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BRISTOL TRIALS CENTRE

NHS
Bristol, North Somerset and South Gloucestershire
Integrated Care Board

Trial of food allergy IgE tests for Eczema Relief (TIGER): individually randomised controlled trial of test-guided dietary advice for children with eczema, with internal pilot and nested economic and process evaluations

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TRIAL SUMMARY

Trial	Trial of food allergy IgE tests for Eczema Relief (TIGER)
Aim	To determine the clinical effectiveness of test-guided dietary advice versus standard care, for the management of eczema.
Secondary objectives	To evaluate the cost effectiveness of test-guided dietary advice in children with eczema. To assess adherence to and safety of test-guided dietary advice in children with eczema. To identify sub-groups who may preferentially benefit from food allergy testing.
Design	Pragmatic, multi-centre, parallel group, individually randomised, controlled superiority trial, with internal pilot and nested economic and process evaluations.
Participants	Children with eczema between 3 months and 2 years of age.
Inclusion criteria	Eczema diagnosed by a healthcare professional; and aged between 3 months and less than 2 years of age; with mild, moderate or severe eczema (Patient Orientated Eczema Measure (POEM) score>2); and accompanying adult (who is able to give consent)
Exclusion criteria	Confirmed or probable immediate (IgE-mediated) food allergy; and/or previous SPT or IgE blood test for study foods; and/or another child in the household already taking part in the trial.
Intervention	"Good eczema care" leaflet plus standardised dietary advice, based on skin prick tests to milk, egg, wheat, and soya, delivered by trained researcher/practice nurse.
Comparator	"Good eczema care" leaflet, to standardise treatment.
Primary outcome	RECap for AtoPic eczema (RECAP) collected four-weekly for 24 weeks
Secondary outcomes	Child: Patient-Oriented Eczema Measure (POEM), Numerical Rating Scale Peak Pruritis during last 24 hours, Eczema Area Severity Index (EASI), Infant Dermatitis Quality of Life (IDQOL), Child Health Utility 9D scale (CHU-9D), head circumference, weight-for-age, stature-for-age and weight-for-stature Main carer: EuroQol-5 Dimension (EQ-5D-5L), Care Related Quality of Life (CarerQol), Generalised Anxiety Disorder 7 (GAD-7) Breastfeeding status of mother Adverse events
Follow up duration	36 weeks.
Sample Size	493 children will detect a difference of 1.95 on eczema control measured by RECAP between all children in the two treatment groups assuming a standard

	deviation in RECAP of 6.5, correlation between baseline and 24-weeks of 0.4, 20% loss to follow-up, 90% power and 5% significance level.
Internal pilot	First six months of recruitment, with criteria and thresholds for progression.
Process evaluation	Using qualitative and quantitative methods, to assess fidelity, dose and reach of the intervention; clarify causal mechanisms; and identify contextual factors associated with variation in outcomes.
Health economic analysis	To compare the costs and consequences and estimate the cost-effectiveness of test-guided dietary advice versus standard care, for the management of eczema. The primary perspective will be NHS, with secondary analyses including non-NHS costs at 36 weeks follow-up.
Study duration	Funding start date: 1 August 2022 Anticipated duration: 51 months (total; subject to change) Anticipated end date: 31 October 2026 (subject to change)

KEYWORDS

Atopic eczema/dermatitis; food allergy; disease control

KEY TRIAL CONTACTS

Chief Investigator	Professor Matthew Ridd GP, Professor of Primary Health Care and Principal Investigator for West of England - South West Central RDN, University of Bristol
Co-investigators	Professor Miriam Santer (GP, Professor of Primary Care Research and Principal Investigator for Wessex South West Central and South Central RDN, University of Southampton) Dr Tom Blakeman (GP, Professor of Primary Care and Co-Principal Investigator for Greater Manchester North West RDN, University of Manchester) Dr Hannah Wardman (GP, Co-Principal Investigator for Greater Manchester North West RDN, University of Manchester) Professor Ingrid Muller (Professor of Behavioural Medicine, Process evaluation lead, University of Southampton) Dr Kirsty Garfield (Research Fellow in Health Economics, University of Bristol) Dr Robert Boyle (Reader in Paediatric Allergy and Consultant Paediatric Allergist, Imperial College London) Dr Rosan Meyer (Visiting Reader and Consultant dietitian, Imperial College London) Dr Isabel Skypala (Consultant Allergy Dietitian, Royal Brompton & Harefield Hospitals) Dr Shoba Dawson (Senior Research Fellow, Diversity and inclusion lead, University of Sheffield) Ms Hannah Morgans (Parent/patient representative) Professor Sara Brown (Professor of Dermatology and Consultant Dermatologist, University of Edinburgh) Professor Hywel Williams (Professor of Dermato-Epidemiology and Consultant dermatologist, University of Nottingham)
Lead Statistician	Dr Stephanie MacNeill, Associate Professor in Medical Statistics, University of Bristol
Web address	www.bristol.ac.uk/tiger-study

Protocol contributors

The initial draft and subsequent versions of the protocol were written by MJR, and all coinvestigators and sponsor had opportunity/made comment. The version submitted for NHS Research Ethic Committee approval was reviewed by the funder for consistency with the original funding application.

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National Institute for Health and Care Research Health Technology Assessment Programme Evaluation, Trials and Studies Coordinating Centre University of Southampton Alpha House Enterprise Road Southampton, SO16 7NS Telephone: 023 8059 5586 Email: netsmonitoring@nihr.ac.uk	Funding of the main study
Rosetrees Trust Russell House 140 High Street, Edgware, Middlesex HA8 7LW Telephone: 020 8951 2588 Email: info@rosetreestrust.co.uk and Stoneygate Trust 2 Marlborough Court, Watermead Business Park, Syston, LE7 1AD	Joint funding of analysis of DNA
Bristol Trials Centre University of Bristol, 1-5 Whiteladies Rd, Clifton, Bristol BS8 1NU Telephone: 0117 92 87393 Email: enquiry-brtc@bristol.ac.uk	Methodological expertise
University of Bristol Mr Adam Taylor, Head of Research Governance Research and Enterprise Division Augustine's Courtyard, Orchard Lane, Bristol BS1 5DS Telephone: 0117 455 3343 Email: research-governance@bristol.ac.uk	Sponsorship
NHS Bristol, North Somerset & South Gloucestershire (BNSSG) Integrated Care Board (ICB) South Plaza, Marlborough Street, Bristol BS1 3NX	Host

ROLE OF TRIAL SPONSOR AND FUNDER

The sponsor and funder have commented upon and influenced the design of the trial, and the sponsor will have an on-going oversight of its conduct. The sponsor and funder have no role in the data analysis and interpretation, manuscript writing and dissemination of results.

SIGNATURES

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Trial sponsor:

Signature: Date:

Name: Adam Taylor

Position: Head of Research Governance, University of Bristol

Chief Investigator:

Signature: Date:

Name: Matthew Ridd

Statistician:

Signature: Date:

Name: Stephanie MacNeill

Position: Associate Professor in Medical Statistics

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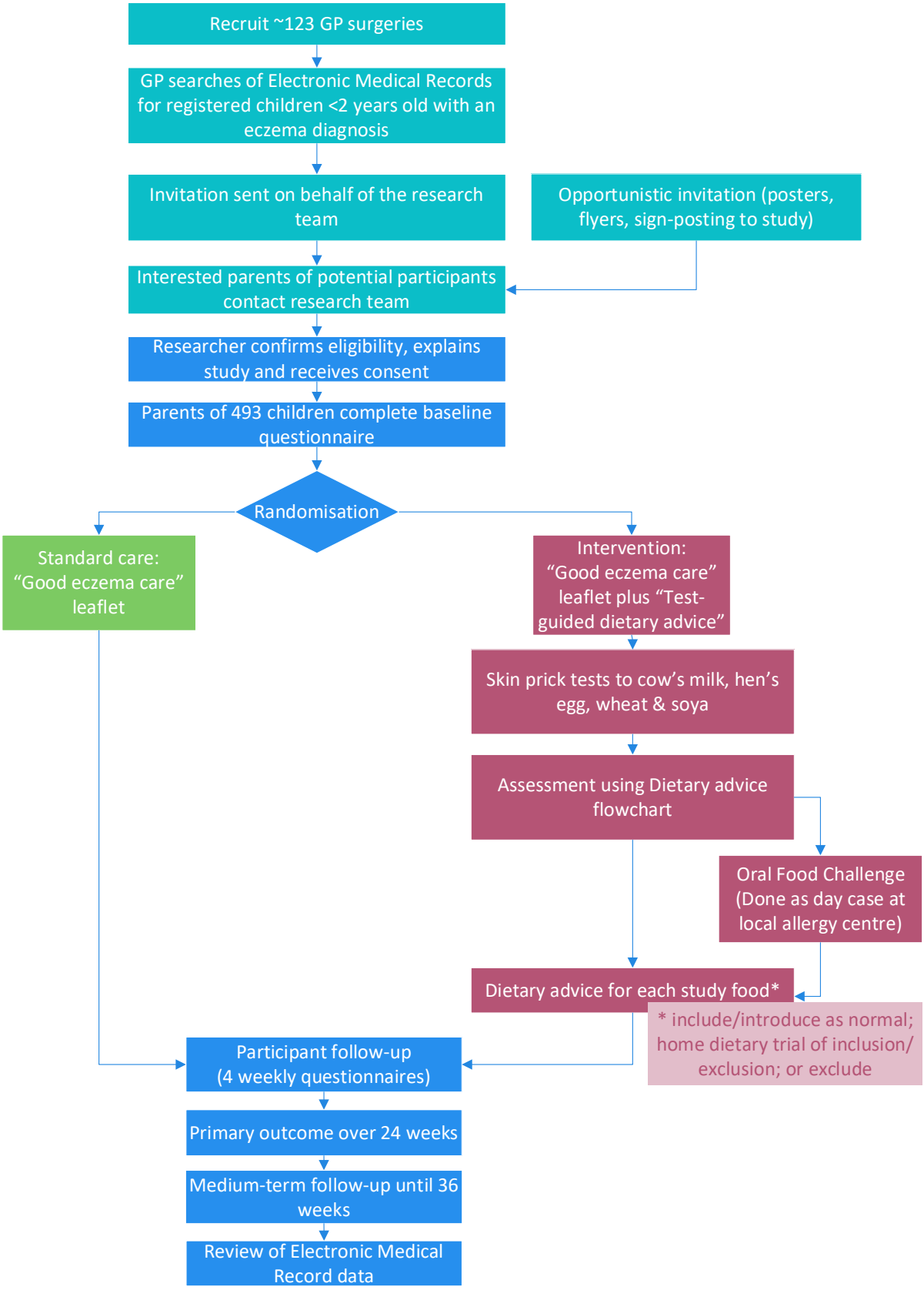
LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
CRN	Clinical Research Network
DMC	Data Monitoring Committee
EU	European Union
GCP	Good Clinical Practice
ICF	Informed Consent Form
IgE	Immunoglobulin E
ISRCTN	International Standard Randomised Controlled Trials Number
OFC	Oral Food Challenge
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RDN	Research Delivery Network
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SPT	Skin Prick Test
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

TRIAL FLOW CHART

Figure 1: Flow of participants through study



1. BACKGROUND

This section describes eczema and briefly summarises what is known about the relationship of this condition to food allergy.

1.1 Eczema

Eczema (synonyms atopic eczema/dermatitis) is a common long-term condition, affecting ~20% of children.[1] It is characterised by dry, itchy skin and has a strong familial (genetic) basis.[2]

In the 2013 Global Burden of Disease Study, eczema was the skin disease with the greatest population-level disability.[3] The burden of disease is seen in preschool children, with significant impact on the physical, emotional and social functioning of the affected child and their family.[4,5] Around 10% eczema persists into adulthood with associated effects on physical health, psychological health and financial status.[6]

In the United Kingdom (UK), most children with eczema are managed in primary care. Effective management includes daily use of topical treatments but treatment adherence can be challenging.[7] One reason for this is that parents/legal guardian (hereafter, parents) may pursue a "cause" rather than "eczema control".[8] Parents may consider undiagnosed food allergy as the cause for their child's recurrent/persistent eczema symptoms, often based on online information.[9]

Dietary restrictions of the affected child (and if breastfeeding, that of the mother) is common, usually without discussion with a health professional.[10,11] In a 2004 review of referrals to a paediatric dermatology out-patient clinic, 75% of patients had tried some form of dietary exclusion.[12] In an online survey by Chan et al (2019), 40% of parents reported excluding one or more foods from their child's diet to reduce eczema symptoms.[13] Children with food allergy are at increased risk of nutritional disorders include poor growth, micronutrient deficiencies and feeding difficulties; and children with eczema and food allergy moreso.[14] In the Health Nuts population-based cohort, children with both food allergy and eczema at one year of age had lower percentiles for mean weight (51.3 vs 58.3 percentile, P = .001) and height (48.4 vs 53.4, P = .028) compared with those with neither condition.[15]

Parents who do discuss the role of diet in eczema with their doctor, often ask about allergy testing to guide dietary exclusions.[5]

1.2 Food allergy and eczema

Food allergy is immune-mediated hypersensitivity reaction, that occurs reproducibly on exposure to a given food. It is distinct from food intolerance, which is a non-immune reaction that can be metabolic, toxic, pharmacologic, or psychological.[16] The terms are often confused and used interchangeably in everyday speech. Furthermore, it is also different from food sensitisation, which is a "positive" allergy test result, without clinical symptoms.

Food allergies are heterogeneous, both in terms of the dose required and the associated clinical signs and symptoms. Evidence on the prevalence of food allergies is blighted by different study settings, designs, case definitions and interpretations of history and test findings.[17] Consequently, there is a mismatch between reported and proven food allergy. In the EuroPrevall birth cohort,[18] 16.2% of parents reported adverse reactions after food consumption, whereas, objective prevalence estimates were between 1.4% and 3.8%. The foods most commonly implicated were cow's milk, hen's egg, peanut, hazelnut and wheat.

Food allergy and sensitisation are highly heritable[19 20] and there is evidence of shared genetic risk factors with eczema.[21-23] While understanding of the pathogenesis of these conditions has improved, promising prevention strategies have been disappointing.[24] It is plausible but currently only speculative that genetically-predisposed children may show differential benefit to a therapeutic or preventative intervention.

