A randomised controlled double-blind trial assessing desensitisation to cow's milk, following partially or extensively hydrolysed formulae feeding regimens, in children with allergy to cow's milk (The DREAM study).

DREAM Protocol v3.0 23/06/2021

Trial Sponsor:
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ISRCTN: ISRCTN37753699

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PROTOCOL APPROVAL

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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 investigation without the prior written consent of the Sponsor.

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

Authorised by Chief Investigator:

Signature: Nikolaos Papadopoulos
Nikolaos Papadopoulos (Jun 23, 2021 20:54 GMT+3)

Date: Jun 23, 2021

Professor Nikolaos Papadopoulos
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Authorised on behalf of Sponsor:

Signature: Lynne Webster
Lynne Webster (Jul 5, 2021 12:32 GMT+1) **Date:** Jul 5, 2021

Dr Lynne Webster
Manchester University NHS Foundation Trust
Cobbett House
Manchester Royal Infirmary
Oxford Road
Manchester
M13 9WL

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

Authorised by the Lead Statistician:

Signature: Michaela Brown (Jun 24, 2021 11:46 GMT+1) **Date:** Jun 24, 2021

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General Information

This document describes the DREAM trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Liverpool Clinical Trials Centre (LCTC)) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator, Professor Nikolaos Papadopoulos, via LCTC.

This protocol defines the participant characteristics required for trial entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section 12.

This project will be conducted in accordance with the study protocol and the ethical principles outlined by Good Clinical Practice (GCP) and the Declaration of Helsinki in its most current version.

Relationship Statements

Roles and responsibilities are fully described in section 15.

Manchester University NHS Foundation Trust is the Sponsoring organisation and will formally delegate specific sponsoring roles to the Chief Investigator and Clinical Trials Unit, but remains legally responsible for the trial.

Clinical Trials Unit (CTU): The LCTC at the University of Liverpool in collaboration with the chief investigator, Professor Nikolaos Papadopoulos, will have overall management responsibility for the trial from a CTU perspective and will be responsible for the coordination of centres.

The Liverpool Clinical Trials Centre (LCTC) brings together a wealth of expertise built on the experience of the Liverpool Trials Collaborative which has held full registration status with the UK Clinical Research Collaboration CTU network since its establishment in 2007 (www.ukcrc.org). The LCTC has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and core standard operating procedures.

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Additional Contacts:

The contact details of other individuals involved in the trial are detailed in documents supplementary to the protocol and stored in the Trial Master File (TMF):

Contact	Document Title
Trial Management Group (TMG) Trial Steering Committee (TSC) Independent Data and Safety Monitoring Committee (IDSMC)	DREAM Trial Oversight Committee Membership
Principal Investigators (PIs)	DREAM Participating Centres

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Glossary

AE	Adverse Event
BSACI	The British Society for Allergy & Clinical Immunology
CI	Chief Investigator
CM	Cow's Milk
CMA	Cow's Milk Allergy
CRF	Case Report Form
CRN	Clinical Research Network
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
DBPCFC	Double Blind Placebo Controlled Food Challenge
DoH	Department of Health and Social Care
EASI	Eczema Area and Severity Index
eHF	Extensively Hydrolysed Formula
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
IDSMC	Independent Data and Safety and Monitoring Committee
IgE	Immunoglobin E
ISF	Investigator Site File
ISRCTN	International Standard Registered Clinical Study Number
LCTC	Liverpool Clinical Trials Centre
MHRA	Medicines and Health Care Products Regulatory Agency
NICE	National Institute for Health and Care Excellence
NIHR CRN	National Institute for Health Research Clinical Research Network
NRLS	National Reporting and Learning System
OIT	Oral Immunotherapy
pHF	Partially Hydrolysed Formula
PI	Principal Investigator
PIC	Patient Identification Centre
PISC	Parent Information and Consent form
R&D	Research & Development
REC	Research Ethics Committee
RN	Research Nurse (Registered)
RSI	Reference Safety Information
RSO	Research Support Office
RUSAE	Related Unexpected Serious Adverse Event
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPT	Skin Prick Test

TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

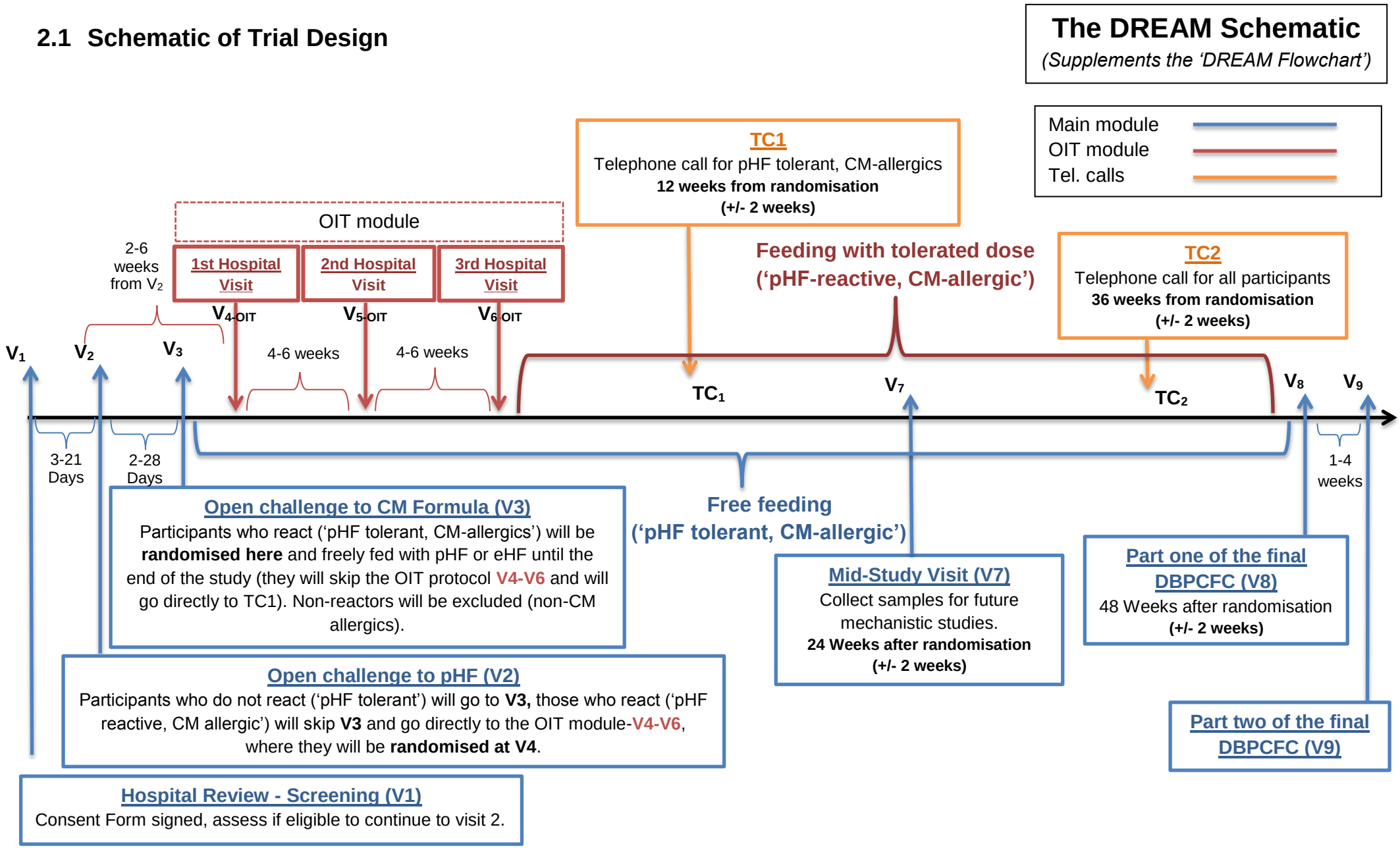
2 PROTOCOL SUMMARY

Full Title	A randomised controlled double-blind trial assessing desensitisation to cow's milk, following partially or extensively hydrolysed formulae feeding regimens, in children with allergy to cow's milk.
Acronym	DREAM
Phase	III
Target Condition	Infants aged 6 – 12 months with moderate-severe IgE-mediated Cow's Milk Allergy.
Sample size	206
Inclusion Criteria	The participant must fulfil *all* of the following criteria to be randomised in the study. Eligibility will be assessed in a staged manner: **Visit 1 Inclusion Assessments** 1. Infant aged 6 to 12 months, inclusive, at visit 1. 2. Convincing medical history of *IgE-mediated* allergic reaction following ingestion of cow's milk formula, as determined by trial physician. 3. Infant fed with formula, either exclusively or mixed with breastfeeding. 4. Weight of at least 7.5kg. 5. Written informed consent by parent/legal guardian prior to completing any study-related procedure. 6. Titre of cow's milk-specific IgE in serum, equal or higher to 2 kU/L (collected at visit 1, confirmed prior to visit 2/3), at inclusion **or** wheal reaction of equal or over 5mm to SPT* to CM at inclusion. **Visit 2/3 Inclusion Assessments** 7. Positive result in the challenge to pHF (V2) **or** positive result in the challenge to CM (V3). * SPT to whole, fresh milk
Exclusion Criteria	*Any* of the following will exclude someone from the study. Eligibility will be assessed in a staged manner: **Visit 1 Exclusion Assessments** 1. Unequivocal history of severe anaphylaxis to CM in the past requiring more than one dose of adrenaline. 2. Doctor diagnosis of *non IgE-mediated* allergy to cows' milk or cows' milk formula (eosinophilic esophagitis, gastritis, gastroenteritis, FPIES, enteropathies and proctocolitis). *Onset*

