do not necessarily mean the child has an allergy to that food, and for many, their eczema persists regardless of any changes to the diet. Potential disadvantages of allergy tests include cost to the NHS, anxiety and potentially unnecessary elimination diets with the accompanying social challenges, risk of nutritional problems and risk of severe reactions because of loss of tolerance to the avoided foods. This area is particularly topical because of emerging evidence (e.g. LEAP,[21] EAT[22] studies) around the potential benefits of earlier introduction of potentially allergenic foods, to induce tolerance and prevent sudden, severe (anaphylactic) reactions. However, studies to date have focused on high risk populations and findings suggest that differences in efficacy might be affected by the populations studied or the specific intervention (for example, raw as opposed to cooked hen's egg).[23]

An RCT is needed to determine the clinical and cost-effectiveness of food allergy testing and advice in primary care, on severity of eczema in children. There are potentially significant benefits for the NHS of improving long-term eczema management, avoiding serious allergic reactions, and targeting child nutrition. This study is opportune for three main reasons. First, there is significant interest among patients/carers, clinicians, researchers and policymakers in this issue.[12] Second, a pragmatic RCT of an allergy intervention in older children with asthma and/or rhinitis, similar in concept to the one we envisage in children with eczema, showed a reduction in rhinitis symptoms and an improvement in quality of life at 12 months.[24] Third, there is emerging evidence around the importance of the timing (earlier introduction) of potentially allergenic foods. Evidence is needed to discourage parents from unnecessarily avoiding foods because of a perceived link with eczema and, therefore, potentially increasing the chances of the child developing an allergy to that food.

NHS allergy services cannot cope with the high number of referrals they are receiving. In principle, allergy testing (in the form of skin prick tests) and advice could be routinely delivered in primary care, but evidence is needed to demonstrate both the feasibility and value of doing so. For the proposed feasibility study (and probably the definitive trial), we will recruit prevalent cases of children with eczema. If undertaking skin prick tests in primary care were shown to be feasible, worthwhile and acceptable, then their place in the care pathway will be better defined by the findings of the definitive trial. That is, incident cases of children with eczema (i.e. when first diagnosed) would be offered, if appropriate, skin prick tests; with reassurance, dietary advice and/or

onward referral as appropriate to secondary care. Providing the evidence and, if appropriate, the necessary training and materials on how to perform and interpret skin prick tests in children with eczema, has the potential to both improve long-term disease control for children with eczema and reduce use of NHS resources (GP consultations, prescribed medications and allergy out-patient referrals).[25 26]

There are clearly many uncertainties regarding food allergy testing for eczema in primary care and the relationship between structured allergy history, interpretation of skin prick tests, subsequent dietary advice and how parents act on this, both in terms of their child's diet and other treatments for their child's eczema. In addition, because of the likely size and cost of a definitive trial, and a number of key uncertainties regarding its viability, we wish to first conduct a feasibility study.[27] In this trial, we will explore recruitment, retention, acceptability, adherence and trial processes that will determine the feasibility and inform the design of a future, full-scale clinical and cost-effectiveness RCT. This intervention involves a number of interconnected components and variability of potential outcomes (see 5.3 Logic model) and we will follow the MRC guidance for developing and evaluating complex interventions. We will draw on the extended Common-Sense Model,[28] which is highly relevant to theorising how the beliefs of patients and carers concerning symptoms and treatment may relate to actions regarding health behaviour.

7 Research question, aims and objectives

7.1 Research question

What is the clinical (disease severity) and cost-effectiveness of routine food allergy testing plus advice compared to current standard practice for the management of eczema in children?

7.2 Aims

- To determine the feasibility of conducting a definitive randomised controlled trial to evaluate whether structured allergy history plus food allergy testing and advice can reduce the severity of eczema in children compared with usual care
- To assess the feasibility of conducting an economic evaluation of the definitive RCT
- To describe and explore GP and parent/carer beliefs and practices about food allergy, food avoidance and allergy tests in children with eczema

7.3 Objectives

1. To determine the feasibility of the definitive trial with economic evaluation:

1.1. To compare recruitment and retention rates by method of recruitment and participant characteristics.
1.2. To investigate the acceptability of recruitment, intervention and follow-up procedures to parents/carers.
1.3. To assess the acceptability of trial processes and procedures to GPs.
1.4. To develop and refine a manual on the interpretation and dietary advice to be given according to allergy history/skin prick test +/- oral food challenge +/- home dietary trial findings, with accompanying patient information leaflets
1.5. In the intervention group, to determine the number of participants with positive/negative structured allergy histories, skin prick tests and oral food challenges/home dietary trial (where done), thereby informing estimates for the main trial
1.6. To assess adherence to dietary advice.
1.7. To examine for evidence of contamination of the control group.
1.8. To assess the acceptability and feasibility of collecting clinical outcomes (proposed measures of effectiveness of the interventions), and hence determine the primary outcome of the definitive trial
1.9. To assess the feasibility and optimise collection of patient-level data on NHS and personal resource use
1.10. To determine the feasibility of using the CHU-9D in children under 5 years of age
1.11. To inform eligibility criteria for the future definitive trial.
1.12. To examine for evidence of detection bias in the collection of patient-reported outcomes.
1.13. To test trial processes and logistics.

2. To explore GP and parent/carer beliefs and practices about food allergy, food avoidance and allergy tests in children with eczema

2.1. Nested qualitative study:

- To conduct in-depth interviews with GPs and parents to explore perceptions and opinions about food allergy, food avoidance and allergy tests in children with eczema.
- To explore the acceptability of trial procedures and allergy tests/dietary advice.

2.2. Screening questionnaire:

- To ascertain prevalence of beliefs regarding the role of food allergy in eczema, self-reported/medically diagnosed food allergy and dietary modifications amongst parents of children with eczema.

8 Trial design

8.1 Study design

A single centre, two-group, individually randomised, feasibility RCT with economic scoping and nested qualitative study.

8.2 Setting

Primary care (GP practices) in the west of England.

8.3 Population

Children with eczema.

8.3.1 Inclusion criteria

Children must:

- be aged between 3 months and less than 5 years
- have eczema diagnosed by an appropriately qualified healthcare professional (registered doctor, nurse or health visitor)
- mild, moderate or severe eczema (Patient Orientated Eczema Measure (POEM) score>2)

The person giving consent must:

- have parental responsibility for the participant
- be willing for their child to have allergy skin prick tests (SPTs) and oral food challenges.