Food allergy is more common in children with eczema.[1] Children with earlier onset, persistent and more severe disease are at increased risk of immediate (immunoglobulin E (IgE)-mediated) food allergies,[25] symptoms of which usually occur within two hours of ingestion. While alarming (and potentially life-threatening), this type of reaction is generally easy to recognise and can be managed with clear guidance to avoid the causal food. However, the question most parents raise is in relation to possible delayed (non-IgE mediated) reactions causing their child's eczema to worsen, which occur hours to days after ingestion. The relapsing-remitting nature of eczema and the role of several different environmental factors in causing eczema to worsen[26] makes causal associations more difficult to identify, especially for foods that are ubiquitous.

Furthermore, children with eczema benefit from early introduction of some allergenic foods. Introducing peanut and cooked hen's egg into the infant diet, as part of complementary feeding, may reduce the risk of peanut or egg allergy.[27] It is uncertain whether excluding these or other foods to which infants are sensitized but tolerant may increase the risk of food allergy developing, and if this is the case, how long after allergen exclusion this is likely to occur.

1.3 Evidence base and on-going research

Parental belief that foods may be causing their child's eczema to worsen can be strong yet evidence to guide food allergy testing is weak. Consequently, opinions on its value are divided, leading to variation in clinical practice and confusion for parents. There is a need for better-designed and conducted trials.[28 29] A Cochrane review[30] of dietary exclusions for adults and children with eczema published in 2008, identified one trial (Lever *et al* 1998), that suggested infants with eczema and suspected egg allergy, who have positive specific IgE to eggs, may benefit from reduced eczema symptoms with an egg-free diet.[31] A more recent systematic review of "test-guided dietary exclusions" did not identify any relevant publications that improve understanding of eczema and food allergy testing.[32] We have not identified any economic evaluations in this area.

We have searched clinical trial registries (CENTRAL, WHO, clinicaltrials.gov & www.clinicaltrialsregister.eu) and have not identified any relevant on-going studies.

2. RATIONALE

This section sets out the rationale for the study, its potential benefits and feasibility.

2.1 Recommendations for research

It is unclear whether test-guided dietary decisions improve eczema symptoms, or negatively affect children by unnecessarily reducing dietary choices[14] and distract from the use of conventional treatments. [30]

NICE recommends investigation of food allergy in children with eczema who have immediate symptoms after ingestion of a food, or for children with moderate-to-severe atopic eczema that is not controlled by optimum management. [33 34] NICE recommends research into "When and how should children with eczema be tested for allergies (skin prick tests …)" and that "… research should encompass clinical outcomes (for example, control of atopic eczema) in children who are diagnosed with allergies and undergo interventions to avoid exposure to relevant allergens".

In 2013, the James Lind Alliance eczema research priority setting partnership[35] identified the following questions as key areas for research: "What role might food allergy tests play in treating eczema?" and "What is the role of [exclusion] diets in treating eczema?" These questions remain unanswered.

2.2 Food allergy tests

There are no specific diagnostic tests for delayed food allergies and in theory the use of IgE-specific blood or Skin Prick Tests (SPTs) to investigate non-IgE mediated reactions is non-sensical. However, the Lever *et al* (1998) trial suggests that IgE test-guided dietary exclusion of egg in children with eczema improves disease severity, and clinicians report using IgE tests to guide decision making in suspected non-IgE food allergy. In addition, some clinicians do use these tests to guide dietary advice.

In a survey of 129 clinicians who manage children with eczema, allergists and paediatricians were more likely to request an IgE food allergy test than GPs or dermatologists. [36] Notably, in children with no history of a reaction to food, allergists and paediatricians used IgE food allergy tests more often than GPs or dermatologists, with reported use increasing with worse disease (15% in mild, 45% in moderate,74% in severe and 79% in very severe disease; all specialities). This is reflected in the literature, where dermatological journals largely report negative statements about the relationship between food allergy and eczema, whereas allergy journals consistently affirm the association. [37]

2.3 Potential benefits

Research is needed to determine whether test-guided dietary modifications improve eczema symptoms. The findings may improve disease control and/or "release" some families from unnecessary restrictions and reduce the risk of dietary deficiencies, especially as infants and breastfeeding mothers have high nutritional demands. [38 39] An important contextual factor is concern about over-diagnosis of food allergies, especially to cow's milk. There is a several-fold difference between the prevalence of reported and proven cow's milk allergy; and prescriptions of specialised formula products for managing cow's milk allergy have risen, yet there is no evidence of an increase in disease prevalence. [40] This is important from the perspective of families affected by eczema, clinicians in primary and secondary care, and the NHS.

For parents, worries about undiagnosed food allergy causing eczema often go unvoiced and can act as a barrier to use of safe and effective topical treatments. [41] Consequently, some parents

circumvent or supplement professional advice by seeking information online or from alternative therapists, which can be inaccurate or harmful; [42] or by purchasing self-test allergy kits, which are not validated and not recommended. [34] Furthermore, delaying the introduction of some foods, or excluding them, may contribute to feeding difficulties[43 44] and/or loss of immunological tolerance and food allergy development. [27]

Many General Practitioners (GPs) avoid asking parents about food allergy concerns because of uncertainty about evidence. [10 11] Parents' suspicions of food allergies in general and especially in children with eczema are higher than proven food allergy. Depending on the specific population studied and the definitions used, 15%–36% of children with eczema compared with about 6% of the general population have a food sensitivity (a positive test result, without clinical symptoms) or allergy (a positive test result in keeping with symptoms). [16] In addition, most GPs do not undertake allergy tests in primary care because most practices do not have ready access to skin prick tests; venesection, especially in young children, can be difficult and stressful for all concerned; and concerns about interpreting the results. Therefore, if a decision to investigate is made, a costly referral to secondary care is required. In the UK, food allergy and eczema are the two most common reasons for GP referral to an allergy clinic. [45] Unpublished audit data suggests ~8% of children with eczema are referred, of which ~50% are because of food allergy concerns. However, the chance of a child receiving an allergy test depends on which specialist they see. [36]

In the UK, provision of allergy services is poor. [46] Limiting referrals for potentially helpful food allergy tests and advice (to either allay concerns and maintain a breadth of diet; or to improve disease control through supervised dietary substitutions) on the basis of availability rather than need, is inequitable. Conversely, if routine food allergy testing in children with eczema, including time-consuming, hospital-based oral food challenges for some, is unnecessary, the limited resource of specialist allergy services could be freed up to serve other patients. In principle, allergy testing and advice could be routinely delivered in primary care, but evidence is needed to demonstrate both the value and feasibility of this. Providing the evidence, and the necessary training package on how to perform and interpret skin prick tests in children with eczema, has the potential to improve long-term disease control for children with eczema, reduce unwarranted exclusion diets (thereby improving growth and micronutrient status) and reduce use of NHS resources (GP consultations, prescribed medications and allergy out-patient referrals). [47 48]

Genetic factors affecting the need for food allergy testing remain understudied but offer an opportunity for personalised medicine. This would be of benefit to patient care and may also play a role in the cost-effective targeting of allergy testing and dietary intervention if implemented through the NHS.

2.4 Trial of eczema allergy screening tests (TEST) feasibility study

We have completed an feasibility randomised controlled trial[49] (TEST), funded by NIHR School for Primary Care Research, which established the feasibility of delivering test-guided dietary advice to children with eczema in primary care. [50] In six months, we recruited 17 GP surgeries and randomised 84 participants, with 95% retention after six months of follow-up. Skin prick testing and dietary advice were delivered to all 42 children in the intervention group. Nested qualitative[11] and economic scoping work has directly informed the design of this main trial.

3. AIM, OBJECTIVES AND OUTCOMES

This section lists the research question, aim, objectives and outcomes.

3.1 Research question

The research question we want to answer is: Does dietary advice based on routine food allergy tests (Intervention) improve disease control (Outcome) compared with standard care (Comparator) in children with eczema (Population)?

3.2 Aim

To determine the clinical and cost effectiveness of test-guided dietary advice versus standard care, for the management of eczema.

3.3 Objectives

- To evaluate the clinical effectiveness of test-guided dietary advice in children with eczema
- To evaluate the cost effectiveness of test-guided dietary advice in children with eczema
- To assess adherence to and safety of test-guided dietary advice in children with eczema
- To identify sub-groups (through family history or with genetic risk variants) who may preferentially benefit from food allergy testing

3.4 Outcomes

A complete list of outcomes is shown in Table 1. The timing of collection of each outcome is shown in Table 2.

3.4.1 *Primary outcome*

The primary outcome is the caregiver reported version of RECap for AtoPic eczema (RECAP), collected four-weekly for 24 weeks. [51] RECAP is a seven item parent completed measure of eczema control. It is recommended as a core outcome, [52] and has been shown to have good validity, reliability and responsiveness to change. [53 54] Each of the seven questions in RECAP carries equal weight and is scored from 0 to 4 (total score of 0-28), where high scores indicated worse control.

3.4.2 *Secondary outcomes*

Secondary outcomes and their associated objectives are listed in Table 1.

Regarding licensing and ownership:

- No licence: RECAP and POEM (University of Nottingham, UK); CarerQol (Institute for Medical Technology Assessment, The Netherlands); GAD-7 (Pfizer, USA); RUM (including ModRUM and bespoke questions) (University of Bristol, UK); global AD severity (Jonathan Silverberg, Northwestern University, Chicago, USA)
- Free, non-commercial licence: IDQOL (Cardiff University, UK); CHU-9D (University of Sheffield, UK); EQ-5D-5L and EQ-VAS (EuroQoL, The Netherlands); PP-NRS (MAPI research trust, PROVIDE™ France).

3.5 Process measures

To assess adherence to test-guided dietary advice and any effect on treatment use, ingestion of study foods and use of emollients and flare control creams will be measured by parent-completed questionnaire. (Ingestion of study foods is therefore both a process and outcome measure).

To identify sub-groups who may preferentially benefit from food allergy testing, parents will be asked about family history of atopy and permission sought for collection of saliva DNA sample from the child, for analysis of genetic risk variants.

Table 1: Objective, measure and source

Objective	Measure	No. of items	Score range	Source
To evaluate the clinical and cost effectiveness of test-guided dietary advice in children with eczema	Eczema control: caregiver-reported version of RECap for AtoPic eczema (RECAP)*. Questions capture the experience of eczema control over the previous week, with each questions carrying equal weight and responses scored from 0 to 4.	7	0 (excellent control) to 28 (very poor control)	Parent-completed questionnaire
	Eczema severity: the proxy-completion version of Patient-Oriented Eczema Measure (POEM)*.[55] Questions ask about eczema symptoms over the previous week, with each question carrying equal weight and responses scored from 0 to 4.	7	0 (clear/very mild) to 28 (very severe)	
	Pruritis: Peak Pruritis Numerical Rating Scale (PP-NRS)*†.[56] A single item asks about worst itch during the previous 24 hours, from 0 (no itch) to 10 (worst itch imaginable).	1	0 (no itch) to 10 (most severe itch)	
	Global eczema severity: Single item asking for parent global assessment of disease severity	1	Mild, moderate or severe	
	Child quality of life: the Infant Dermatitis Quality of Life (IDQOL)*.[57] Questions which ask about the impact of eczema over the previous week and responses are scored from 0 to 3.	10	0 (no impact) to 30 (maximum impact).	
	Eczema severity: Eczema Area Severity Index (EASI)*.[58] It is calculated based on a physical assessment of the child's eczema and incorporates both severity and extent of symptoms on different parts of the body.	20	0 (clear) to 72 (very severe)	Researcher-completed skin assessment

Objective	Measure	No. of items	Score range	Source
	Child quality of life: Proxy completion version of Child Health Utility 9D scale (CHU-9D).‡ Nine-item preference-based measure of health-related quality of life, with recall period of today/last night. [59]	9	0.33 to 1 (where 0 is equivalent to death and 1 equivalent to perfect health)	Parent-completed questionnaire
	Parent quality of life: EQ-5D-5L (Mobility, Self-care, Usual activities, Pain & discomfort, Anxiety & depression). [60]	5	-0.225 to 0.96 (where 0 is equivalent to death and 1 equivalent to perfect health)	
	Parent quality of life: EQ-VAS	1	0 (worst imaginable health) to 100 (best imaginable health).	
	Parent quality of life: Care Related Quality of Life (CarerQol) measures care-related quality of life in informal caregivers. [61]	8	0 (worst informal caregiving situation) to 100 (best informal caregiving situation)	
	Healthcare resource use: Resource Use Measure (RUM) (including ModRUM and bespoke questions).▼ [62]	17	-	
To assess adherence to and the safety of test-guided	Ingestion of study foods: bespoke questionnaire, based on TEST feasibility study. [50]	Variable (4-44)	-	

Objective	Measure	No. of items	Score range	Source
dietary advice in children with eczema	Breastfeeding status of mother: questions from Infant Feeding Survey[63]	Variable (4-9)	-	
	Parent anxiety: Generalised Anxiety Disorder 7, GAD-7. [64]	7	-	
	Adverse events (including development of food allergy): ED attendance or hospital admission; and/or notification by parent of healthcare professional. [50]	-	-	Parent-completed questionnaire; and/or researcher-completed CRF
	Participant head circumference, weight-for-age, stature-for age and weight-for-stature	-	-	Researcher-completed assessments

* Harmonising Outcomes Measures for Eczema (HOME)-recommended core outcome[65]

† Published validation data for PP-NRS is in adults but HOME suggests using the instrument for anyone who can self-report. Our unpublished data from TEST supports its use by parents in children under 5 years.

‡ currently validated for children five years and older. A pilot version will be included, based on that used in TEST.

▼ ModRUM was developed for self-completion by adults. See section 11.3 Validation of a proxy version of ModRUM and bespoke questions for under 2-year-olds for more information on validating its use by parents for their children.

The number of items changes at different timepoints and also depends on answers given to stem questions (branching logic)

4. TRIAL OVERVIEW

This section provides an overview of the trial design, setting and underpinning theoretical framework.

4.1 Trial design

TIGER is a pragmatic, multi-centre, parallel group, individually randomised, controlled superiority trial, with internal pilot and nested economic and process evaluations.