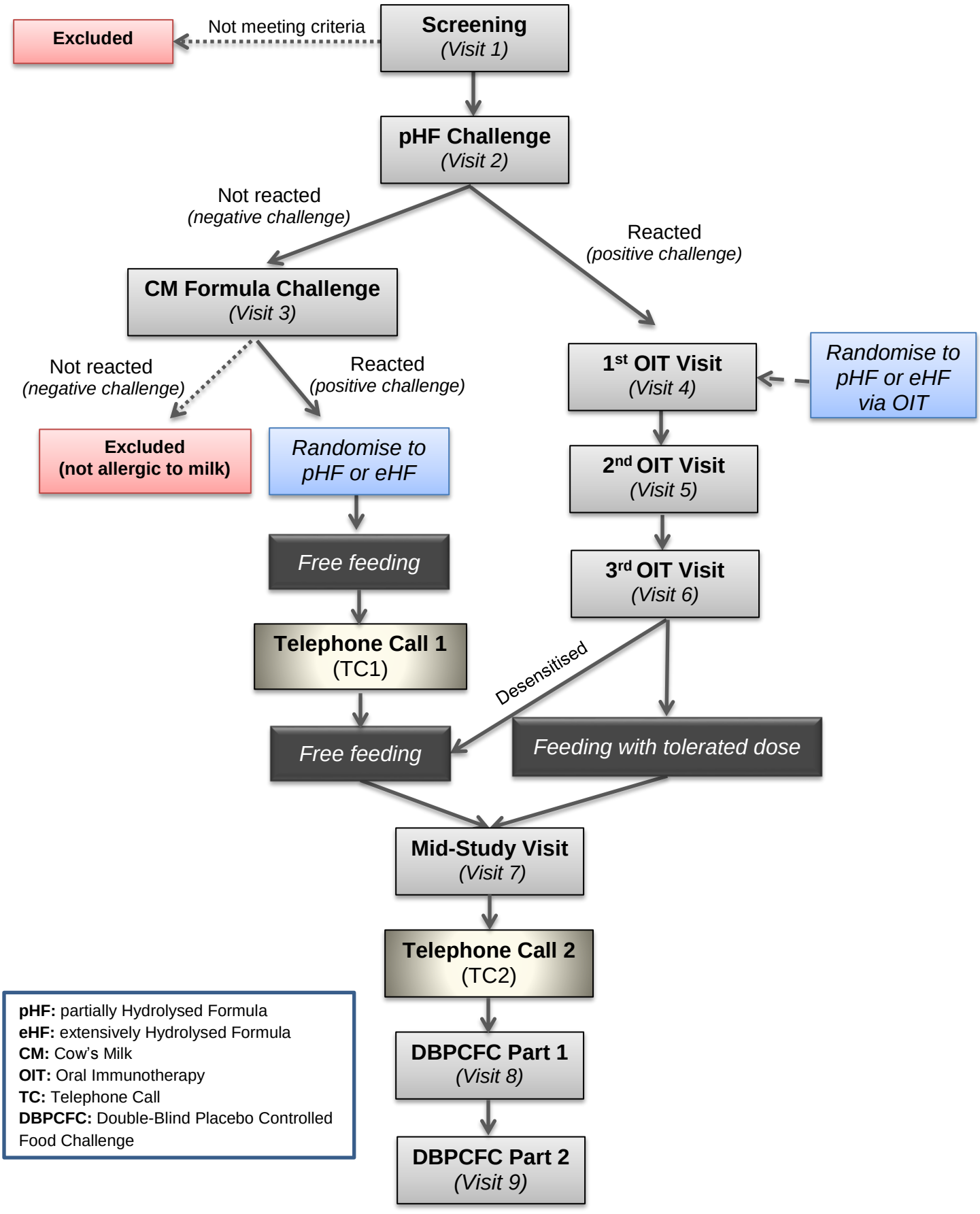
	or worsening of pre-existing eczema due to CM consumption is not an exclusion criterion. 3. Any significant clinical condition that may interfere with patient's safety or the study outcomes. These diseases include, but are not limited to, cardiovascular disease, malignancy, hepatic disease, renal disease, haematological disease, neurological disease, immunological and endocrine disease. 4. Requirement for continuous or frequent (monthly or more) intermittent use of oral corticosteroids for other conditions. 5. Requirement for pharmacotherapy for any other clinical condition, if it could interfere with the patient's safety or the study outcomes. 6. Parents or guardians, who, by investigator judgment, are unlikely to comply with the study protocol for any reason (language barrier, communication issues, inability to understand procedures, etc). 7. History of overnight hospitalisation (only A&E attendances not included) for wheeze and/or bronchiolitis on more than one occasion. 8. Currently participating in another clinical trial that may interfere with the patient's safety or the study outcomes. **Visit 2/3 Exclusion Assessments** 9. *Severe* anaphylaxis (anaphylaxis refractory to a single dose of intramuscular adrenaline) during challenge to pHF **or** CM.
Trial Centres and Distribution	Multicentre trial involving 12 tertiary care centres across the UK, that provide paediatric and allergy care and have the capacity to conduct food challenges to infants 6 months old or older.
Patient Study Duration	A maximum of 54 weeks post-randomisation.