8.3.2 Exclusion criteria

Child:

- medically-diagnosed food allergy or awaiting referral/investigations for possible food allergy
- previous investigations for food allergy (does not include home tests)

The person responsible for consent:

- is unable to give informed consent
- has insufficient written English to complete outcome measures

Another child in the family already taking part in the trial.

8.4 Intervention

Structured allergy history: The Clinical Studies Officer (CSO) will first take a structured allergy history. There are recommendations for what a structured allergy history should comprise,[29] but no validated questionnaires. With reference to published guidance,[19 30] we will therefore use modified versions of questionnaires developed by co-applicants Boyle and Chalmers for the BEEP trial (NRES: 14/WM0162).[31] These questions capture relevant symptoms (skin, respiratory and gastrointestinal) and timing of onset in relation to ingestion of the study foods.

Skin prick tests: The CSO will carry out the skin prick tests from a standard panel of cow's milk, hen's egg, wheat, peanut, cashew and codfish (allergens commonly associated allergies in young children with eczema with eczema), along with positive (histamine) and negative (saline) controls.[32 33] Sharp lancets will be used to prick drops of allergen (and one positive and one negative control) placed on the skin (volar surface of the forearm, outer upper arm or back) into the epidermis and superficial dermis. The diameter (mean of longest and shortest perpendicular axis if ovoid or irregular) of any wheal reaction, resulting from the release of histamine and other mediators, will be measured in millimetres after 15 minutes.

Where the child's history and the results of the skin prick test results are equivocal, participants will be offered repeat skin prick tests and/or oral food challenges and/or home dietary trial of exclusion or inclusion. Repeat skin prick tests will be done either at the same appointment or 12 weeks after the baseline appointment.

Oral food challenge: An oral food challenge is a supervised exposure to a potential allergen. These will usually be undertaken within 1-2 weeks of the baseline appointment in "research bed" at the day case unit of the Bristol Royal Children's Hospital, supervised by co-applicant Marriage. Consent specifically for oral food challenge will be received and standard hospital protocols for each allergen will be followed. For pragmatic and cost reasons, they will be un-blinded as in normal clinical practice, rather than the diagnostic "gold standard" of the double-blind, placebo-controlled food challenge.[34]

Home dietary trial: For participants whose history and investigation findings suggest the possibility of a delayed-type reaction, they will be advised to either exclude or reintroduce (as appropriate to their path in the study) the possible allergen from/into their diet over a 2-4 week period, as per current clinical practice.[19]

Dietary advice: A standard protocol (again, drawing on published guidance[35 36] and based on an algorithm that has been developed for the BEEP trial) will be developed to guide what action should be taken based on the combined allergy history, skin prick test results +/- oral food challenge:

i. reassurance and told to ingest food(s);
ii. avoidance of food(s) with dietary advice; and referral to the local NHS allergy services via GP for longer-term follow-up

All participants' results will be reviewed by an expert allergy panel (including co-applicants Ridd, Boyle, Marriage and/or Wadell) and advice on food ingestion/avoidance relayed to their family accordingly. Advice will be tailored accordingly for mothers who are breast-feeding and/or babies who have not yet been weaned.

8.5 Comparator

Participants in the comparator group will not receive any additional assessments or tests. Care after allocation will be as usual, described in the NICE eczema and allergy in children guidelines.[19 37] Any allergy tests and subsequent advice will be monitored as part of this feasibility study.

Regardless of allocation, all management after randomisation, including investigations and/or referrals for possible new, incident food allergies, will remain under the care of the participant's GP.

8.6 Outcomes

A complete schedule of data collection can be found in the table presented on page 12.

In the definitive trial, the impact of allergy testing on eczema severity will be evaluated, as well as quality of life and cost-effectiveness. The purpose of this study is to determine the feasibility of conducting the trial (recruitment, retention, contamination) and collecting the required data. [38] In line with the recommendations of the core outcome group for eczema, HOME,[39] data will be collected in the key domains of symptoms, clinical signs, long-term control and quality of life.

Symptoms and signs will be captured using the recommended outcome measures (POEM[40] and EASI[41] respectively):

- POEM (collected monthly) will be completed by proxy (parent report) and captures symptoms of importance to parents and patients.[42] Emerging data suggests that monthly, as

opposed to weekly, collection is adequate for the purpose of capturing long-term control.[43] It demonstrates good validity, repeatability and responsiveness to change.[44 45]

- EASI[46] (baseline and 24 weeks) is a validated scoring system that grades the physical signs of eczema. Administered by a trained researcher, it will provide an independent assessment of effectiveness.

Child and family-oriented quality of life measures will be collected at baseline, weeks 8 and 24 using the below measures:

- Disease-specific – child ADQoL;[47] IDQoL[48 49]
- Generic – child CHU-9D[50 51] (currently validated for children aged 7 and over, additional guidance notes and validation questions for those under 5)

We will use repeated measures of the key domains (monthly POEM for 24 weeks, EASI at 24 weeks and quality of life at 8 and 24 weeks) for long-term control as recommended by HOME.

Other data collection:

- Eczema 'bother' score
- Itch intensity
- Parent global assessment of eczema
- Other possible symptoms of food allergy
- UK Diagnostic criteria for atopic dermatitis (baseline)[52]
- Main carer anxiety (GAD-7, baseline & 24 weeks)[53]
- Diet of child and/or mother if child being breast-fed by her)
- Adverse events (including hospitalisations for eczema/food allergy-related problems)
- Satisfaction with trial processes, procedures and paperwork (exit questionnaire at 24 weeks)

With consent, participants' electronic medical records (EMR) will be reviewed at 24 weeks (from four weeks before and for the duration of time in the study) for data on NHS consultations, treatments and referrals for eczema/allergies.

For participants in the intervention group, the following data will also be collected:

- Structured allergy history
- Results of Skin Prick Test (SPT) +/- Oral Food Challenge (OFC) +/- home dietary trial

9 Trial procedures

9.1 Selection and training of recruiting sites

At least 12 GP surgeries will be recruited via the West of England Clinical Research Network (CRN). Practice criteria will include having at least one Good Clinical Practice (GCP) trained GP; a willingness to undertake patient mail-outs and sign-post potential participants opportunistically; and provide a room for baseline and follow-up assessments.