Trial design and delivery will be pragmatic. We seek to include a population that is relevant for the intervention, offer the control group an acceptable standard of care, and collect outcomes that are meaningful to end users.

In terms of eliminating potential allergens from the diet, we favour an effectiveness real-life approach (i.e. primarily leaflet-based dietary advice), rather than an efficacy approach (e.g. intensive dietitian input to eliminate all possible dietary allergens). Our study will incorporate features designed to encourage and support behavioural change in making recommended dietary changes, but not over and above what might be feasible in routine clinical care.

The study will be delivered in the context of relatively recent advances in our understanding of the benefits of early introduction of allergenic foods for reducing the risk of IgE-mediated food allergy. Therefore, we favour an inclusive approach, to mitigate against nutritional problems, food fussiness and/or "loss of tolerance". In doing so, the study will also extend our understanding of the role of test-guided dietary advice in the development of food allergy in children <2 years with eczema.

In accordance with NICE guidelines for health technology appraisal and to estimate value for money for the NHS, the nested economic evaluation will be conducted from a primary NHS perspective. Secondary analyses will incorporate a broader perspective including personal expenses.

4.2 Trial setting

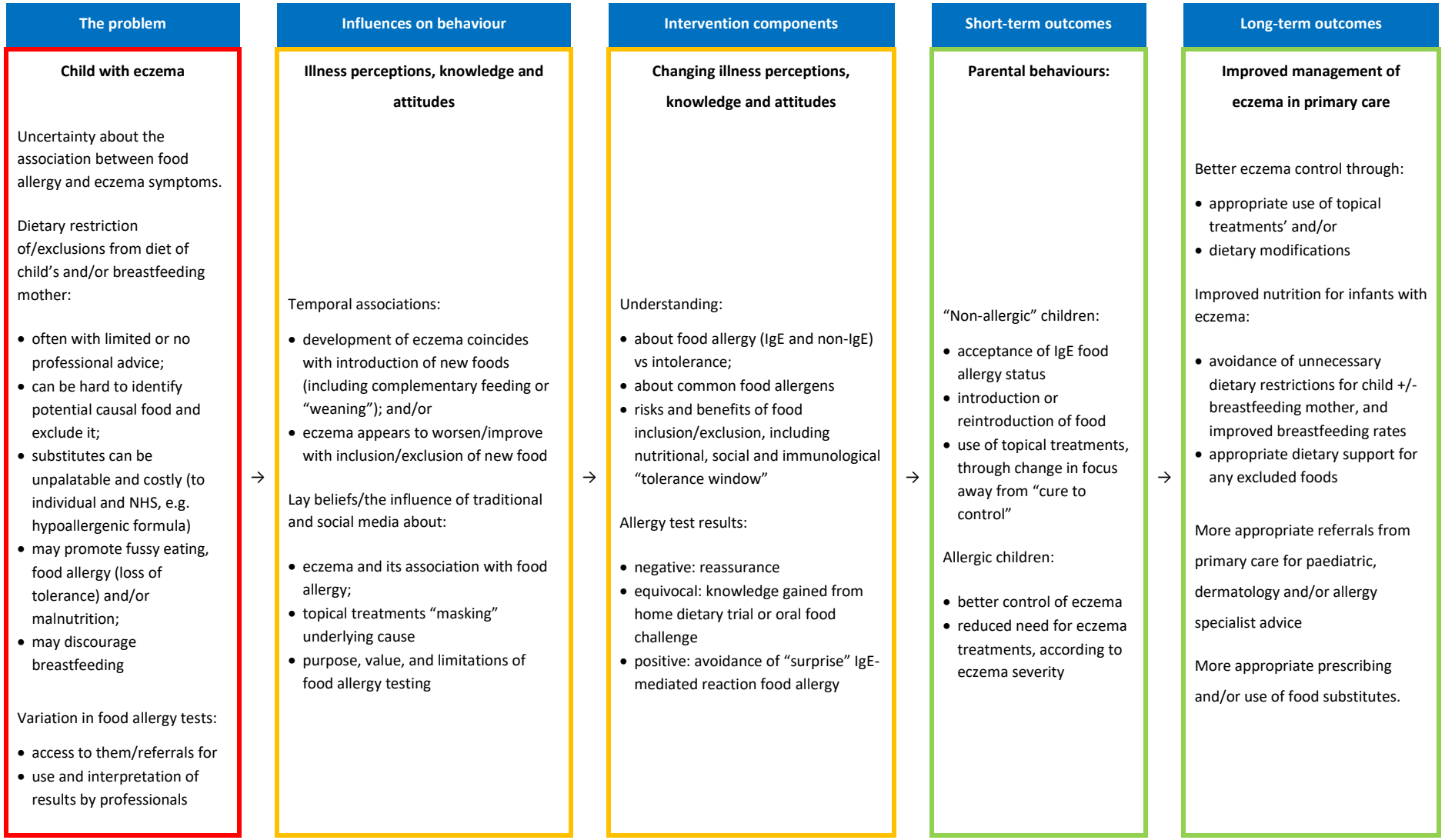
Participants will be recruited in primary care (GP surgeries) via NIHR Research Delivery Networks including (but not limited to) South West Central (previously West of England Clinical Research Network), South Central (was Wessex, Thames Valley and South Midlands CRN), and North West (was Greater Manchester and North West Coast CRN).

Any children needing oral food challenges will receive them as a day case at their nearest participating allergy centre (Bristol Royal Hospital for Children, University Hospitals Bristol and Weston NHS Foundation Trust; Royal Manchester Children's Hospital, Manchester University NHS Foundation Trust; Southampton Children's Hospital, University Hospital Southampton NHS Foundation Trust; Oxford Children's Hospital, Oxford University Hospitals NHS Foundation Trust). These centres will be led by Dr Deborah Marriage, Dr Vibha Sharma, Prof Graham Roberts, and Dr Thisanayagam Umasunthar (respectively, these may be subject to change).

4.3 Theoretical framework

While skin prick tests are relatively simple, the accompanying dietary advice and behaviour change make this a complex intervention.[66] We will draw on the extended Common-Sense Model,[67] which is relevant to theorising how the beliefs of patients and carers concerning symptoms and treatment may relate to health behaviours. With our patient partners, we have mapped out the context for the trial, the different influences on behaviours that may determine uptake of dietary advice based on food allergy tests, and the short and longer-term outcomes (see figure 2).

Figure 2: Logic model



4.4 Inclusivity and diversity

People from ethnic minority groups are under-represented in research and therefore the research findings have limited relevance and generalisability. To ensure that research benefits all it seeks to serve, it is important to tailor research methods and approaches to meet the needs of different groups.

Members of the patient and public study advisory group are from diverse backgrounds. The centres (Bristol, Southampton and Manchester) serve diverse populations and have strong track records in recruitment to primary care trials. We will work with different community groups locally to foster inclusion.

Overall, 13% of UK's population identify themselves as Black, Asian or minority ethnic. We will take a pragmatic approach and aim to recruit at least 15% of our study sample from ethnic minority groups. We will work with our PPI&E group and staff from the participating primary care centres to identify languages most appropriate to the minority ethnic groups in Bristol, Manchester, and Southampton.

It is not possible to translate all of the patient facing materials into the languages most commonly spoken across the three recruiting areas. Diet and food allergy is complex and not all English words have direct/are conceptually equivalent in other languages. In addition, many of the parent-completed outcomes have not been translated/validated in other languages. Where possible, we will use professional interpretation services to help with recruitment, consent and data collection.

People whose first spoken language is English but who have low (health) literacy may still find the text and detailed information in the participant information leaflet off-putting. The study summary provides a two-page overview of what the trial is about and what taking part involves. We have also developed an "Easy Read" version of the participant information leaflet which presents the key information in bite-sized chunks, with illustrations. The researcher will use this to talk to parents who struggle or are unable to digest all the full participant information leaflet.

Members of the PPI&E group will also be involved in co-developing promotional videos (based on the participant information leaflet) and lay summaries of findings, which will be translated into languages commonly spoken in the UK.

5. PARTICIPANT ELIGIBILITY CRITERIA

This section details the target population and the inclusion and exclusion criteria for participants.

5.1 Population

Children with eczema. In keeping with previous pragmatic trials in primary care, a diagnosis by a healthcare professional is sufficient for entry into the study, but we will also report the proportion meeting UK diagnostic criteria for atopic eczema/dermatitis. [68 69]

5.2 Inclusion criteria

To be eligible, children must:

- be aged between 3 months and less than 2 years; and
- have eczema diagnosed by an appropriately qualified healthcare professional; and
- have mild, moderate or severe eczema (Patient Orientated Eczema Measure (POEM) score>2 within the previous 28 days); and
- be accompanied by an adult who is able to give consent

5.3 Exclusion criteria

Ineligible children will have:

- confirmed or probable* immediate (IgE-type) food allergy to the study foods; and/or
- previous SPT or IgE blood test for the study foods; and/or
- another child in the household already taking part in the trial.

* Parents who report symptoms, which in the opinion of the allergy panel/their GP, are suspicious of an immediate-type reaction.

5.4 Co-enrolment in other research studies.

Co-enrolment in the TIGER study and any other research study will not be permitted due to potential impact on the study objectives and burdens of co-enrolment. Participants should not have participated in any other research study in the last three months. Any queries regarding co-enrolment will be considered on a case-by-case basis by the Central Research Team.

6. TRIAL PROCEDURES

This section describes how GP surgeries will be recruited; participants identified, and consent received; the procedures for randomisation, data collection, follow-up; and the arrangements for masking and ending the trial.

6.1 Selection and training of GP surgeries

Practices will be recruited via NIHR Research Delivery Networks (RDNs) and "GPs at the deep end" networks. Participating practices will be given training by the research team before they approach any patients. First, they will be given instructions of how to run the participant search, screen the results and invite potential participants. Next, arrangements for baseline visits for participants in the practice will be agreed.

6.2 Training of researchers and study dietitian

Participant consent, baseline data collection, the delivery of the intervention and follow-up will be undertaken by trained researchers. This includes research nurses/clinical research practitioners employed by Research Delivery Networks and participating GP surgeries.

Training will be provided by the lead centre (Bristol), supported by local allergy clinics in Bristol, Manchester and Southampton. Competence in the study procedures, including skin prick testing, will be signed-off before any individual undertakes patient-facing activity. On-going support and advice will be provided as needed by the local principal investigators, allergy panel and study dietitian.

The study dietitian will be trained in the study-specific procedures by the lead centre and supervised by senior dietitian co-applicants Meyer and Skypala.

6.3 Trial advertising

The study will be advertised via local media. Participating GP surgeries and local community dermatology/hospital clinics will display posters and flyers in waiting rooms and put information about the study on practice websites and social media. These will direct potentially eligible patients to their GP and the study website.

The study website will contain the patient information documentation for the study and contact details. A short animation, based on the Study summary, will also be produced. Social media (e.g. X/Twitter, Facebook) will be used by the research team to raise awareness of the study and will be for information purposes only.

6.4 Identification and screening of participants

Parents of potentially eligible children will be invited to take part by two routes.

First, by invitation from participating GP surgeries. The GP or a delegated member of the practice team will search their electronic medical records for children under two years with a history of eczema. They will screen the search results for any known adverse medical or social circumstance that would make invitation to the study inappropriate and record the reason for any exclusions. The practice will then send out written invitations on the research team's behalf. This will be in the form of a letter though the post and/or text message with a copy of the Study summary. A reminder (letter, text or telephone call) will be sent after 2-6 weeks. The invitations will sign-post interested parents to the study website and the Participant information leaflet.

Second, parents or their clinician may contact the research team via the study website or by email in response to advertising or when they are seen in clinics for their eczema or other reasons (e.g. routine vaccinations).

Parents will express an interest in participating by completing an online questionnaire or by returning a paper form using a pre-paid envelope. The expression of interest reply form will inform parents/carers that by completing and returning the form, they are giving consent for their personal details to be stored by the Central Research Team until eligibility has been determined (for the purpose of contacting them). This includes children whose eczema is currently clear/almost clear (POEM<=2). Eczema is a fluctuating condition and with the parent's permission we will contact them again to see if their child's eczema has worsened and they have now become eligible (POEM>2). If they are otherwise not eligible or decline to take part, their personal details will be removed from the study records.

6.5 Participant recruitment

The research team will send interested parents the participant information leaflet/"Easy Read" version to read. They will follow this up with a telephone or video call, during which they will check understanding about the study and answer questions. If appropriate, they will seek consent and schedule a baseline visit. Consent may be received from participants who are only able to read the "Easy Read" version of the participant information leaflet with support from the researcher to ensure full understanding.

6.6 Consent

Informed consent will be received from the child's parent (or legal guardian) prior to any procedures that are specifically for the purposes of the trial and are outside routine care. Details of all participants approached for the study and reason(s) for non-participation (e.g. reason for being ineligible or participant refusal) will be recorded in the study Case Report Forms (CRFs). Patients are not required to provide reasons for taking part in the trial, or not, but if reasons are given, then they will be documented. Similarly, it will be made clear that parents are free to stop their child's participation in the trial at any time, without giving reasons and without prejudicing their future treatment.

The consent appointment will take place remotely (via telephone or video call) with an appropriately trained member of the research team. Written consent will be received on paper or online, using REDCap. The acceptability of e-consent has been confirmed by our Sponsor and PPI and is in-line with Health Research Authority guidance.[70] For paper consent, a copy of the consent form will be posted with the participant information leaflet and a freepost envelope, will be completed by the participant and returned to the research team to countersign. The participant will then be sent a copy of the fully signed form for their records. For participants who cannot read/write an impartial witness (as defined by ICH GCP) will be involved in the consent process. An impartial witness cannot be a member of the research team, regardless of who employs them, but could be an allied health professional/nurse/doctor (if they are not on the study delegation log) or a friend/relative of the participant.

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes the receiving of informed consent. They will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and

competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

6.7 Pre-baseline

Pre-baseline will occur remotely after consent has been received but before the baseline visit occurs. It will be split into two parts as detailed below and in Table 2 (B-). This additional time point reduces the length of the in-person baseline visit, a learning from the feasibility trial.