Overall Study duration	Trial recruitment and follow-up duration: 4 years.
Description of Agent / Intervention	**Intervention:** Partially Hydrolysed Formula (pHF) **Control:** Extensively Hydrolysed Formula (eHF) (Normal clinical care)
Randomisation ratio	1:1
Primary objective	To determine whether one year of feeding with pHF is more efficacious than with eHF as a treatment for 6-12 month old infants with IgE-mediated CMA.

Secondary objectives	1. To evaluate the safety of feeding with pHF or eHF. 2. To determine whether one year of feeding with pHF is more efficacious than with eHF in inducing CM desensitisation for 6-12 months old *pHF-tolerant* infants with IgE-mediated CMA. 3. To determine whether one year of feeding with pHF is more efficacious than with eHF in inducing CM desensitisation for 6-12 months old *pHF-reactive* infants with IgE-mediated CMA. 4. To evaluate the efficacy of a pHF OIT regimen in pHF reactive infants. 5. To collect samples (stool, blood and buccal) to be stored for future investigations (these investigations are not part of the DREAM trial).
Primary outcome	Characterised as CM protein-tolerant in a double-blind, placebo-controlled food challenge 12 months after randomisation.
Secondary outcomes	1. The dose at which reactivity occurs in the DBPCFC 2. The maximal wheal size of skin prick test to cows' milk 3. Specific IgE levels to cows' milk, casein, a-lactalbumin and b-lactoglobulin 4. EASI scores for Eczema 5. Wheeze (during last 12 months, use of systemic steroids, hospitalisations) 6. Doctor diagnosis of other food allergies 7. Height 8. Weight 9. Adverse events