9.2 Recruitment of participants

The stages of participant recruitment are shown in the 'Participant flowchart' (page 11). We will identify children aged between 3 months and less than 5 years with eczema via an electronic query-based records search developed by the research team and run by practice staff at the GP surgeries. A GP or a delegated member of the practice team will screen the search results for inclusion/exclusion criteria and any other known adverse medical or social circumstance that would make invitation to the study inappropriate. Surgeries will be asked to provide the research team with the number of participants excluded by the GPs, along with a brief reason for exclusion. Parents of potentially eligible children will be sent an invitation pack, comprising an invitation letter, study flyer and response to invitation to participate form.

In addition, we will also recruit participants opportunistically, by placing posters in participating GP surgeries and supplying study flyers for practice staff and health visitors to hand out.

9.3 Confirmation of eligibility and consent

Interested families will be asked to complete an expression of interest form along with a brief screening questionnaire that the research team will use to assess potential eligibility. Anyone found to be not eligible will be contacted to thank them for their interest and explain why they are not suitable for the study.

Parents of potentially eligible participants will then be contacted by a member of the research team to explain more about the study and schedule a baseline assessment at a participating GP practice. At this visit, consent will be received, baseline data collected, and randomisation undertaken.

9.4 Allocation

Individual randomisation to intervention or comparator groups (1:1 ratio), stratified by age (less than 1 year, 1 year to less than 2 years, 2 years and above) and eczema severity (mild, moderate/severe)[54] using the Bristol Randomised Trials Collaboration (BRTC) web-based system.

The research team will notify the appropriate GP surgery of the participant's allocation and the outcome of any tests/investigations and food allergy diagnoses. Because the parents of children in the trial and all treating clinicians will know their allocation, un-blinding procedures are not required.

9.5 Follow-up of participants

Participants will be followed-up by means of parent-completed questionnaires every 4 weeks (online or paper, according to parent preference) with a final face-to-face follow-up assessment at 24 weeks with the participant and their carer at a venue of their choosing, usually their home.

9.5.1 Duration of participant involvement

From the point of randomisation, participants will take part in the trial for 24 weeks.

9.5.2 Withdrawal from the study

Parents or their clinicians will be free to withdraw the participant at any time, without any consequences for their usual care or follow-up. Withdrawal from the study will be classed as "active" (the participant/clinician contacts the research team saying that they no longer want or are unable to take part) or "passive" (parents of participants stop completing study questionnaires, fail to attend the 24-week appointment and/or do not respond to communications from the research team).

Parents of participants who withdraw will be asked to provide a brief reason for why they would like to withdraw, and some will be invited for an interview as part of the qualitative study.

9.6 Blinding

It is not possible to blind participants, their families or treating clinicians to allocation.

The CSO undertaking the baseline visit cannot be blinded, but all baseline data (including EASI) will be collected before randomisation. Whenever possible, the follow-up visit will be done by a different CSO, who will be blinded to allocation. Parents will be asked not to disclose allocation to the CSO doing the follow-up visit. Blinding will be monitored by means of self-report.

9.7 Stopping rules and discontinuation

Participant recruitment will cease after 6 months or 80 participants have been recruited, whichever happens first.

9.8 Participant stipends and payments

Participating families will receive no monetary payment for taking part in this trial. However, in recognition of participant's time and to encourage retention in the study/data collection, parents of participants will be offered £10 vouchers at the baseline and around the 24-week visit. We may also offer the child a small gift of about £5 in value.

9.9 End of trial

The end of the trial will be the last data collection item of the last subject, defined as no more than 28 weeks after randomisation of the last participant.

10 Data collection

A complete schedule of data collection can be found on page 11. Data will be collected by means of researcher visits, parent-completed questionnaires and EMR review.

10.1 Response to invitation to participate letter

Parents of potentially eligible participants who receive an invitation letter from their GP surgery will be asked to complete and return (by post or online) an expression of interest form indicating their willingness to find out more about the study and potentially take part. The form asks if they currently have eczema/a medically diagnosed food allergy and the POEM questions.

In addition, respondents not interested in taking part in this study will be asked to give their reasons for declining, e.g. too busy, eczema is currently clear or not interested in the study.

10.2 Participant baseline assessment

Interested and eligible participants and their parent will attend a baseline appointment with a researcher at a participating GP practice. At this visit, consent to take part in the trial will be received and permission to be contacted regarding possible interview sought.

Baseline data collected will include: socio-demographics; relevant medical history of child, parents and siblings; UK diagnostic criteria for atopic dermatitis[52]; POEM;[42] Eczema Area Severity Index, EASI[55]; and quality of life measures.

Randomisation will then be undertaken (see 9.4 Allocation) and parent told which group they have been allocated. Those children allocated to the intervention group will complete the structured allergy history, skin prick tests will be performed and advice/onward referral for an oral food challenge/home dietary trial where appropriate.

10.3 Participant follow-up questionnaires and assessment

Parents will be given the option of completing follow-up questionnaires either online or on paper (freepost). Those who choose to provide data online will receive email prompts, while those who opt to complete on paper will be offered SMS reminders, when their questionnaire is due. All participants will receive SMS and/or telephone reminders when questionnaires are overdue. For those parents who struggle to complete the questionnaires or for those questionnaires returned with missing data, an option to complete these over the telephone will be offered.

The four-weekly questionnaires will include questions on dietary intake to assess adherence to prescribed dietary advice.

10.3.1 Researcher follow-up visit

A researcher will meet with the parent and child at 24 weeks (+/- 10 days) at a time/location of their choosing, usually the family home when an objective assessment of the participant's skin will be made (using EASI).

10.4 Electronic medical record (EMR) review

Participant's primary care EMR will be reviewed (from 4 weeks prior to the date of randomisation until 24 weeks after) and data extracted on the following: prescriptions relating to eczema and possible food allergy, for example emollient(s), topical corticosteroids, antihistamines, colic relief medication; eczema and allergy related consultations (GP, nurse), referrals, out-patient and emergency appointments.

11 Qualitative study

11.1 Background and aims

The value of qualitative research in RCTs is established, especially in feasibility studies for RCTs.[56] The aims of this study are to help interpret and explain the quantitative feasibility findings (including experience and acceptability of study processes/intervention); and to generate new knowledge around the issues of food allergy, allergy tests and dietary modification in children with eczema, from the perspective of parents and GPs. In the design, conduct and reporting, we will follow the guidance set out by O'Cathain et al.[57]

11.2 Methods and setting

In-depth, cross-sectional qualitative interviews will be conducted either by telephone or face-to-face, depending on the preference of the interviewee.