6.7.1 *Pre-baseline questionnaire – staff administered:*

Parents will be asked questions administered by the researcher about characteristics of their child and family, including food allergy symptoms and dietary history of the child and (if applicable), the diet of the breastfeeding mother.

If symptoms are reported via this questionnaire which raise concern, e.g., are suggestive of an immediate-type allergy following ingestion of one of the study foods, this will be reviewed on a case-by-case basis and, where necessary, referred back to the participant's GP to re-review symptoms. Following review, if symptoms indicate an immediate-type allergy, the participant will be withdrawn from the study.

6.7.2 *Pre-baseline questionnaire – self complete:*

Parents will be sent (via post/email) a pre-baseline questionnaire containing questions about their and their child's quality of life.

6.8 Baseline visit

As detailed in section 6.2 (Training of researchers and study dietitian) above, the baseline visit will be delivered by a trained researcher. GP surgeries will be able to work in a "hub and spoke" model, where patients from practices ("spokes") may attend a neighbouring participating practice ("hub") for the baseline visit. GP surgeries increasingly deliver research and clinical care this way, through primary care networks.

For the face-to-face baseline visit to take place, the participant must be generally well and <u>not</u> have:

- taken oral anti-histamine within the previous 72 hours;
- acute asthma (audible wheeze) or rhinitis;
- generalised severe eczema or other erythrodermic condition such that there is no suitable site for skin prick tests.

Just prior to the baseline visit, a member of the research team may contact the parent to confirm that they are still able to attend and ensure that none of the above apply.

At the baseline visit and before randomisation:

- The parent will complete a short baseline questionnaire ("B", Table 2)
- The researcher will measure the child's weight, length and head circumference; undertake the skin assessment; and optionally collect the saliva for DNA analysis ("B", Table 2)

The researcher will then randomise the participant.

6.9 Randomisation

Children will be randomised using an online randomisation system (provided by a company called "Sealed Envelope", www.sealedenvelope.com), which will allocate the participant to intervention or

comparator groups (1:1 ratio), stratified by eczema severity (POEM) and centre (Bristol/Southampton/Manchester).

The researcher will tell the parent to which group they have been allocated, and either just give them a copy of the "Good eczema care" leaflet and information about study follow-up (standard care); or in addition, undertake the skin prick tests and give dietary advice (intervention).

The research team will notify their GP surgery of the participant's allocation and the outcome of any tests/investigations and food allergy diagnoses.

6.10 Schedule of assessments

Table 2 sets out what data will be collected when. RECAP, POEM, PP-NRS, EASI, and IDQOL are the Harmonising Outcomes Measures for Eczema (HOME)-recommended core outcomes[65] for capturing eczema control, symptoms (including itch intensity), signs and disease-specific quality of life respectively.

Most data will be parent-reported, collected by online or paper questionnaires, according to preference. Skin prick tests will be done in primary care by the trained researcher/practice clinician; and oral food challenges in secondary care, when required.

Completion of core data over the telephone or by video call will be offered if necessary. With permission, we will extract data from the patient electronic medical records after nine months for additional data on use of healthcare resources.

6.10.1 *Participant follow-up questionnaires*

Parents will be sent four-weekly questionnaires for 36 weeks. Those who choose to provide data online will receive email prompts to complete them within two weeks of when they are due, while those who opt to complete on paper will be offered text reminders. All other participants will receive text 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, with support from a study researcher, will be offered.

6.10.2 *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); the child's weight, length and head circumference measured; and optionally saliva collected for DNA analysis (if not already done at baseline).

6.10.3 *Electronic medical record (EMR) review*

Participant's primary care EMR will be reviewed (from birth until 36 weeks after the date of randomisation) and data extracted on the following: prescriptions, consultations, referrals, out-patient and emergency appointments.

6.11 Masking

It is not possible to mask the researcher conducting the baseline visit to allocation. However, baseline data (including EASI) will be collected before randomisation and where possible, the researcher conducting the follow-up visit will be different/masked to their allocation. Parents will be asked not to reveal their allocation status to the research team unless given explicit permission to do so.

Table 2: Schedule of data collection

	Topic	Measure			Week									
			B-	B	B+4	B+8	B+12	B+16	B+20	B+24	B+28	B+32	B+36	B>36
1	Expression of interest		●											
2	Characteristics of child and family†	Bespoke	○											
3	Diet‡	Infant Feeding Survey/bespoke	○		●	●	●	●	●	●	●	●	●	
4	Child quality of life (disease specific)	IDQoL	●							●			●	
5	Child quality of life (generic)	CHU-9D	●				●			●			●	
6	Parent quality of life	EQ-5D-5L & EQ-VAS	●				●			●			●	
7	Parent quality of life	CarerQol	●							●			●	
8	Parental anxiety	GAD-7	●							●			●	
9	Eczema control	RECAP		●	●	●	●	●	●	●	●	●	●	
10	Eczema symptoms	POEM		●	●	●	●	●	●	●	●	●	●	
11	Itch severity	PP-NRS		●	●	●	●	●	●	●	●	●	●	
12	Parent-reported global eczema severity	Global eczema severity[71]		●	●	●	●	●	●	●	●	●	●	
13	Use of topical treatments for eczema	Bespoke		●	●	●	●	●	●	●	●	●	●	
14	Eczema/food allergy genes	DNA saliva sample		▼						▼				
15	Growth of child	Weight, height and head circumference		○						○				
16	Eczema signs	EASI		○						○				
17	Food sensitisation	Skin Prick Tests		□										

18	Food allergy	(Oral Food Challenge)		◊										
19	Home dietary trial outcome				□									
20	Health service utilisation	RUM#					●			●			●	
21	Out-of-pocket expenses/time off work	Bespoke					●			●			●	
22	Trial participation experience	(Exit questionnaire)											●	
23	GP consultations, prescriptions and referrals	EMR notes review												●

Key:

Primary outcome/period

B- = pre-baseline visit; B = baseline visit

○ Case report form ● Self-complete questionnaire; ▼ optional, collected at either baseline or 24 week appointments; □ participants in intervention group only; ◊ participants in intervention group only with equivocal/abnormal allergy results;

†: Participant demographics and medical history, UK eczema diagnostic criteria for atopic dermatitis, family history of atopy, parent health literacy (Single Item Literary Screening, SILS) and prior expectations. ‡ Diet of child and breastfeeding mother, if applicable

Includes ModRUM and bespoke questions

It is not possible to mask parents of children in the trial and treating clinicians to the child's allocation. Consequently, unmasking procedures are not required.

The Trial Management Group will be masked to allocation although the Trial Manager, Chief/Principal Investigators and allergy experts may need to be unmasked for operational and safety reasons on an as required basis.

6.12 Loss to follow-up and changes in participation

Participants will remain in the trial unless they choose to stop their participation, or they are unable to continue for a clinical reason, without any consequences for their usual care or follow-up. Any changes to a participant's continuation in the study should be recorded on the appropriate study document (e.g. Change of Permissions Form). Stopping participation in 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" (participants stop completing study questionnaires, fail to attend the 24 week appointment and/or do not respond to communications from the research team).

Participants who actively stop participation will be asked to provide a brief reason for why they would like to stop and some may be invited for an interview as part of the process evaluation.

Participants can choose to stop their participation in the study completely, or they choose to stop participation in part of the study, e.g. questionnaires, or any of the optional elements of the study.

6.13 Participant payments and communication

To part recompense parents for potential loss of earnings, they will be offered a £10 voucher at baseline; and a £10 voucher around 24 weeks.

Participants will be sent a newsletter (up to three times a year) with updates about the study progress and, at the end, a summary of the trial findings.

6.14 End of trial

Participants end their involvement with the trial when their last follow up questionnaire is completed (or efforts to obtain final questionnaire have been unsuccessful), or they (or their clinician) have requested to stop participation in the study.

The end of trial will be when the last patient has completed their last follow-up questionnaire, data extracted from the medical records, all data queries have been resolved, the database has been locked, with subsequent data analysis completed and post (cellular) sample destruction (acellular (DNA) samples may be kept beyond this point, see section 9.4).

6.15 Trial stopping rules

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

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the Funder, who will be advised on whether to continue or discontinue the by the TSC. If the trial is prematurely discontinued, no new participants will be recruited, and a decision on data collection on active participants will be made in discussion with the TSC/DMC and Sponsor.

7. INTERVENTION AND STANDARD CARE

This section describes the intervention (test-guided dietary advice, based upon the results of skin prick tests to four allergenic foods) and what constitutes standard care.

7.1 Current pathways

Currently, food allergy testing is not routinely offered to children with eczema. Children in whom food allergy testing is clinically indicated, or parents request it, are referred by their GP to secondary care, with wait times of at least 6 months and variability in use of tests (when, type of test and for which foods). [36]

7.2 Intervention

7.2.1 *Intervention remit*

In addition to receiving the "Good eczema care" leaflet, intervention participants will receive "test guided dietary advice", based on skin prick tests to cow's milk, hen's egg, wheat and soya.

7.2.2 *Intervention design*

The intervention was developed and evaluated in our feasibility trial (TEST). [49 50] The majority of resources were developed and tested in the feasibility trial, with minor modifications/additions for this study.

The intervention has been further refined for the main trial using the TIDIER framework. [72] We recognise that if our study demonstrates the value of skin prick test-guided dietary advice, it must be feasible to deliver the intervention in routine primary care.

The key components of the intervention are:

- skin prick tests (+/- oral food challenge)
- dietary advice

Dietary history and oral food challenge are primarily included for safety, i.e. to ensure that advice to include foods at home are not at risk of sudden, IgE-mediated, potentially life-threatening reactions. Dietary history and dietary advice pertain to the child only, not breastfeeding mothers.

Training for researchers delivering the intervention was developed in the feasibility study. We have experience, from the TEST and BEEP studies, of training researchers with no prior experience to conduct skin prick tests, [73] in the community. The training includes information about skin prick testing and interpretation of the results; and practical sessions learning how to perform SPTs.

The dietary advice flowchart is presented in figure 3. It is based on published guidelines, [33 34] flowcharts employed in the BEEP study, [74] findings from the TEST feasibility study, and has been further refined through a recently completed consensus exercise.[Ridd 2022, unpublished] It is designed to enable a trained, but non-specialist, clinician to correctly, consistently and safely interpret the results of the SPTs. It is used on a food-by-food basis and is a graphical way to determine what dietary advice should be given. We established in the feasibility study that a trained researcher can independently and safely apply it. Decision-making is primarily determined by the results of the skin prick tests. Combining the SPTs with the findings of the dietary history, we can identify participants who may be at risk of an immediate, IgE-type reaction from ingestion of a study food at home and offer them an oral food challenge before dietary advice is given. It will be further evaluated during the pilot phase, with refinements made if necessary.

Possible food allergy will be evaluated using skin prick tests. We favour these over blood (immunoglobulin E specific) tests, because:

- concordance between *in vitro* specific IgE antibody assays and skin prick tests results is between 85% and 95% (depending on the allergen being tested and the method used to detect specific IgE); [75]
- skin prick tests are easy to perform, less invasive/painful and cheaper than blood tests;
- we have demonstrated that it is feasible to perform these in community settings in young children; [50 73]
- skin prick tests could be routinely undertaken in primary care, and in this study, we will determine the feasibility of training general practice nurses to deliver the intervention.

Cut-offs for SPT wheal size will be: [76]

- <3 mm = negative
- >=3 mm = sensitised

The study foods are milk, egg, wheat, and soya, chosen for the following reasons:

- these foods most commonly cause allergy/concern in children and among parents; and are among the most common foods excluded by parents of children with eczema without professional advice; [9 13]
- hen's egg and cow's milk are the most common cause of food allergies in young children with a prevalence of 2%[77] and 1%[78] respectively; and
- Lever *et al*[31] trial which suggested that infants with suspected egg allergy who have positive specific IgE to eggs may benefit from an egg-free diet.

Specifically, the following reagents will be used for each food:

- Milk = commercial cow's milk extract
- Egg = commercial egg white extract
- Wheat = commercial wheat flour extract
- Soya = commercial soya flour extract

For children advised a dietary trial of exclusion, parents will be asked to exclude the specified study food for 2-4 weeks (minimum 2 weeks, up to 4 weeks if the parent is uncertain as to any effect). This interval is supported by our recent survey of 49 UK dietitians, where four weeks was the most common period. [79] The consensus is that exclusion for four weeks is insufficient for oral tolerance to food allergens to be lost, and risk of immediate-type allergies, increased. Where two or more foods are to be excluded, parents will be given the option of either removing all foods from their child's diet and reintroducing them one-by-one; or serially excluding and reintroducing one food at a time.

After completing any dietary trial, the parent will decide whether to continue to include or exclude the food, according to whether they think it has had any effect on their child's eczema. Parents will be contacted after 4-6 weeks to ask if they implemented the advice, whether they thought it made any difference to their child's eczema, and what their intentions regarding future food inclusion or exclusion are.

As a safety measure, participants who decide to exclude one or more foods long-term will be offered a consultation with a study dietitian (by phone or video call), to ensure the child's individual dietary

needs are met, and they will not be at risk of any nutritional deficiencies due to the exclusion. We will inform the child's GP of this consultation and provide them with a summary of the discussion and any actions required.

Implementation of dietary advice will be supported by standard information sheets written by the Food Allergy Specialist Group (FASG) of The British Dietetic Association (BDA) (www.bda.uk.com) and, if appropriate, iMAP milk[80] and BSACI egg[81] reintroduction ladders.

7.2.3 *Skin prick testing kit*

The skin prick testing kits will comprise the relevant allergen solutions (plus positive and negative control), lancets, portable sharps bin, tissues, pen, timer, and ruler. The components will be sourced from reputable suppliers and assembled by the lead research team in Bristol before distribution to the other centres or GP surgeries by means of courier. Allergen solutions will be stored in an appropriate fridge when not in use, as per the supplier's instructions.

7.2.4 *Intervention delivery*

The intervention will be delivered by a trained researcher or practice-based nurse.

First, they will administer and read the skin prick tests for the four study foods along with positive (histamine) and negative (saline) controls.[82 83] 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.