2.1 Schematic of Trial Design



2.2 Trial Flowchart



pHF: partially Hydrolysed Formula
eHF: extensively Hydrolysed Formula
CM: Cow's Milk
OIT: Oral Immunotherapy
TC: Telephone Call
DBPCFC: Double-Blind Placebo Controlled Food Challenge

3 INTRODUCTION

3.1 Background

Cow's Milk Allergy as an important health priority in the UK

IgE-mediated (immediate) Cow's Milk Allergy (CMA) is one of the most frequent food allergies in infants [1-7], with a significant adverse impact on quality of life (QoL). UK guidelines report prevalence in infancy of 1.8%-7.5% [1-8]. There is a significant unmet need for effective management. For example, hospitalisations for food allergy in the UK have increased >5-fold in the past decade [9], and CMA prevalence has risen by 700% since the 1990s [9]. Cow's milk (CM) is behind a continuously rising number of fatal episodes [10, 11] and is now the most common cause of fatal anaphylaxis in children in the UK and elsewhere [12, 13] causing 21% of anaphylaxis-related deaths in this age group [14]. Hence, there is a need for approaches that could speed up the outgrowth of CMA and prevent mortality. Mortality aside, CMA impacts greatly on QoL from an individual, household and societal perspective. Milk avoidance entails severe dietary limitations which could cause malnutrition [15, 16], and require long-term dietary counselling [15]. Additionally, CM is ubiquitous in our diet and complete avoidance is very difficult [17], hence QoL is further affected by the ever-present stress of a potentially severe accidental reaction; indeed, inadvertent intake of CM in processed foods is frequent, with as many as 40% of CMA children accidentally eating some form of milk within a single year [18]. These events are often associated with severe allergic reactions [18]. Furthermore, food allergy has been shown to underpin disruption of daily activities [19, 20], social limitations, self-esteem issues, and disturbed family cohesion [21, 22], during a critical period for the child's personality development.

Current management of cow's milk allergy and timelines of the project

There is no satisfactory treatment for CMA; the British Society for Allergy and Clinical Immunology (BSACI) guidelines recommend CM avoidance, feeding with 'hypoallergenic' formulas (extensively hydrolysed formulas – eHFs), emergency management of accidental reactions and waiting for the allergy to resolve spontaneously [23]. Feeding with processed CM products (the 'Milk Ladder') is also supported, but this approach is empiric and non-standardised [24]. Thus, CMA patients are currently advised to strictly avoid CM and may need to carry an adrenaline autoinjector to treat accidental reactions [18]. This, however, may fail to prevent mortality [25], further underscoring the inadequacy of current management. Furthermore, according to NICE guidelines, soya–based formulas are not suitable as first-line management for CMA and should only be used under exceptional circumstances with specialist advice (e.g. vegan parents, alternatives unacceptable). Soy formulas are not hypoallergenic and there is a high rate of reactions to soy in CMA infants (up to 35%) [26]. Additionally, soy formulas should not be used in infants under 6 months of age because of nutritional concerns, low absorption of minerals/trace elements and because they contain appreciable amounts of isoflavones [27, 28]. For the above reasons, in normal clinical care no approved management can lead to cure or expedite tolerance, highlighting the urgent need for novel management approaches.

The proposed project is timely from an additional perspective. For several decades the management of CMA has largely remained the same [15] due to a general view that CMA would 'spontaneously' resolve with no interventions. However, recent evidence shows that 'spontaneous' resolution of CMA is probably not as fast nor as certain as previously believed, and that the condition often persists into adulthood [16-19]. Indeed in a large cohort of moderate/severe CMA patients [29] the authors reported that only 21% of patients with severe CMA were tolerant by age 8 years, and 55% by age 16 years. Another study in such patients [30] demonstrated a resolution rate of just over 50% through age five, and in another study [31] CMA still persisted at age ten in 57% of the patients. This recent evidence indicates that CMA may

have a protracted course in more patients than previously expected, who may also remain allergic in adulthood. These patients, as shown by the researchers, are mainly the moderate/severe allergics with high CM-specific IgE titre and/or large CM Skin Prick Test (SPT) results.