11.3 Sampling

All parents and GPs at participating surgeries will be asked whether they are willing to be contacted to take part in an interview. Purposive sampling will be used to help ensure maximum variation of the parent and GP samples.

Parents will be sampled from both intervention and usual care groups, with the former over-sampled to explore the acceptability of the intervention across parent groups. Further purposive criteria for parent interviews are mild/moderate (<17) vs severe (≥17) POEM symptom score (using most recent data available), socio-economic status (assessed via postcode, using the Index of Multiple Deprivation Database (categories: high (8-10)/medium (5-7)/low (1-4)), and length of time in the trial (shortly after baseline visit or OFC, or later in the trial). For participants in the intervention group, we will seek to speak to parents of children with negative, positive and (in the case of SPTs) ambiguous test results.

Sampling of GPs will capture diverse populations served by practices, length of time in the trial (baseline, during, after), and attitudes to allergy testing in eczema (as captured by the GP questionnaire).

The number of interviews will be guided by the research questions, and sampling will stop when we have sufficient "information power" relevant to the study aims.[58] We anticipate a total of 20 parent and 10 GP interviews.

In addition, we will conduct brief telephone interviews with ~5-8 parents who are ineligible, decline to take part or withdrawal from the trial but indicate that they are willing to discuss reasons why. This information may provide information about barriers to recruitment and will be useful in designing any future definitive trial.

11.4 Recruitment and consent

Parents will be informed about the qualitative component of the study in the trial information sheet provided with the invitation to participate. Parents declining to take part in the trial will have the option to agree to be contacted for possible interview as part of the invitation and response letter.

At the baseline assessment and consent visit, parents will be asked to indicate whether they are happy to be approached regarding participating in an interview, and if so the best way to contact them and to send them further information. This will generate a pool of potential interviewees for sampling for the qualitative interviews. Once parents have been selected for invitation for an interview, the qualitative researcher will send the parent an invitation to participate, information

sheet and consent form via email or post. The researcher will then contact the parent by email or phone to determine consent and arrange the interview.

GPs will be invited to participate in an interview by an initial email from the research team with an information sheet and consent form. GPs willing to be approached will be contacted by the research team by email or phone to determine consent and arrange the interview.

All interviewees will have received an information sheet and consent form to read in advance of the interview. Written informed consent will be taken in face-to-face interviews, and verbal consent will be taken for telephone interviews. The researcher will verbally explain consent to the participant before the interview starts and, if the participant confirms their agreement to the interview, the verbal consent agreement will be repeated, and audio recorded. Verbal consent is considered standard practice in studies where telephone interviews are conducted and has been used previously in several HRA-approved BRTC-portfolio trials across a range of clinical populations, e.g. UPSTREAM, CEDAR, HepCATT and RADAR. Verbal consent reduces burden and is resource-efficient, as it removes the need to send and return paperwork.

11.5 Data collection

In-depth interviews will be conducted face-to-face or by telephone, and at varying time-points to capture issues that might be related to different stages of trial participation. Topic guides will be developed (see table below), based on the focus of the trial and existing research literature, and refined with input from the study's Public and Patient Involvement (PPI) group. However, flexibility will be maintained, and topic guides modified over the course of different interviews (where appropriate) to enable exploration of new issues that arise throughout this process.

Table: Topics to be explored in Parent and GP interviews

Parent interviews	GP interviews
• Reasons for participating or declining/withdrawing • Beliefs about food allergy testing and their origin • Perceived or experienced acceptability of allergy investigations, including blood and skin prick tests • Facilitators of and barriers to uptake of skin prick tests and dietary advice • Worry or social difficulties related to food allergies • Understanding of distinctions between food allergy, intolerance and local skin irritation • Knowledge and use of "unsanctioned" allergy testing outside of the NHS • Adherence to allocated group • Strategies to manage their child's eczema, e.g. excluding particular foods • Views on barriers/enablers to engagement with the trial • Length of follow-up in a future trial	• Beliefs about food allergy testing and equipoise • Acceptability of allergy tests among parents • Facilitators of and barriers to uptake of allergy investigations, including blood and skin prick tests; and dietary advice in primary care either within or outside of a trial setting • Most appropriate primary outcome for the main trial and the validity of eczema severity as the putative outcome • Views on barriers/enablers to engagement with the trial • Length of follow-up in a future trial • Interest in and/or concerns about hosting the trial • Views of the intervention • Willingness to host a future definitive trial

The issues of contamination and/or performance bias will be explored by asking about/probing for cues that suggest conscious or unconscious changes in clinical practice (GPs) and/or advice sought by/given to other parents because of being in the study.

After each interview the researcher will provide the interviewee with a voucher as an acknowledgement of their contribution (£20 voucher for parents, £50 for GPs). Interviews are expected to last between 45-60 minutes and will be recorded using an encrypted digital voice recorder, professionally transcribed and anonymised to protect confidentiality.

11.6 Analysis

Analysis will take place alongside data collection and guide further data collection. For instance, analytic insights from data gathered in earlier interviews will help guide amendments and additions to the topic guide during later interviews. We will conduct a thematic analysis, using both inductive and deductive (informed by the Common Sense model[28]) coding to develop a systematic coding framework that will help us to identify patterns in the data relevant to the research question.[59] Data will be compared across groups (e.g. views of parents and healthcare professionals) and within groups (e.g. parents allocated to the intervention).

Analysis of the qualitative data will be led by the qualitative research associate with support from other team members (particularly qualitative lead, Selman), who will read and code a sub-set of the data and agree the final coding framework. Data will be handled using NVivo.

12 Statistics

12.1 Sample size

As this is a feasibility RCT, a formal sample size calculation is not appropriate. There is little consensus on how large feasibility studies need to be. On a pragmatic basis we have determined that 80 children (40 in each group) will be sufficient to provide estimates of recruitment, retention, adherence, assessment of contamination within practices and between groups (which, if found to be significant, might necessitate a cluster design for the definitive RCT, with practices as the clusters). This is broadly in-line with published "rules of thumb".[60 61]

12.2 Data analysis

The aim will be to determine the feasibility of undertaking the main trial and explore acceptability. We will report our findings following the pilot and feasibility extension of the CONSORT guidance (2010), including a CONSORT diagram, descriptive and summary statistics, along with all important harms or unintended effects in each group.