Using the flowchart (figure 3), they will then determine the dietary advice and provisionally inform the parent of the outcome for each food. The recommendations for each food will be:

- introduce/continue to include in diet as normal
- home dietary trial of inclusion or exclusion
- exclude from diet until oral food challenge, or
- exclude until review

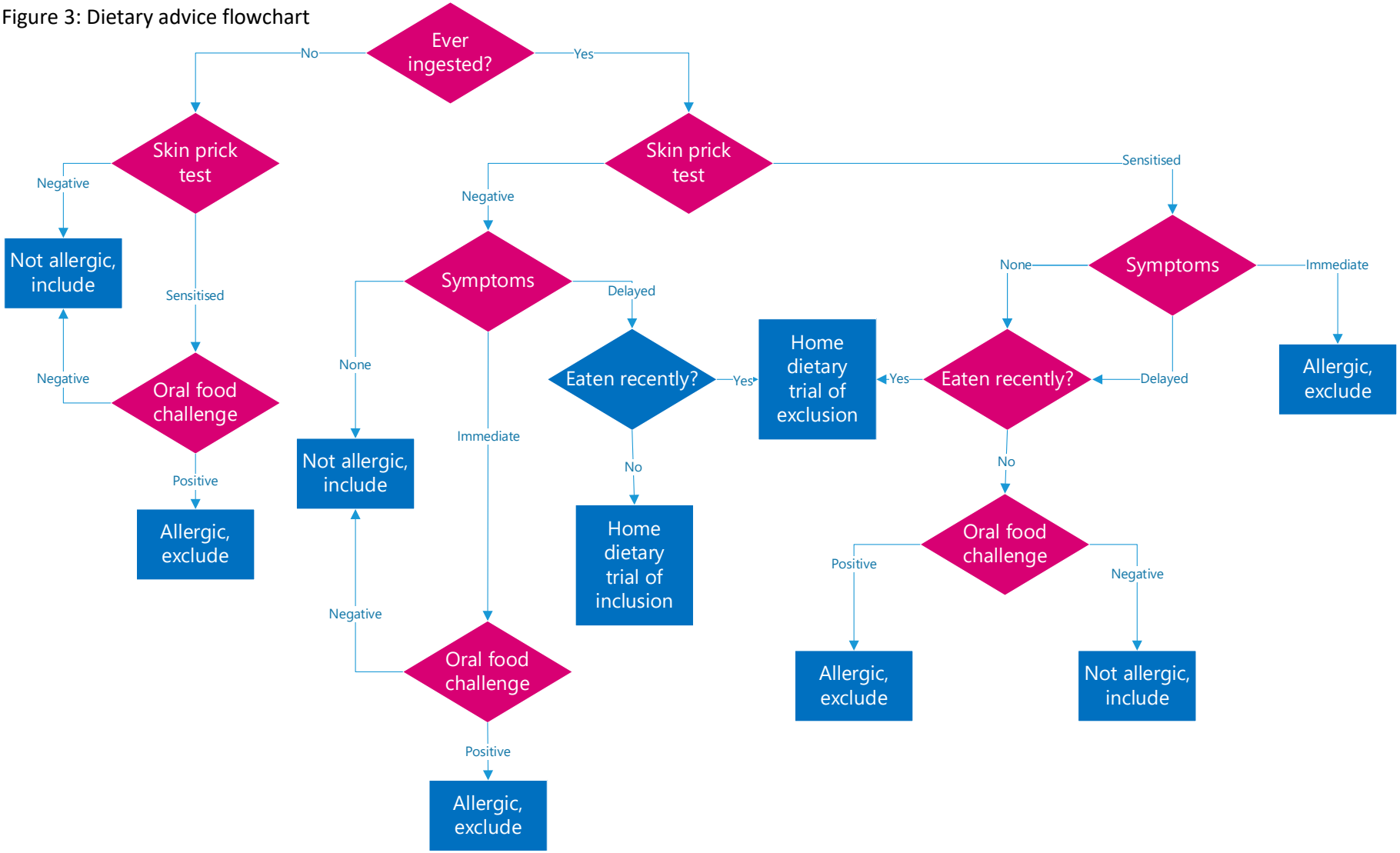
Home dietary trials of study food(s) will be undertaken by parents at home, supported by written information on what foods contain the target allergens. Parents will be contacted 4-6 weeks after starting the home dietary trial to find out the outcome.

Oral food challenges will be performed at the child's nearest allergy centre as a day case, usually within four weeks (target time of two weeks) of the baseline visit. Participants will be invited to undergo these when there is uncertainty as to the safety of ingesting one of the study foods at home. Agreed, standard care procedures will be followed.

Oral food challenges will only be undertaken in an age and developmentally-appropriate manner. If a participant is sensitised to a food, but not eating it because they have not yet been weaned, the challenge will be deferred until solid food has been introduced. Children judged to have immediate hypersensitivity will be advised to exclude it, and they will be referred by their GP to an allergist for follow-up.

The study team will contact parents around 1 week after the oral food challenge to ask whether the child had any delayed symptoms.

Figure 3: Dietary advice flowchart



Exclusion until review has been added in case the situation arises where a food allergy is likely and an oral food challenge at this time would be inappropriate.

We will inform the child's GP of the outcome and any advice given to parents regarding inclusion or exclusion of foods. We will also send a letter to parents to confirm the findings and dietary advice.

7.3 Standard care

Standard care (and intervention) participants will be provided with a "Good eczema care" leaflet, which will contain information in the public domain that one would normally expect to be given as part of standard care, such as avoidance of potential skin irritants, and use of emollients and topical corticosteroids. This is to standardise, but not enhance, care across groups; and will not be supplemented with additional advice from research or practice nurses. Existing advice around weaning and early introduction of allergenic foods forms the basis of "standard care". [84] As per current NICE guidance, [33] any child (standard care or intervention) who during the course of their time in the study develops possible food allergy symptoms or who GP thinks needs investigation, can be referred via usual care pathways.

7.4 Allergy panel

An allergy panel, comprising clinicians on the research team with experience of diagnosing and managing children with food allergy, who will oversee the advice being given to participants and will be available for guidance for the duration of the study.

The panel will regularly review the dietary history and skin prick test findings, and advice given to individual participants. In the event of any discrepancy between the researcher/nurse, flowchart and panel, the opinion of the allergy panel will prevail, and the intervention of the panel recorded.

Any questions relating to the interpretation of the skin prick tests or dietary history, and/or what advice should be given to participants, which are not answered by this protocol or study working instructions, will be addressed by an allergy panel.

7.5 Concomitant medication

All treatments for eczema and any other comorbidities can be prescribed and used, as per usual clinical practice. (With the exception of antihistamine in the 72 hours prior to baseline appointment).

7.6 Assessment of adherence

In keeping with the pragmatic design of the study, adherence will not be monitored or enhanced beyond what might be expected in "real life". We will capture by means of parent-completed questionnaires what foods are included/excluded from the child's diet.

8. SAFETY

8.1 Operational Definitions

Table 3 lists the definitions and classifications will apply to all safety reporting in this trial.

8.2 Identification of Adverse Events

Site teams are responsible for identifying AEs for their participants during the trial; during trial related appointments and any other appointments or admissions, as reported by participants and/or healthcare colleagues. All Adverse Events should be documented in patient records.

8.3 Classification of Adverse Events

All Adverse Events must be assessed by a local Investigator (a clinician with delegated study responsibilities) to determine Relatedness and whether they meet the Serious Criteria.

8.3.1 *Adverse Reactions (Related but not Serious)*

Events which are determined to be Possibly, Probably or Definitely Related to a trial procedure or intervention, as per Table 5 above, and are determined **not** to meet the Serious criteria, as per Table 3 above, will be recorded in the participant's CRF.

8.3.2 *Serious Adverse Events (Serious but not Related)*

Events which are determined to meet the Serious criteria, as per Table 3 above, and are determined to be Unlikely or Not Related to a trial procedure or intervention, as per table 5 above, will be recorded in the participant's CRF and the SAE Summary Log in the eCRF.

The central research team will review the SAE Summary Log regularly for monitoring and reporting purposes and will prepare regular summary reports of all SAEs for discussion at relevant oversight meetings, including with the DMC.

8.3.3 *Serious Adverse Reactions (Serious and Related)*

For events which are determined to be Possibly, Probably or Definitely Related to a trial procedure or intervention, as per Table 5 above, and are determined to meet the Serious criteria, as per Table 3 above, follow this procedure:

Record: Record in the SAE Summary Log in the eCRF, as above.

Review Expectedness: the following event is an Expected Reaction if it is determined to be related to the skin prick test or the oral food challenge, and no further action is required:

- Anaphylactic reaction (rare) (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).

If an anaphylactic reaction is determined to be related to the ingestion of one or more of the study foods in a participant in the intervention group, following study-administered dietary advice, this would be classified as an unexpected reaction (SUSAR) and should be reported as detailed below.

Table 3: Definitions of adverse events and reactions

Term	Definition
Adverse Event (AE)	Any unfavourable and unintended sign or symptom that develops or worsens during trial participation, whether or not it is considered to be related to the trial intervention. The following are not classed as AEs: continuous and persistent disease or symptoms, present before the trial, which fail to progress; signs or symptoms of the disease being studied; or treatment failure.
Adverse Reaction (AR)	An adverse event which is determined by a medically qualified professional to be Possibly, Probably or Definitely Related to a trial intervention or procedure. (See table 5, below.)
Serious Adverse Event (SAE)	A serious adverse event is any adverse event that: • results in death • is life-threatening[A] • requires inpatient hospitalisation or prolongation of existing hospitalisation[B] • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
Serious Adverse Reaction (SAR)	An adverse reaction that meets one or more of the serious criteria above.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with previous events related to the trial procedures, as described in section 8.3.3.

[A]The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

[B]The definition of hospitalisation is an unplanned overnight stay. Note, however, that the patient must be formally admitted – waiting in outpatients or an Accident & Emergency Department (A&E) would not count as hospitalisation (even though this can sometimes be overnight). Prolongation of an existing hospitalisation qualifies as a SAE. Planned hospital stays would not be counted as SAEs, nor would stays in hospital for "social reasons" e.g. respite care or the fact that there is no-one at home to care for the patient. Also, if patients had a day-case operation, this would not qualify as hospitalisation. However, if a planned operation was brought forward because of worsening symptoms, this would be considered as a SAE. Hospitalisations for the purpose of the intervention are an exception to SAE reporting unless complications occur.

'Serious' should not be confused with 'severe'. Severity describes the intensity of an event and the degree of its impact upon the sufferer. An event is 'serious' or not based solely on whether it meets one of the above criteria.

Table 4: Classification of Severity

NB. Severity is relevant when Reporting events to the Sponsor, on an SAE reporting form.

Mild event	An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
Moderate event	An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe event	An event that prevents normal everyday activities.

Table 5: Classification of Relatedness

Not related	Temporal relationship of the onset of the event, relative to administration of the intervention, is not reasonable or another cause can by itself explain the occurrence of the event.
Unlikely to be related	Temporal relationship of the onset of the event, relative to administration of the intervention, is unlikely and it is likely there is another cause which can by itself explain the occurrence of the event.
Possibly related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable but the event could have been due to another, equally likely cause.
Probably related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and the event is more likely explained by the intervention than any other cause.
Definitely related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

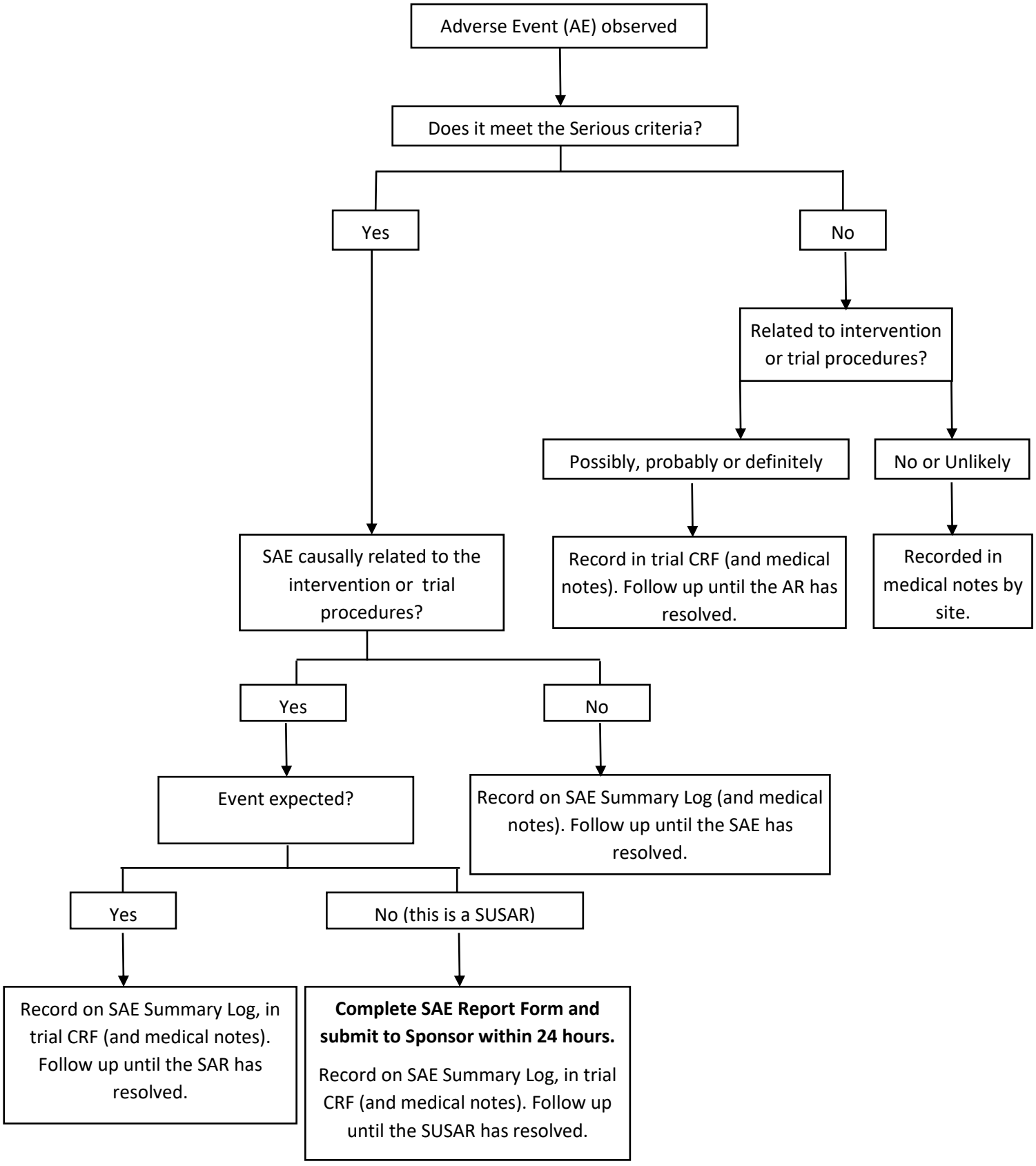
If the event is not on the list of Expected Reactions or is a reaction to any other intervention, continue to Report:

> *Report:* Report the event to the Sponsor (University of Bristol) within 24 hours of becoming aware of it - via University Hospitals Bristol and Weston, in accordance with section 6.2.2 of their Safety Reporting SOP. Ensure that in section 8 “was the SAE unexpected?” is answered “Yes”.
>
> When reporting, copy to Prof Matthew Ridd (CI) m.ridd@bristol.ac.uk.