3.2 Rationale

Currently, the only potentially curative regimen for CMA is Oral ImmunoTherapy (OIT), i.e. exposing patients with CMA to increasing doses of CM using a strictly-controlled schedule. However, OIT is not used in clinical practice due to risk of reactions [15, 32-35]. In the current literature, the importance of finding a novel management approach for milk allergy is reflected in the numerous OIT trials that were undertaken in the past or are currently underway [36-43]. These efforts are fuelled by a novel prevailing paradigm which suggests that allergy may be treated via early increasing allergen exposure (especially during infancy); this further emphasises the timeliness of this trial. An extensive literature search uncovers a large number of OIT studies with unmodified CM in older children; these have already proven in principle that this approach results almost uniformly in desensitisation and in many patients in complete tolerance [36-42]. Therefore, there is already ample proof of concept of the capacity of early feeding with the culprit food to expedite tolerance. However, adverse events are frequent with OIT, meaning that this is not currently an option in routine clinical practice [44]. Indeed, two recent systematic reviews including a Cochrane analysis [17, 45], and a European position paper from EAACI in 2018 [46] have underscored the potential of CM OIT to facilitate CMA resolution, but all reports note that this remains unrealised due to frequent adverse events. A novel form of management focusing on this already established premise, but with less or no adverse events could have significant health implications.

This context ideally sets the stage for the DREAM trial. However, this trial is essentially different from previous OIT trials in several critical aspects: OIT is typically used in patients >5 years old [36-43] (as second-line management when patients fail to develop natural tolerance); however the “window of immunologic susceptibility” is shown to be within infancy [47, 48] and it would therefore be more appropriate for OIT to start around that time. An important feature of this trial is that feeding will, indeed, start in infancy as first-line management; a trial of OIT in two-year-olds with CMA demonstrated a tolerance rate of up to 90% [49], providing strong evidence that the intervention is more successful when applied at a younger age. Another key feature that differentiates our trial from OIT trials is the use of pHF, which is processed in order to have lower allergenicity than normal CM [50, 51]. Although this is the first time that a pHF intervention will be used in a clinical trial, there is sufficient evidence to support the concept that regular intake of processed forms of CM favours resolution of CMA [52, 53]: it is well-established that frequent ingestion of baked milk (in which CM proteins are broken down due to baking, analogous to the consequences of processing of CM proteins in pHF) can facilitate tolerance induction in CMA patients [52, 53]. This is acknowledged in UK guidelines from the BSACI [23], which propose that CM reintroduction could start with less allergenic, processed forms in order to facilitate tolerance. This provides strong proof of concept that a formula appropriately processed to have reduced allergenicity (e.g. pHF) could facilitate disease resolution in patients with CMA. Additionally, use of a low-allergenic formula is likely to improve not only the efficiency of the intervention, but also its safety compared to conventional OIT. Indeed, most CMA patients can tolerate processed milk in various forms, e.g. up to 83% of CMA children tolerate baked milk [54-57], and 50%-70% tolerate pHF [58, 59]. Therefore, there exists available evidence of non-reactivity of the majority of CMA patients to processed milk, and to pHF in particular, further supporting another important feature of this trial that sets it apart from OIT trials, i.e. free-feeding. Most participants will be able to receive pHF freely, which is the ‘normal

routine' way of feeding formula to infants – a significant departure from strict dose-based OIT, and much easier to implement in routine care compared to dose-based regimens.