Regarding the first objective, the following will be reported:

1. Proportion of GP surgeries approached who are willing to host the study
2. Recruitment and retention rates by method of recruitment (self-referral vs opportunistic), characteristics of participant and their family (e.g. eczema severity, age of child, and prior beliefs about food allergy) and allocation (as "moral resentment" may be an issue for families in the control group)
3. Proportion of potentially eligible children who enrol, attend baseline and follow-up visits, and (in the intervention group) take-up and complete the allergy tests. We will also report reasons for declining to take part and failure to obtain skin prick test and oral food challenge results
4. Proportion of participants in the intervention group with positive/indeterminate/negative structured allergy history, skin prick tests, oral food challenges and home dietary trials (where done); and proportion of cases that require allergy panel review.
5. Proportion of participants with high, medium and low levels of adherence to dietary advice
6. The proportion of participants who receive an allergy test (serum IgE or skin prick), see a dietitian, are referred to an allergy clinic and/or undergo an oral food challenge/home dietary trial as part or outside of the study
7. Completion/missing data rates for clinical outcomes, quality of life measures and cost data that might be included in the definitive trial; estimates, variances and 95% confidence intervals for POEM, EASI, IDQoL, CHU-9D, ADQoL and DFI (possible primary outcomes)
8. Proportion of children of who would/would not be eligible using different age and eczema severity cut offs (using POEM or EASI), and the implications for recruitment and retention
9. Associations for parents between beliefs about food allergy, allocation and parent-reported outcomes; un-blinding of researchers and association between knowledge of allocation and collected outcome (EASI)
10. Proportion of baseline and follow-up visits, oral food challenges and dietitian appointments completed as scheduled; time from referral to completion of these investigations; and mean duration of follow-up data after investigations completed/advice given
11. Parent satisfaction with trial processes and procedures

The above quantitative outcomes will be supplemented by/explored through the nested qualitative work (see below).

12.3 Economic scoping

We will gather data on key costs and outcomes to assess the feasibility of carrying out a cost-effectiveness study from the primary perspective of the NHS and from a wider perspective including parental costs and time off work.

Data on healthcare contacts and prescribed medications will be extracted from EMRs. Additional healthcare contacts, information about parental out-of-pocket expenses and time off work will be collected by four-weekly parent-completed questionnaires. The overall level of missingness will be recorded and the pattern of missingness, by item, will be explored. Relevant unit costs will be identified and, once resource use has been costed, we will identify which items are important cost drivers. The resources required for the intervention will be identified and the feasibility of costing these established.

NICE recommends the use of Quality-adjusted life-years (QALYs) as the preferred outcome measure in economic evaluations, but it is unclear what the most appropriate measure for this population is. Therefore, will test feasibility and validity of using both condition-specific (ADQoL)[47] and generic (CHU-9D) [50 51] preference-based measures of health in children (measured at baseline, eight and 24 weeks) to estimate QALYs. The CHU-9D is currently validated for children aged 7 and over, with pilot versions for those aged 5-7 and additional guidance notes and validation questions for those under 5. One key component of the economic work will be to determine the feasibility of using the CHU-9D in this pre-school age group.

13 Data management

Formal procedures will be developed for each aspect of trial data management and entry. The database and randomisation system will protect patient information in line with the Data Protection legislation. Trial staff will ensure that participants' anonymity is maintained through protective and secure handling and storage of patient information at the trial centre. All documents will be stored securely and made accessible only to trial staff and authorised personnel.

Data will be anonymised as soon as it is practical to do so. Accordingly, each participant will be assigned a trial participant identification (ID) number, for use on Case Report Forms (CRFs), questionnaires, other trial documents and the electronic database.

CRFs are the data collection tool where all source data is recorded. CRFs will be treated as confidential documents and held securely in a secure, locked cabinet and/or password protected location in accordance with regulations. Only those personnel approved by the Chief Investigator will have access to the CRFs.

Any questionnaire data completed on paper about the participant will be entered onto the study database in electronic form by a member of the research team. The system will incorporate data entry and validation rules to reduce data entry errors, and management functions to facilitate auditing and data quality assurance. All parents will be consented using paper consent forms. Consent forms and paper CRFs will be stored and archived at the University of Bristol.

Patient identifiers will be kept on a separate system from the clinical data and data protection requirements will be further enforced by best practice trial management procedures. Following the end of the trial, the database will be cleaned and locked. Procedures will be developed to describe these processes.

Qualitative interview data will be transcribed verbatim by an approved individual, checked and anonymised by the research team, and imported into NVivo (or similar software package) for analysis. The audio recordings and transcripts will be stored securely at the University of Bristol and only accessed by members of the research team.

During the trial, a data archiving plan will be developed. After the trial has finished and the database has been locked, all data will be archived for five years in accordance with the Sponsor's and NIHR guidance. This will be in a secure location and available on request for audit and inspection by regulatory bodies. The Chief Investigator is responsible for authorising retrieval and disposal of archived material.

14 Safety, quality assurance and indemnity

This study will be conducted in accordance with: UK Policy Framework for Health and Social Care Research; European Union Directive 2001/20/EC on clinical trials; and International Conference for Harmonisation of Good Clinical Practice (GCP) guidelines.

GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of participants are protected, consistent with the principles that originated in the Declaration of Helsinki and that the clinical trial data are credible.

As the interventions in this study rarely cause any serious adverse effects, risk-based monitoring will be implemented in line with a risk-assessment.

For the day-to-day delivery of the trial to the required standard, a 'Study Manual' covering all trial activities will be drawn up and developed in conjunction with the Sponsor. These will be dated/version tracked and monitored/revised accordingly.

14.1 Safety

Skin prick tests in a community setting is a common research procedure in the UK and worldwide (routine skin prick tests in UK general practice were proposed at 18 years ago[62]), with an excellent safety record. Many such studies have performed skin prick tests in children to a large number and variety of allergens. Published data suggest that the risk of a systemic allergic reaction is 1 in 10,000 for each patient tested.[63 64] Most systematic reactions are not severe, occur within 30 minutes and resolve within a few hours with or without treatment. Approximately 1 in 100 systemic reactions in allergic people are severe (anaphylaxis).[65] The risk of anaphylaxis with SPT is therefore approximately 1 in 1 million, which is the same as the observed rates of anaphylaxis or anaphylactic-type reactions following routine immunisation.[66] While approximately 1 in 1000 episodes of anaphylaxis are fatal,[65 67] we are not aware of any reports of fatal anaphylaxis caused by skin prick testing. Despite this, all tests will take place on practice premises, where a GP and emergency equipment are immediately available in the unlikely event that they are required, as per any reactions to vaccinations given in primary care.