8.4 Follow-up

All Serious Adverse Events, Adverse Reactions and Serious Adverse Reactions should be followed up by the site until the event resolves or an outcome has been reached. Any new information must be forwarded once available.

Figure 4: Recording and Reporting Framework for Safety Events



9. SAMPLE MANAGEMENT AND ANALYSIS

This section describes the basis for and processes of collecting and analysing DNA saliva samples from participants in the trial.

9.1 Background

This study is a unique opportunity to collect and analyse DNA from saliva samples to test for genetic variants associated with eczema and food allergy. It will enable us to explore genetic variants (null mutations in *FLG,* and an intergenic SNP on chromosome 11q13.5 identified by genome-wide meta-analysis) associated with eczema/food allergy. [85-87]

9.2 Consent

Collection of saliva for DNA analysis is an optional part of the study. Consent will be sought from parents via the main study consent form.

9.3 Collection, labelling and storage of samples

Samples will be appropriately labelled in accordance with the trial procedures to comply with the Data Protection Act 2018. Samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the Human Tissue Act 2004 and the Human Tissue (Scotland) Act 2006.

Samples will be collected by a researcher at the baseline or week 24 visit. Samples will either remain in a participating GP practice or be brought back by the researcher to the local academic centre. They will be stored in an appropriate place (e.g. locked cupboard) until they are posted in batches using an approved courier to the Brown Laboratory within the Institute of Genetics and Cancer, at the University of Edinburgh for analysis. Samples are stable at room temperature (up to 30 degrees Celsius). Above this temperature, they will be refrigerated.

The collection, storage, transit and receipt of samples will be recorded using an online system for tracking. Each sample will have two identifiers, for example date of collection and participant study ID code.

9.4 Sample analysis and destruction

Sample analysis will be overseen by the University of Edinburgh, under the direction of co-applicant Professor Sara Brown. Saliva samples will be stored securely in the Brown Lab, received and sent in batches to the University of Edinburgh for DNA extraction and SNP genotyping. The four most prevalent loss-of-function mutations in *FLG* (R501X, 2282del4, S3247X and R2447X) and rs2212434 on chromosome 11q13.5 will be genotyped using KASP™ technology as previously reported. [24]

Samples will be stored until the study is completed and reported and then destroyed within six months of the study results being published.

9.5 Feedback of genetic results to participants

The results of genetic testing in the TIGER trial will not be fed back to individual participants or their families for two reasons. First, testing will be conducted in a research laboratory that is not accredited to NHS standards for clinical genetic testing. Second, the effects of the genetic variations that we are testing have a measurable effect on a population level but not for each individual. Therefore, a positive or negative result cannot be used to advise an individual on their health or disease risk and hence would not be useful/actionable information for the child or family.

10. STATISTICS AND DATA ANALYSIS

This section sets out the sample size calculation, planned participant recruitment rate, internal pilot and outlines the statistical analysis plan.

10.1 Sample size

We estimate a baseline SD for RECAP of 6.5 and correlation between baseline and 24-week RECAP of 0.4. Treatment groups will be compared as randomised and the size of the difference in RECAP scores between groups will be influenced by the proportion of children in the intervention arm who are "test positive".

Assuming 30% of children in the intervention group are given advice (i.e. sensitised to at least 1 allergen) to modify their diet and that these children will have a RECAP score 6.5 units lower than the control group, the intervention group overall will have a mean RECAP score 1.95 units lower than the control group. Therefore, for 90% power and at 5% significance level, 493 children will detect a difference of 1.95 on RECAP between the two treatment arms assuming 20% loss to follow-up.

We estimate that our sample size will allow for 90% power even if 5% of standard care children seek allergy testing advice as long as the overall loss to follow-up does not exceed 10%.

10.2 Participant recruitment rate

We plan to recruit participants via ~120 GP surgeries in three centres. This equates to ~164 participants per centre or ~4-6 participants per GP surgery.

10.3 Internal pilot

The first six months of participant recruitment will constitute an internal pilot, with the criteria and thresholds for progression shown in Table 4. Interpretation and recommendations will be made in conjunction with the Trial Steering and Data Monitoring Committees.

If all the criteria are green, the trial will as continue as planned. If any of the criteria are in the amber or red zones, the Trial Management Group will consider remediable issues and, if supported by the Trial Steering Committee, the trial will proceed with regular monitoring. In the event of intractable issues arising that cannot be remedied, the trial will be terminated.

Table 4: Progression criteria for internal pilot

Progression criteria	Green	Amber	Red
Threshold	100%	70-99%	<70%
Recruitment/month	22	15-21	<15
Recruitment total	129	90-128	<90
Retention at 3 months of follow-up	64	44-63	<44

10.4 Statistical analysis plan

A full statistical analysis plan (SAP) will be completed and approved by the TSC prior to the end of patient recruitment. The DMC will review an early draft of the SAP before seeing any data presented by study arm.

Analysis and presentation of the trial data (led by MacNeill) will be in accordance with CONSORT[34] and CONSORT PRO[35] guidelines. Baseline characteristics of patients will be compared by reporting descriptive statistics; numeric variables will be summarised using means, medians, standard deviations and ranges as appropriate and categorical variables will be summarised using frequencies and proportions. These will be used to determine whether there are meaningful differences between the treatment groups at baseline and inform any subsequent sensitivity analyses adjusting for such imbalances for those variables that could be prognostic of the outcome.

The primary statistical analyses will be conducted on an intention-to-treat (ITT) principle, analysing patients in the groups to which they were randomised. The primary analysis for the RECAP score will be performed using a multilevel mixed linear model framework with observations over time for weeks 4 to 24 (level 1) nested within participants (level 2). The model will adjust for baseline RECAP score and variables used in the randomisation.

As secondary outcomes analyses, we will study RECAP and POEM scores over weeks 4 to 36 using the multilevel mixed linear model framework outlined for the primary analysis. Generalised Estimating Equations with logistic link will be used to analyse the 4-weekly binary outcomes. Linear regression models will be used to study IDQoL, GAD-7, weight-for-age, stature-for-age and weight-for-stature at 24- and 36-weeks separately after adjusting for baseline measures. EASI scores at 24 weeks will be studied using linear regression models adjusting for baseline measures. All models will adjust for variables used in the randomisation.

Descriptive analysis of safety endpoints will be presented according to treatment received. This will include the accuracy of the provisional dietary advice given by research and practice nurses, compared with allergy panel assessment.

Sensitivity analyses of the primary analysis will adjust for variables demonstrating a marked imbalance at baseline; and examine the impact of missing data. The approach taken to handling missing primary outcome data will depend on the patterns/nature of missingness.

A small number of pre-specified subgroup analyses will be carried out to assess the difference in intervention effect on the primary outcome according to baseline characteristics, the basis of the dietary advice and who delivered the intervention. These include:

- eczema severity at baseline – the intervention may be effective in severe compared with mild/moderate or moderate/severe compared with mild disease
- dietary advice – outcomes for children who excluded foods based on SPTs may differ from those based on possible delayed symptoms only; and excluding one or two specific foods (e.g. egg or milk) may be more effective than excluding others (e.g. wheat or soya)
- delivery of intervention by university, RDN or practice-employed researcher/nurse – the intensity of the intervention may differ between university/RDN and GP surgery-based researchers/nurses.

A “per protocol” analysis of the primary outcome will be done, with data restricted to participants who fully complied with dietary advice.

11. ECONOMIC EVALUATION

This section outlines the economic evaluation, led by Dr Garfield, including the perspective; how resources will be identified, measured and valued; outcomes; and analysis.

11.1 Aim and perspective

The aim is to compare the costs and consequences and estimate the cost-effectiveness of test-guided dietary advice versus standard care, for the management of eczema. The primary perspective will be NHS, with secondary analyses including non-NHS costs at 36 weeks follow-up.

11.2 Identification and measurement of resources

Resources associated with the intervention will be recorded on case report forms. NHS resource-use data (including out-patient appointments and in-patient admissions) will be collected from primary care electronic medical records (EMRs) and parents at weeks 12, 24 and 36. Parents will report resource use related to their child's eczema or food allergy only. NHS resources (including primary and secondary care) will be captured from parents using an adapted version of a generic resource-use measure that has undergone validity testing in adults.[62] Non-NHS resource use will be collected via bespoke questions. Non-NHS data which will be captured in the diaries include: over-the-counter medications, personal expenses (e.g. food or clothes), private or alternative treatments or tests, parental time off work and child time off nursery/day care.

11.3 Validation of a proxy version of ModRUM and bespoke questions for under 2-year-olds

The validity of ModRUM completed by proxy for children under two years of age is unknown. ModRUM has brief core questions and depth questions that can replace core questions to capture additional detail or alternative resources. Items have been selected based on the likelihood of being cost drivers or highly utilised resources, and an adapted version of ModRUM constructed. Bespoke questions used in the TEST feasibility study have been revised based on findings from TEST and formatted for consistency with ModRUM. ModRUM and the bespoke questions will be referred to as the RUM hereinafter.

We have already undertaken work with members of our PPI group to assess the wording and length of the RUM. To further test the validity and ensure the RUM is comprehensible to parents and captures the information it is intended to measure, the following processes will be undertaken:

- A purposeful sample of around five parents will be asked to take part in cognitive 'think-aloud' interviews in the month following their randomisation. We will only approach those who agreed at baseline (via the main study consent form) to be contacted and verbal consent will be received at the beginning of the interview. The process for taking and recording verbal consent will be detailed in study instructions which will be followed by the researcher. Interviews will take place via video call and verbal consent for the interview will be audio-recorded (a member of the study team may act as a witness for verbal consent). Parents will be sampled by health literacy, ethnicity, and eczema severity. Parents will be asked to verbalise their thought process as they complete resource-use questions. The interviewer will ask follow-up questions on comprehension (including areas where struggle is observed) and acceptability. Interviews will be audio recorded and transcribed verbatim. Transcripts will be scored to identify errors in comprehension, recall, judgement and response, and analysed qualitatively to identify common themes. Based on the findings the

RUM will be revised, prior to being used to collect resource-use data at week 12. To part recompense parents for potential loss of earnings, they will be offered a £20 voucher.

- Following the same approach as above, around week 12, a second round of cognitive interviews will be undertaken with five different parents to test the revised questions. Analyses will be conducted as described above. If contradictory views occur, they will be explored in later interviews until a suitable solution is reached.
- Following the internal pilot, week 12 resource-use data will be reviewed, in addition to RUM follow-up questions on completion time and ease of completion. Response rates will be reviewed to identify problematic questions, and mean utilisation will be estimated, to identify questions which can be revised, condensed, or omitted.
- The RUM will be revised based on findings from the second round of interviews and the internal pilot. The revised RUM will be used in the remainder of the trial. Once this final version is agreed, an explicit plan for dealing with changes will be detailed in the health economics analysis plan. We anticipate the following rules will be applied: (1) if questions are omitted following the pilot, the given resource will not be included in the final analysis; (2) if questions are condensed (i.e. binary information is collected instead of binary and free-text), free-text information collected in the earlier version will be used to inform the most appropriate unit cost to use for both versions; (3) other revisions (e.g. changes to examples or terminology) will not result in changes to the analytical approach. A record will be kept of question changes to compare results from the different versions.
- During the final analyses we will assess agreement between ModRUM and EMR data by estimating sensitivity (proportion of participants that have use of a resource recorded in their EMR, whose parents also report using that resource), specificity (proportion of participants who have no use of a resource recorded in their EMR, whose parents also do not report using that resource) and a concordance correlation coefficient. Acceptability of the RUM will be assessed via questionnaire response rates and feasibility via question completion rates.
- For information on data collection and storage, please see section 12.5.

11.4 Valuation of resources

The intervention and NHS resources will be valued using the following sources: Unit Costs of Health and Social Care, National Schedule of NHS Costs and British National Formulary/Prescription Cost Analysis.[88] [89] Parent costs will be presented as reported. Time off work will be valued using the Annual Survey of Hours and Earnings.[90] As it is unclear how best to value time off preschool/nursery;[91] this will be reported in physical units, valued using the best approach available at the end of the trial, and subject to sensitivity analysis.

11.5 Outcomes

Quality-adjusted life years will be estimated using the CHU-9D for the child (currently validated for children aged 5 and over, a pilot version for under 5-year-olds will be included, which includes additional guidance notes and validation questions) and the EQ-5D-5L and CarerQol for the main carer.

11.6 Analysis

A full health economic analysis plan will be completed and approved by the TSC and DMC prior to the end of patient recruitment.

Cost-consequences will relate costs from each perspective (NHS and non-NHS) to a range of outcomes. Cost-utility analysis will compare QALYs for the child and main carer to costs incurred to the NHS. Uncertainty will be addressed by bootstrapping, plotting cost-effectiveness acceptability curves and in sensitivity analyses.

12. PROCESS EVALUATION

This section outlines the process evaluation, led by Dr Ingrid Muller, including how it will be conducted, analysed and reported.

12.1 Aim

To evaluate intervention processes, fidelity, mechanisms of action, experiences of the trial and intervention, and the influence of context.