An oral food challenge is the gold standard test to assess the presence of IgE-mediated food allergy. Oral food challenges, especially in the research/hospital setting, are safe.[68 69] Published data reports that up to 86% of challenges result in no reactions. Challenges will be supervised in a day-care facility with trained nursing staff who perform the challenges regularly as part of routine NHS care; and medical support to manage any allergic reactions.

Home dietary trials will only be advised when the prior structured allergy history, skin prick test +/- oral food challenge results have established the absence of immediate-type reactions.

14.2 Quality assurance

A random sample of 10% of CRFs will be checked against the computerised database and relevant source data for quality purposes. This percentage will be increased if a significant error rate (more than 10% of those checked) is found.

14.3 Direct access to source data/documents

The CI and study sites will allow monitors (from UH Bristol on behalf of the Sponsor), persons responsible for the audit and monitoring, representatives of the ethics committee and of the

regulatory authorities to have direct access to source data/documents. This is reflected in the participant information leaflet and consent form. Trial monitoring will be undertaken on behalf of the Sponsor by UH Bristol following their standard monitoring procedure.[a]

14.4 Insurance and indemnity

This study will be sponsored by the University of Bristol. The University has Public Liability Insurance to cover the liability of the University to research participants.

If a participant is harmed and this is due to someone's negligence then they may have grounds for a legal action for compensation against Bristol University or the NHS Trust or one of the other parties to the research, but they may have to pay their own legal costs.

[a] http://www.uhbristol.nhs.uk/research-innovation/information-for-researchers/setting-up-and-running-a-clinical-research-study/what-to-do-when-approval-is-received/monitoring/

15 Ethics and regulatory approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including, but not limited to, the UK Policy Framework for Health and Social Care Research and the Health Research Authority (HRA) guidance.

This protocol and related documents will be submitted for HRA review that includes the application to an NHS Research Ethics Committee (REC). Any subsequent protocol amendments will be submitted to the HRA, on the agreement of the Sponsor.

Annual progress reports will be submitted to the HRA/REC. The first report will be submitted 12 months after the date on which the favourable opinion was given, and thereafter until the end of the trial. Progress reports will also be submitted to the funder, in line with NIHR SPCR reporting requirements. Copies of these reports will be sent to the Sponsor prior to submission. Copies of all relevant reports will be made available to the TS/DM-C as appropriate.

16 Adverse event reporting

Serious and other adverse events will be recorded and reported from the time a signed and dated informed consent form is obtained until completion of the patient follow-up at 24 weeks after randomisation, in accordance with Good Clinical Practice (GCP) guidelines and UH Bristol Research Related Adverse Event Reporting Policy

The CI will record their opinion concerning the relationship of the adverse event to trial interventions. UH Bristol, on behalf of the Sponsor, assumes responsibility for overseeing the appropriate reporting of serious adverse events to the regulatory authorities. Participant safety and adverse events will be reported and discussed at all TMG and TS/DM-C meetings. Any significant adverse events notified to the trial team will be reported to Sponsor and the chair of the TS/DM-C.

16.1 Serious Adverse Events (SAEs)

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- results in death
- is life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation[b]
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect

Expected SAEs as defined below will not be reported to the Sponsor through expedited reporting channels. Information on expected SAEs will be collected in the Case Report Forms (CRFs) and, if required, periodically reported to a trial DMSC.

Expected SAEs from SPTs include:

- Severe localised reaction (redness, swelling, itch) to one or more SPTs necessitating medication and/or hospitalisation
- Anaphylactic reaction (generalised flushing of the skin, hives, swelling of throat and mouth, difficulty in swallowing or speaking, tachycardia, severe asthma, abdominal pain and/or nausea and vomiting, hypotension and/or collapse and unconsciousness) requiring medication +/- hospitalisation

Expected SAEs from OFCs include:

- Anaphylactic reaction (generalised flushing of the skin, hives, swelling of throat and mouth, difficulty in swallowing or speaking, tachycardia, severe asthma, abdominal pain and/or nausea and vomiting, hypotension and/or collapse and unconsciousness) requiring medication +/- hospitalisation

Unexpected SAEs and any fatal SAEs will be notified to UH Bristol ((fax 0117 3420239 or research@uhbristol.nhs.uk) as soon as the research team become aware of the event

[b] Exceptions to this are hospitalisations for: social reasons in absence of an adverse event; in-clinic protocol measures; surgery or procedure planned before entry into the trial (must be documented in the CRF)

If a responsible clinician or other member of the research team becomes aware that a trial-related serious adverse event (SAE) has occurred beyond the 24-week period, this will also be reported to the Sponsor.

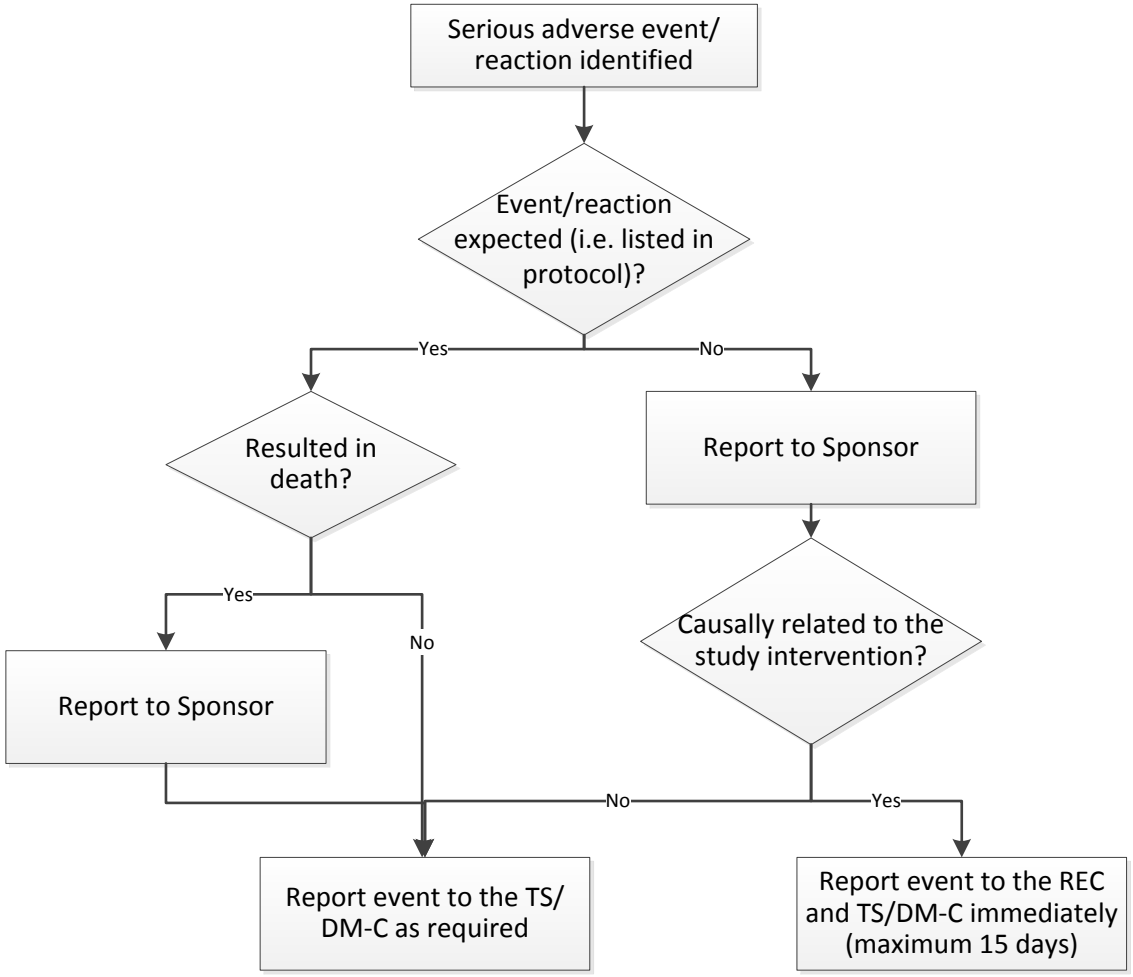


Figure: Flowchart for reporting of SAEs

All SAEs that have not resolved by the end of the trial (i.e. by the end of the 28 days of the post-randomisation follow-up period), or that have been not resolved upon discontinuation of the participant's participation in the trial, must be followed until any of the following occurs:

- the event resolves
- the event stabilises
- the event returns to baseline, if a baseline value is available
- the event can be attributed to agents other than the trial drug or to factors unrelated to trial conduct
- when it becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

16.2 Treatment Stopping Rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Funder based on new safety information or for other reasons given by the Trial Steering/Data Monitoring Committee or ethics committee concerned.

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the Trial Steering/Data Monitoring Committee, who will advise on whether to continue or discontinue the trial and make a recommendation to the Sponsor.

17 Project management

17.1 Trial Management Group (TMG)

The Trial Management Group (TMG) comprises all investigators, the trial manager, research and administrative staff, with input from patient/public representatives.

Members of the TMG will contribute to the trial in the following ways: trial design and methods; participant recruitment and trial conduct; trial management; trial logistics and cost management; economic evaluation; qualitative study statistical data analysis; and publication. This research will also be overseen by a joint TS/DM-C. The TMG will meet on a regular basis to oversee the management of the trial. The TMG will be provided with detailed information by the centre staff regarding trial progress. Meetings will be face-to-face with teleconference facilities for TMG members who are unable to be present.

This study is designed and conducted in collaboration with the Bristol Randomised Trials Collaboration (BRTC), a UKCRC Registered Clinical Trials Unit (CTU) in receipt of National Institute for Health Research CTU support funding. Members of the BRTC will attend the TMG.

17.2 Trial Steering/Data Monitoring Committee (TS/DM-C)

Because this is a low-risk trial, the funder has agreed that the roles of both guiding the TMG and monitoring trial data will be undertaken by a single Trial Steering/Data Monitoring Committee (TS/DM-C).

The role of the TS/DM-C will be to provide overall supervision of the trial on behalf of the funder. The TS/DM-C will focus on progress of the trial, adherence to the protocol, patient safety and consideration of new information. The committee will review the accruing data and assess whether there are any safety issues that should be brought to the Sponsor's or the participants' attention or any reasons for the trial not to continue. Terms of reference will be drawn up and agreed with members of the TS/DM-C.

Membership comprises of four independent members: a chairperson, a biostatistician, a clinician, and a patient representative (parent of child with eczema). One or more members will be an experienced primary care trialist and/or have allergy expertise. The CI will attend all meetings, accompanied by the trial manager, statistician and other TMG/trial staff as appropriate. Observers from the funder and the Sponsor will be invited to each meeting.

The TS/DM-C will meet at least three times over the course of the study. The first meeting will be to agree terms of reference, review the protocol and study timelines. It is anticipated that further meeting(s) will occur during participant recruitment and/or analysis/write-up.

17.3 Role of Sponsor and funder

The Sponsor (University of Bristol) will have overall responsibility for the initiation and management of the trial, but on a day-to-day basis this responsibility will be delegated to the chief investigator, trial manager and trial management group.

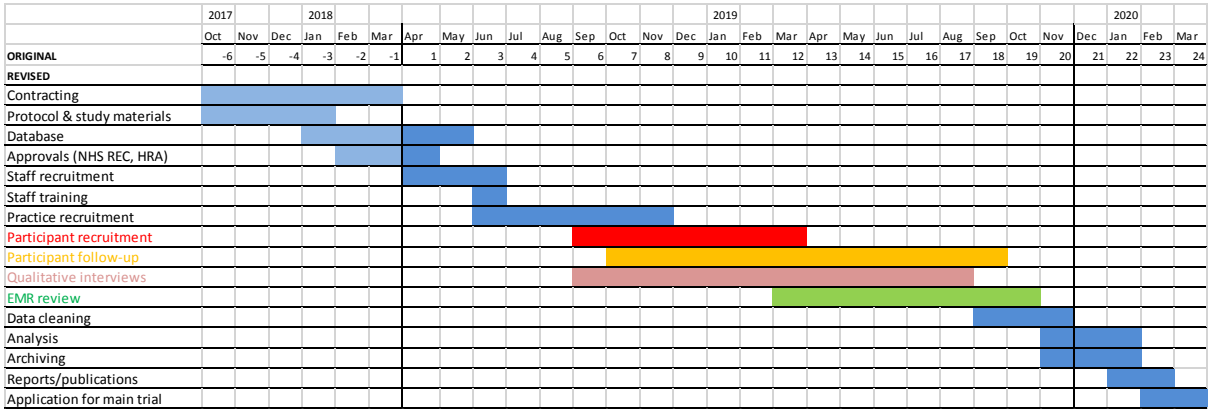
The funder will remotely monitor study progress against key targets by means of reports from the TMG and TS/DM-C. They will review and approve outputs (abstracts, conference presentations, academic papers and final report) from the study, but will not seek to influence the reporting of findings. In this regard, the views expressed in the outputs will be those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