12.2 Overview

Process evaluations within trials explore the implementation, receipt, and setting of an intervention and help in the interpretation of the outcome results. [92]

The process evaluation in TIGER will use qualitative and quantitative methods to assess fidelity, dose and reach of the intervention; clarify causal mechanisms; explore participant and health professional experiences of the trial and intervention and their social and cultural contexts; and identify contextual factors associated with outcomes. [93] We will distinguish between adaptations to make the intervention fit different contexts and changes that undermine intervention fidelity.

12.3 Participant recruitment, sampling and consent

We will conduct in-depth interviews with ~30 parents, ~15 GPs/allied health care practitioners or commissioners working in primary care and ~15 researchers and practice nurses (sampled by centre, experience, and role).

We will interview parents from the intervention group and the comparator group who agreed at baseline (via the main study consent form) to be contacted for an interview and use purposive sampling to ensure variation by health literacy, ethnicity, social contexts, eczema severity, allergy status and region. Parents will have previously given written consent to be approached for interviews and will be asked to confirm their consent verbally prior to the interview. Verbal consent and the interviews will be audio-recorded (a member of the study team may act as a witness for verbal consent). The process for taking and recording verbal consent will be detailed in study instructions which will be followed by the researcher. To part recompense parents for potential loss of earnings, they will be offered a £20 voucher.

GPs/allied health care practitioners and practice nurses will be recruited from participating GP surgeries or Integrated Care Boards. We will aim to sample a range of health care professionals working in a variety of practice settings. GP practices will be able to claim back the costs (£45) to cover the time of healthcare professionals who take part in their professional capacity. GPs/allied health care practitioners, practice nurses and researchers will be given an information leaflet to read and will be asked to confirm their consent verbally prior to the interview. Verbal consent and the interviews will be audio-recorded. The process for taking and recording verbal consent will be detailed in study instructions which will be followed by the researcher.

12.4 Qualitative interviews and analysis

Interviews will be carried out throughout the trial period to ensure experiences at all stages are captured. Interviews will start during the internal pilot phase to help assess if changes are needed before the main trial.

Interviews will be conducted remotely via telephone or video call and take between 30-60 minutes. Interviews will use a combination of open-ended and focussed questions to explore participants'

views and experiences of eczema and food allergy and their experiences of the trial and the intervention to help improve understanding of factors that influence participants' experience of the intervention, intervention delivery, engagement, and adherence.

Interview audio-recordings will be transcribed verbatim and analysed using inductive reflexive thematic analysis[94] to explore views and experiences of the trial and intervention from a health professional and parent perspective.

12.5 Observation of researcher training and trial delivery

We will audio-record (and may also observe) some of the researcher training sessions and a sample of study appointments with participants (sampled by centre, researcher/nurse and participant characteristics). Verbal consent will be received from researchers and parents and will be audio-recorded.

Observed researcher sessions will be monitored for fidelity using a bespoke checklist. Audio-recorded visits may be transcribed and will be analysed using inductive content analysis[95] to explore what happened during the visit.

12.6 Qualitative data collection and storage

All electronic data will be stored securely on a university secure server until the transcriptions for the qualitative interviews have been completed and the observed researcher and nurse sessions have been analysed. Once these have been carried out and unique identifiers have been assigned then the digital recordings will be destroyed.

Research data will be stored in accordance with the procedures agreed by the sponsor. Once it is appropriate, it will go to an approved storage facility that has been agreed by the sponsor.

12.7 Quantitative data collection and analysis

We will use baseline data (characteristics of parents as above; and nurse delivering the intervention) to examine factors that moderate intervention engagement and outcome. We will also capture and explore potential mediators of adherence and intervention outcomes, in particular, associations between health literacy, parental expectations and adherence to dietary advice/outcomes.

Process measures will be summarised using descriptive statistics; means and SDs or medians and inter-quartile ranges for numeric measures and frequencies and proportions for categorical measures. [96]

12.8 Process evaluation analysis

We will triangulate findings from the qualitative and quantitative process analyses to explore the proposed mechanisms of action in our logic model. Process evaluation findings will also be used to help inform interpretation of trial results and determine how the intervention could be improved in the future and how it could be implemented into clinical practice.

13. DATA MANAGEMENT

This section describes the procedures for data collection, recording and handling.

13.1 Data handling and record keeping

Data will be collected and retained in accordance with the Caldicott Principles, UK Data Protection Act 2018 and General Data Protection Regulation (GDPR).

When a participant consents to enter the trial, they will be allocated a unique participant number, which will be used thereafter by the research team to identify that individual and to link personal and clinical data. Participants will be asked to consent to their name, date of birth, and contact details being stored on the secure database with the central research team. Personal data will only be accessible to members of the central research team. Any data stored on laptops will be encrypted. Participant details will be anonymised in any publications that result from the trial.

Paper consent forms and any other documents with personal identifiable data will be stored separately in a locked filing cabinet. Data obtained by paper will be entered onto a password protected database. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to trial staff. Information capable of identifying participants will not be removed from University of Bristol or clinical centres or made available in any form to those outside the trial.

No identifiable data will be shared with Sealed Envelope™ for the randomisation process as randomisation will be stratified by eczema severity and centre.

For this trial, research data will be kept until the youngest participant's 25th birthday or 8 years after death. Personal data will not be kept for longer than is required for the purpose for which it has been acquired. Documents will be reviewed by the CI before being destroyed.

13.2 Data collection tools

The components and timing of data collection are shown in Table 2.

If a participant stops their participation in the study, they will be asked if they are willing to give a reason (but they will not be required to do so); data on any adverse events that need to be reported will be collected from the participant's GP using a standard proforma.

13.3 Source data

Source data is defined as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)." Source permits not only reporting and analysis but also verification, for example for quality control or inspection.

Source data for this trial will consist of certified scanned copies and/or electronic/paper copies of the consent form, participant completed questionnaires, case report forms (CRFs) designed specifically for the study and audio recordings of appointments and interviews. We will adhere to the principles of source data being: accurate, legible, contemporaneous, original, attributable, complete, consistent, enduring, and available when needed.

13.4 Data collection and entry

Data will be collected by means of researcher-completed CRFs and participant-completed questionnaires. The database will be set up to prompt the central research team when participant questionnaires are due.

Data will be recorded directly into CRFs and questionnaires (paper and/or online), and where applicable, will either be entered at site by delegated clinical/research site staff into a trial specific database, or transferred securely (electronically or by post) to the central research team (study office, University of Bristol) for entry into the trial specific database.

The eConsent (online) forms and online questionnaires will be completed via the REDCap database system and process (see below for REDCap details), which can be securely accessed via the internet.

EASI, saliva samples, weight and height will be recorded by training the researcher to follow standardised processes.

Interviews will be recorded on an encrypted device in accordance with University of Bristol information security guidelines. Standard digital recorders will be used for interviews via telephone. If interviews are held via video call, researchers will use Microsoft Teams record function. Recordings will be stored securely on a university secure server until the transcriptions have been completed. Audio recordings of interviews and appointments will be transcribed verbatim by a University of Bristol-approved transcription service/transcriber that has signed the necessary confidentiality agreements. Audio-recordings will be sent for transcription without identifying details.

13.5 Database platforms

All administrative and clinical study data will be stored in University of Bristol datacentres using clustered MySQL databases driven by REDCap. REDCap is a secure, web-based electronic data capture system designed for the collection of research data. The system has been developed and supported by Vanderbilt University. Bristol Trials Centre (BTC), at the University of Bristol (UoB), has set up its own infrastructure so that all systems are hosted at and supported by UoB.

A Relational Database Management System may be used to provide integration services between administrative and clinical databases. This data will be temporarily stored in a SQL Server system maintained by UoB, to support the workflow of the study team. This data will not be made available for analysis.

13.5.1 *Administrative Data*

Administrative data will be kept in a secure REDCap database that is only accessible from within the UoB firewall. All users will require (at least honorary) contracts with UoB to access it.

13.5.2 *Clinical Data*

The clinical data will be stored on a separate server to the administrative data. Anonymised clinical data is linked by a study identifier. If an email address is collected, the “email address” field is flagged as an identifier and not included in the export for the statistician, so the data set can be considered pseudonymised at export and does not need further processing.

13.6 Access to Data

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections, in line with participant consent.

The BTC IT Development Team will manage access rights to the data set under instruction from the trial manager (on behalf of the CI). Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released.

13.7 Access to the final trial dataset

Anonymous research data, which may include qualitative audio-recordings and/or associated data such as anonymised transcripts, will be stored securely and kept for future analysis with participant consent. We anticipate that anonymised trial data will be shared with other researchers to enable meta-analyses.

Members of the TMG will develop a data sharing policy consistent with University of Bristol policy. Data will be kept anonymous on research data storage facility (RDSF). Requests for access to data must be via a written confidentiality and data sharing agreements available from the RDSF website which will be confirmed by the CI (or appointed nominee).

The data sharing agreement should cover limitations of use, transfer to third parties, data storage and acknowledgements. The person applying for use of the data will be scrutinised for appropriate eligibility by members of the research team.

13.8 Archiving

The data custodian is the University of Bristol. Paper consent forms and CRFs will be stored and archived at the University of Bristol. All research data will be retained in a secure location during the conduct of the trial and until the youngest participant's 25th birthday, when all paper records will be destroyed by confidential means. An archiving plan will be developed for all trial materials in accordance with the University of Bristol archiving policy.

14. PUBLIC AND PATIENT INVOLVEMENT

This section describes how patients and members of the public have been, and will continue to be, involved in the design and delivery of this study.

14.1 Overview

We use the INVOLVE definition of Patient and Public Involvement in research, as being "Research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them."

We are dedicated to genuine PPI throughout our research, from design to dissemination. Continued involvement by parents of children with eczema will help the study to stay focused on delivering meaningful, clinically important answers. Our previous experience is that good PPI often heads-off problems and reassures the relevant regulatory authorities (sponsor, ethics committee, etc.) about the design and acceptability of clinical trials.

We will observe the six principles set out in the UK Standards for Public Involvement, by: [97]

- using plain language for well-timed and relevant communications;
- building and sustaining relationships, valuing all contribution;
- involving people in research governance, management and decision making;
- communicating with a wider audience about public involvement and research, using a broad range of approaches that are accessible and appealing.

We will prospectively record how parent and public members are involved, and how they influence decisions and actions, and report these at the end, using the GRIPP2 checklist. [98]

14.2 How patients and the public have been involved in developing this project

Patient and public involvement (PPI) runs through the study like the lettering on a stick of "Blackpool rock". The questions "What role might food allergy tests play in treating eczema?" and "What is the role of [exclusion] diets in treating eczema?" were identified by as a research priority for patients in a James Lind Alliance exercise. [35]

In the feasibility study, TEST:

- we conducted an online survey (152 parents of children with eczema), which confirmed the continued importance of these questions;
- we met three times with a group of parents of children with eczema;
- two lay contributors attended trial management group meetings and provided ad hoc input as required;
- one PPI representative sat on the trial oversight committee.
- PPI members reviewed and commented on the trial processes, patient facing documents and outputs, including participants newsletters and summaries.

We have presented and discussed our study with patients and stakeholders at meeting of national eczema charity (Eczema Outreach Support) and public engagement events.

In preparation for this application, recognising our need to focus the study on infants, we convened a new "public advisory group" of mothers of young children with eczema:

- At an introductory meeting (March 2020), recognising the importance of building and maintaining good relationships with lay contributors, contributors shared their own experiences as parents of children with eczema,

- The group then read and feedback on a document, which set out the need for, and challenges of conducting, a clinical trial
- At a follow-on meeting (June 2020), six parents from diverse backgrounds discussed the research question, what foods to test, how to deliver dietary advice and whether to offer a deferred allergy test to the comparator group.
- At a third meeting (October 2020), seven parents mutually shared their thoughts on the acceptability of the proposed changes from the feasibility trial, what they felt the most important outcome is and how they would feel about their infant having genetic testing as part of a trial (including any cultural or religious considerations).

In summary, the group:

- felt the research question was “strong”, “clear” and “made sense”;
- agreed with the choice of foods to test;
- suggested delivering the dietary advice via telephone, if not face to face, and following up with written advice;
- felt the proposed changes from the feasibility study and the addition of genetic testing were appropriate, though in the interest of child compliance and cultural differences, preference was made for sputum sampling rather than blood.
- identified infant nutrition and parent anxiety as important outcomes

14.3 Ways in which patients and the public will be actively involved in the project

We will ensure meaningful engagement with parents at all stage of the study. We aim to strike the right balance between keeping PPI contributors informed and involved, without over-burdening them. The foundations for mutually respectful and productive working together has been laid in our work with PPI pre-application.

The Centre for Academic Primary Care PPI coordinator will support the planning, organisation and running of PPI meetings and other communications, and will support PPI co-applicant and Trial Steering Committee members, providing or signposting to appropriate training and resources.

Our PPI co-applicant, Hannah Morgans, is a parent of a young child with eczema and food allergies. With support from the PPI coordinator, Ms Morgans will ensure representation of patient/carer perspectives and provide continuity with the Public Advisory Group for the duration of the study. She will be offered further formal (local courses) and informal (regular mentoring) support, and we have costed for her training, time and travel. “PPI” will be a standing item in Trial Management Group meetings, and the meeting chair/PPI coordinator will specifically seek lay opinion on matters as they arise.

We will continue to work with our public advisory group (of seven parents/carers). Comments and suggestions from members over the three previous meetings have shaped this application and all are interested in supporting the funded study by attending meetings and responding to requests by email. We plan to meet with them at least five times, which will provide opportunity for the research team to seek members’ opinions on questions and tasks arising during the study, from recruitment to interpretation of results and dissemination of findings:

1. An initial meeting to agree terms of reference and activities that will support PPI; review the aims and design of main trial; consider any feedback from the funding committee; and to

involve the group in the development of the protocol and design of study materials, helping ensure all patient-facing materials are as appealing and simple to understand as possible.
2. Early during the internal pilot, to review progress and to discuss/problem solve any issues (for example slow recruitment, low adherence, protocol deviations).
3. After the internal pilot, aims as per the second meeting.
4. At the end of recruitment, to discuss analysis and dissemination, planning pathways to impact.
5. At the end of the study, to assist with lay summaries and presentation of findings at local and national events.