18 Timetable and milestones

18.1 Milestones

Months	Milestone
-6 to +3	Protocol, study materials and study manual written; ethics and HRA approvals received; databases developed and tested; staff recruited and trained
+3 to +12	Practices and participants recruited
+7 to +18	Participant follow-up and qualitative interviews/analysis complete
+12 to +194	EMR review complete
+18 to +22	Data cleaning & analysis complete
+20 to +24	Archiving and reporting/dissemination; application for main trial

18.2 Study activities



19 Patient and Public Involvement (PPI)

The PPI strategy has been developed in collaboration with the Bristol-based PPI co-ordinator, who will continue working with us throughout the study.

We conducted considerable pre-grant PPI to inform the design of the study. First, to help guide the research design we carried out an online survey of parents of children with eczema (n=152). To ensure a wide range of responders, we promoted it via social media and key eczema and allergy websites, including national and local parent/patient support charities and groups. The results confirmed the importance of this topic for parents of children with eczema, a willingness to take part in this type of research and outcomes of greatest importance to this patient group (which varied according to whether their children did or did not have a confirmed food allergy). Consequently, we chose eczema severity, which was rated most important to parents of children without a food allergy (the group targeted in this study), as a key clinical outcome. Second, we have identified two lay collaborators (Gray & McMeechan), both of whom have children with eczema and have previously participated in trials of treatments for children with eczema. These lay team members have commented on the research proposal, and we have incorporated their suggestions around nomenclature and reducing data burden on participants.

We are committed to co-production of research with lay members during the study itself. One PPI member will be invited to attend TMG meetings, a lay member will sit on the Trial Steering/Data Monitoring Committee and we will set-up a local PPI advisory group. The PPI collaborators will be offered training and support (e.g. People in Health West of England offer research design/methods workshops, FutureLearn offers online training) and contribute to monthly Trial Management Group and contribute to publications, including lay summaries and media releases. The research team will utilise clear speech, reduce jargon and build glossaries of terms.

We will work with the PPI coordinator to attract a diverse and socially representative membership for the wider PPI advisory group. We plan up to three meetings. The first will occur towards the beginning of the research to discuss data burden and the design of patient facing materials. This will involve up to eight parents of children with eczema of a duration of ~1½ hours. We will invite the PPI membership to pilot the study materials, gathering feedback remotely via online forms and email, a useful method for busy parents. We anticipate further meeting(s) to happen during recruitment (to discuss and troubleshoot any potential issues arising) and/or towards to end of the study, to help with write-up and dissemination of findings.

20 Publication and dissemination policy

A declaration will be submitted to the REC within 90 days of the end of the study. A final report at conclusion of the study will be submitted to the funder, the Sponsor and the REC within one year of the end of the trial.

A trial publication policy will be developed in line with the University of Bristol guidance. Any trial-related media releases, publications and conference presentations will be submitted to the funder for approval prior to publication.

Study progress, outputs and a summary of findings will be made available via a study website and Twitter account; and summaries distributed to participating families and GP surgeries. Findings will be submitted for presentation at conferences and written up for publication in a peer-reviewed journal(s), which may include mixed-method triangulation and integration of the quantitative and qualitative findings. Should feasibility be demonstrated, the results will be used to inform the design of the main trial.

The study was developed with support from the UK Dermatology Clinical Trials Network (UK DCTN), and all publications will acknowledge the support of the UK DCTN and funder (including the Department of Health disclaimer). Outputs reporting elements of the trial that involved recruited participants should also acknowledge the CRN. Publications will additionally acknowledge the BRTC.

21 Amendment history

Record of protocol version numbers and amendments:

Version		Notes
Number	**Date**	
2.0	18.10.18	Section 5.2: addition of missing data collection points (Diet of child and breast-feeding mother at baseline; ADQoL at 8 weeks) Section 8.4: change "avoidance of food(s) with dietary advice; and referral via GP for follow-up" to "avoidance of food(s) with dietary advice; and referral to the local NHS allergy services via GP for longer-term follow-up" ; and "Any participants with indeterminate results will be reviewed by an expert allergy panel (co-applicants Boyle & Marriage) …" to "All participants' results will be reviewed by an expert allergy panel (including co-applicants Ridd, Boyle, Marriage and/or Waddell) …" Section 9.1: change "Up to 12 GP surgeries" to "At least 12 GP surgeries …"; Section 9.3 & section 10.2: change "in/at their [own] GP practice" to "at a participating GP practice"; Section 10.1: description of expression of interest form corrected from "The form will comprise which will comprise POEM, questions asking their opinion of the role of diet/food allergy in their child's eczema, and any previous food allergy tests, diagnoses and/or dietary modifications" to "The form asks if they currently have eczema/a medically diagnosed food allergy and the POEM questions" Section 11.3: Change from "In addition, we will conduct brief telephone interviews with ~5-8 parents who decline to take part in response to the initial invitation letter or later withdrawal from the trial but indicate that they are willing to discuss reasons why" to "In addition, we will conduct brief telephone interviews with ~5-8 parents who are ineligible, decline to take part or withdrawal from the trial but indicate that they are willing to discuss reasons why" Section 16.1: change "Expected SAEs defined in the study protocol (page 39) …" to "Expected SAEs as defined below …" Section 18.1: revised project duration/milestones Other minor changes (correction of typing errors, changes in research team)
1.0	29.03.18	Submitted/approved by REC/HRA
0.8	20.03.18	Final draft sent to RED for approval

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