We will also communicate between meetings via email and newsletters to help maintain engagement and provide feedback on study progress. We have costed for attendees' time and costs associated with preparing, attending and travelling to/from these meetings, as well as catering costs.

There will be a PPI member on the Trial Steering Committee, who will be offered the same training and reimbursement as co-applicant Morgans.

Finally, we will engage with the wider public via the study website and social media, for example X/Twitter and Facebook. We have discussed this proposal with the charities National Eczema Society, Eczema Outreach Support and Allergy UK, and will continue to update and invite involvement from them and their members.

15. MONITORING, AUDIT & INSPECTION

This section describes the procedures for monitoring, audit and inspection.

15.1 Monitoring

The trial will be monitored and audited in accordance with the sponsor's policy, which is consistent with the UK Policy Framework for Health and Social Care Research. All trial related documents will be made available on request for monitoring and audit by the sponsor, the relevant REC and other licensing bodies.

The University of Bristol holds a Service Level Agreement with University Hospitals Bristol and Weston NHS Foundation Trust (UHBW). Under the Agreement UHBW undertakes to monitor certain University of Bristol sponsored studies. These activities should be carried out in accordance with the Service Level Agreement.

The sponsor usually delegates some of the monitoring to the central research team. Checks of the following would be typical:

- written informed consent has been properly documented
- data collected are consistent with adherence to the trial protocol
- CRFs are only being completed by authorised persons
- SAE recording and reporting procedures are being followed correctly
- no key data are missing
- data is valid
- recruitment rates, changes in participation and losses to follow up.

We will also report to the DMC if requested, preliminary data on adverse event and dropout rates observed in the trial population.

15.2 Protocol compliance

There will be no prospective, planned deviations or waivers to the protocol. Accidental protocol deviations will be documented and reported to the CI and sponsor immediately. They will also be reported to the DMC. In the event of systematic protocol deviations, investigation and remedial action will be taken in liaison with the CI, DMC and the TMG.

15.3 Notification of Serious Breaches to GCP and/or the protocol

Any potentially serious protocol breach will be reported to the sponsor as soon as possible. The sponsor will determine whether it constitutes a serious breach, requiring onward reporting to the REC. A "serious breach" is a breach which is likely to effect to a significant degree:

a. the safety or physical or mental integrity of the subjects of the trial; or
b. the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. They will assess the seriousness of any breach as per the appropriate trial specific instructions.

16. ETHICAL AND REGULATORY CONSIDERATIONS

This section sets out the general guiding principles and specifics of ethical and regulatory approval of the study, including the safety of the interventions, financial and competing interests, indemnity arrangements and how amendments will be handled.

16.1 General principles

This trial will be conducted in accordance with:

- International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines
- UK Policy Framework for Health and Social Care Research
- Data Protection Act 2018
- General Data Protection Regulation

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.

Participation will be entirely voluntary. Information will be given to potential participants regarding what taking part in the trial involves, their right to stop participation and research dissemination plans. All research staff with participant contact will have current Good Clinical Practice (GCP) certification and undergo Disclosure and Barring Service (DBS) checks. Participants' GP surgeries will retain clinical responsibility and usual care otherwise will be unchanged. Participants will be free to stop participating in the study at any time.

16.2 Peer review

As part of the funding process, the study has undergone extensive, independent expert peer review, by members of the NIHR Health Technology Assessment committee, and by five external reviewers.

16.3 NHS Research Ethics Committee and Health Research Authority

Before the start of the trial, approval will be obtained from the Health Research Authority (which includes review by an NHS Research Ethics Committee) for the trial protocol, patient consent forms and other patient-facing documents.

Before any site can enrol participants into the trial, the CI or designee will obtain confirmation of capacity and capability for each site in-line with HRA processes along with other documentation required for the sponsor to grant sites with a sponsorship letter.

Participant recruitment will begin when sponsorship has been granted by the Sponsor. Substantial amendments will be reviewed by the Sponsor prior to submission for approval by Research Ethics Committee and Health Research Authority.

The research team will report to the Research Ethics Committee on an annual basis (within 30 days of the anniversary date on which the favourable opinion was given). The Research Ethics Committee will be notified of the end of the trial and a final report submitted within one year.

A copy of all correspondence with NHS Research Ethics Committee and Health Research Authority will be retained in the Trial Master File.

16.4 Participant safety

The trial and intervention have been designed to minimise the risk of participant harm.

16.4.1 *Faltering growth or abnormal weight gain*

Should concerns be raised, during the course of recruiting or follow-up of a participant, about their growth or weight (abnormal loss or gain, as defined by NICE), [99] [100] we will write to their GP to share this information and ask the parent to follow this up with them.

16.4.2 *Skin prick tests*

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[101]), with an excellent safety record. Many 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. [102] [103] 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). [104] 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. [105]

While approximately 1 in 1000 episodes of anaphylaxis are fatal, [104] [106] 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.

16.4.3 *Oral food challenges*

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. [107] [108] 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.

16.4.4 *Home dietary trials*

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

There is evidence that early introduction of some allergenic foods, peanut and hen's egg in particular, [27] in the diet of infants with eczema reduces the risk of food allergy developing. It is uncertain whether excluding these or other foods to which infants are sensitized but tolerant may increase the risk of food allergy developing, and if this is the case, how long after allergen exclusion this is likely to occur. However, it is common practice when non-IgE mediated food allergy is suspected to exclude/reintroduce foods over 4-6 weeks, with clinical consensus that this is an insufficient period for tolerance to be lost.

16.5 Financial and other competing interests

Dr Rosan Meyer has received honorarium for academic lectures from Nestle, Mead Johnson, Danone and Abbott. Rosan is also on an advisory board for Abbott and on the CoMiss board for Nestle.

Dr Sara J Brown holds a Wellcome Trust Senior Research Fellowship in Clinical Science (106865/Z/15/Z and 220875/Z/20/Z) and receives research funding from the British Skin Foundation, H2020 'BIOMAP' and anonymous philanthropic donors.

Dr Robert J Boyle received honoraria for participating in advisory boards for DBV technologies (2018) and Protatherapeutics (2019), who research or manufacture treatments for people with food allergy, and has acted as a paid expert witness in legal cases related to food anaphylaxis and infant formula health claims. He receives payment from Cochrane for his role as a Senior Editor, from Wiley publishers and the British Society for Allergy and Clinical Immunology for his role as Joint Editor-in-Chief for the journal Clinical and Experimental Allergy and from Public Health England for serving on the UK Nutrition and Health Claims Committee and the Maternal and Child Health Subgroup of SACN.

16.6 Indemnity

As sponsor, the University has Clinical Trial Insurance to cover the liability of the University to research participants arising from the design, management and conduct of the trial. The participant information leaflet provides a statement regarding indemnity.

16.7 Amendments

The research team may consider amendments at any time during a trial. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the Health Research Authority / Research Ethics Committee.

Any amendment will be prepared in line with the latest guidance from the Health Research Authority. The Sponsor will confirm ongoing sponsorship following approval of the amendment and prior to implementation.

Amendments will be recorded in the amendments section and the current version of the protocol will be available via the study website.

17. TRIAL MANAGEMENT GROUPS & COMMITEES

This section describes the roles and responsibilities of the various groups and committees or involved in trial coordination and conduct.

17.1 Host organisation: NHS Bristol, North Somerset and South Gloucestershire (BNSSG) ICB

NHS Bristol, North Somerset and South Gloucestershire (BNSSG) Integrated Care Board (ICB) is the host organisation. It will oversee the implementation of all aspects of the study and will ensure the trial meets its contractual, legal and financial obligations.

17.2 Trial management group

The Trial Management Group (TMG) will be led by Professor Ridd and will comprise all investigators (including PPI co-applicant). It will be responsible for trial design and delivery, including costs, data analyses and publication. The TMG will meet monthly to review detailed monitoring information regarding trial progress against the milestones outlined in the Gantt chart.

The trial manager will be responsible for operationalising TMG strategy and day-to-day trial management. She/he will lead monthly team meeting teleconferences (taking place between the monthly TMGs), consisting of all centre staff (researchers and administrator) to deliver the study.

17.3 Centre Management Groups

The Centre Management Groups located in Bristol, Manchester and Southampton will take responsibility for centre recruitment, with Principal Investigators (Ridd, Blakeman & Santer) meeting with centre teams weekly/fortnightly as required.

17.4 Bristol Trials Centre

Trial management across the three centres will be supported by the clinical trials unit, Bristol Trials Centre. They will develop, test and maintain the study databases; and monitor conduct/provide support and advice in the set-up, delivery and closedown of the study.

17.5 Oversight committees

We will establish a Trial Steering Committee (TSC) and Data Monitoring Committee (DMC), with terms of reference agreed for them to provide oversight of the trial on behalf of the NIHR HTA.[109 110] The primary role of the TSC will be to scrutinise trial progress and the DMC to monitor patient safety. We expect the committees to meet at five critical time points over the course of the study.

17.5.1 *Trial Steering Committee*

The TSC will make recommendations during the trial to the TMG and minutes will be sent to the funder. The TSC will comprise a chairperson, statistician, health economist, qualitative researcher and patient representative. The chief investigator and lead statistician will represent the TMG.

17.5.2 *Data Monitoring Committee*

The DMC will meet once prior to recruitment of the first participant and convene prior to the TSC meeting to review the adverse event data and any other ethical aspects that arise and report to the TSC. The DMC will comprise a chairperson, statistician and clinician as independent members. It will be attended by the chief investigator and lead statistician (open session only) and trial statistician (attending both open and closed sessions).

17.6 Sponsor: University of Bristol

The University of Bristol has agreed to be Trial Sponsor and will ensure the study meets its contractual, legal, insurance, financial and regulatory obligations, including the reporting of Serious Adverse Events (SAEs).

18. DISSEMINATION

A detailed plan for disseminating the trial results will be developed by the TMG.

Working with public contributors, we will develop and maintain a user-friendly website to publicise progress, stories and blogs to generate interest in the study. Through these mechanisms we will reach many of the clinical, academic and lay audiences who have an interest in the subject area. This will generate some pathways to impact at an early stage in the study.

In addition to our final report, we will publish the trial protocol and results in peer-reviewed journals and present at local, national and international meetings. Publications resulting from the quantitative and qualitative components of the study will cross-reference each other and include a universal trial reference number, so that the studies can be located more easily. We will of course feed the results back to participating GP surgeries and participants, including translated summaries.

We will disseminate the study findings to the wider NHS audience, via the Health Innovation Network (Network of Networks) and partner organisations such as Allergy UK, producing a range of tailored outputs that are appropriate for the end user (decision makers, patients, researchers and clinicians), for example executive ("actionable") summaries. In addition, we will produce a short video presentation/animation for sharing on websites such as YouTube, continuing medical educational websites and through local community organisations.

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20. APPENDIX

20.1 Amendment history

Version		Notes
Number	**Date**	
7.0	13DEC2024	Trial Summary: Study duration and end date updated. Key trial contracts: updates to various titles/institutions and trial website address. Changes throughout to reflecting the NIHR's restructuring and renaming (October 2024) of “Clinical Research Network (CRN)” to “Research Delivery Network (RDN)”. 7.2.2 Intervention design: Clarification on wheat and soya flour has been added.
6.0	09APR2024	Professor Coast (withdrew due to other commitments) and Dr Julie Clayton (moved onto another role) removed from list of co-investigators (“Key trial contacts” section). Ms. Kirsty Garfield's title changes to Dr. Trial Flow Chart updated recruitment of GP surgeries. PP-NRS moved from list of outcomes with “no licence” to “free commercial licence” (section 3.4.2). Revised text in the Table 1 Process measures (section 3.5). Revised text regarding translation and interpretation of study materials (section 4.4). Sentence removed related to the number of GP surgeries (in section 6.1) has been removed, and terms "RDNs" and "GPs at the deep end” network have been added. Addition of posters/flyers in local community dermatology/hospital clinics; and change of name (Twitter now “X”) and broadening of research team’s used of other social media options to promote study (section 6.3). Clarification of routes of participant recruitment into the study (invite from own GP surgery or opportunistic recruitment) and form of reminder to written invitation (letter, text or telephone call) from the practice (section 6.4). Clarification that patients at participating and non-participating GP surgeries may attend participating GP surgeries for baseline visits (section 6.8). Clarification that skin prick tests undertaken by the trained researcher or practice clinician (section 6.10). Clarification of frequency (up to three times a year) of participant newsletter (section 6.13).

		Qualification of target times for oral food challenges from point of referral (section 7.2.4) Updated predicted number of GP surgeries required (section 10.2). Additional words have been added: "Commissioners" and "Integrated Care Boards" (in section 12.3). Reference to Dr Clayton specifically supporting PPI removed (section 14.3). Addition of Research Delivery Networks (new name for Clinical Research Networks from 2024) and GPs at the deep end (section 6.1), Health Innovation Network (new name for Academic Health Science Networks, section 18) and correction and other minor errors throughout.
5.0 corrected version number	23AUG2023	Version number corrected on front page due to oversight in previous amendment.
5.0	23AUG2023	Clarification that samples may temporarily be stored at participating GP practices.
4.0	03APR2023	Addition of missing detail on protocol changes v2.0 to v3.0 (below) Addition of child's anthropometric measurements +/- saliva sample collection for DNA at follow-up visit (section 6.10.2) Correction of milk and egg allergens to commercial cow's milk and commercial white egg respectively (section 7.2.2) Exclude until allergy clinic review option added (section 7.2.4) "Home dietary trial of inclusion" box added to flowchart (figure 3). Correction to a typographical error (Sections 8.3.2. and 8.3.3.) Extra detail added to validation of proxy ModRUM questionnaire (as per DMC request, section 11.3).
3.0	16FEB2023	<u>Amendments made to address REC comments:</u> Added names of individuals leading the oral food challenges at allergy centres (section 4.2) Amended wording around participant compensation for loss of earnings in (sections 6.13, 11.3 and 12.3)
2.0	16JAN2023	Amendments made to address REC review comments.
1.0	10NOV2022	Submitted in original REC application, changes requested during initial review – not approved for use.