3.2.1 Risk and Benefits

3.2.1.1 Risks

The risks are the following:

- Infants may experience allergic reactions, including severe anaphylaxis, at any point throughout the trial: during the pHF challenge, the CM formula challenge, the DBPCFC, during OIT (potentially during the hospital visit or at home between visits) or during free-feeding. All care will be delivered by experienced personnel and infants will be monitored continuously during the challenges and OIT visits. Parents will be trained in identifying allergic reactions and managing them with the appropriate medication. They will also have been prescribed adrenaline autoinjectors to have at home and use if needed. The parents will be able to contact the clinical team to get advice. If anaphylaxis occurs, the parents will have been trained how to identify, manage it and contact emergency services. Infants that experience severe anaphylaxis during the early challenges will not be randomised and infants that experience severe anaphylaxis due to the trial products will stop receiving them and will return to standard care.
- There is a risk of bruising during venepuncture for blood sample collection, but this will likely be minor and transient. Venepuncture will be conducted by experienced personnel.

3.2.1.2 Benefits

The potential benefit of pHF is for infants to overcome their allergy faster. By being in the trial, more infants will have follow-up appointments with specialist health professionals, and parents will become more familiar with the condition and how to deal with any allergic reactions.

3.3 Hypotheses and Objectives

The primary hypothesis is that one year feeding with pHF will be more efficacious than with eHF in the treatment of 6–12 month-old infants with IgE-mediated CMA.

Secondary hypotheses are that:

1. one year feed with pHF will be as safe as with eHF for 6-12 month-old infants with IgE-mediated CMA
2. one year feeding with pHF will be more efficacious than with eHF in inducing CM desensitisation for 6-12 months old *pHF-tolerant* infants with IgE-mediated CMA
3. one year feeding with pHF will be more efficacious than with eHF in inducing CM desensitisation for 6-12 months old *pHF-reactive* infants with IgE-mediated CMA
4. infants who cannot tolerate pHF at the start of the study, will be able to tolerate it after a short Oral Immunotherapy Treatment (OIT) regimen to pHF

3.3.1 Primary Objective

The primary objective is to determine whether one year of feeding with pHF is more efficacious than with eHF as a treatment for 6-12 month old infants with IgE-mediated CMA.

3.3.2 Secondary Objective(s)

1. To evaluate the safety of feeding with pHF or eHF.
2. To determine whether one year of feeding with pHF is more efficacious than with eHF in inducing CM desensitisation for 6-12 months old *pHF-tolerant* infants with IgE-mediated CMA
3. To determine whether one year of feeding with pHF is more efficacious than with eHF in inducing CM desensitisation for 6-12 months old *pHF-reactive* infants with IgE-mediated CMA
4. To evaluate the efficacy of a pHF OIT regimen in pHF reactive infants
5. To collect samples (stool, blood and buccal) to be stored for future investigations (these investigations are not part of the DREAM trial)

3.4 Outcome measures/endpoints

3.4.1 Primary Outcome/Endpoint

The primary outcome is whether the infant is characterised as CM protein-tolerant as per the result of a double-blind, placebo-controlled food challenge (DBPCFC) which will take place 12 months after randomisation (randomisation will take place at V4 for pHF-reactive infants and V3 for pHF-tolerant infants).

3.4.2 Secondary Outcomes/Endpoints

1. The dose at which reactivity occurs in the DBPCFC
2. The maximal wheal size of skin prick test to cows' milk
3. Specific IgE levels to cows' milk, casein, a-lactalbumin and b-lactoglobulin
4. EASI scores for Eczema
5. Wheeze (during last 12 months, use of systemic steroids, hospitalisations)
6. Doctor diagnosis of other food allergies
7. Height
8. Weight
9. Adverse events from the visit where infants are put on the study product (V3 for 'pHF tolerant' and V4 for 'pHF-reactive' CMA infants) to the final visit (V9)

4 TRIAL DESIGN

This is a parallel-group, double-blind, randomised, normal-care-controlled trial that will evaluate the efficacy and safety of partially hydrolysed milk formula (pHF) freely fed to infants with moderate/severe CMA, in comparison to the current gold standard of feeding with extensively hydrolysed formula (eHF). At entry, patients with a history of CMA who meet specific criteria for moderate/severe CMA (Skin Prick Test (SPT) result to fresh CM of ≥ 5mm *or* a CM-specific IgE blood value of ≥2kU/L) and additional inclusion criteria will undergo a pHF food challenge and those who do not react will undergo an open challenge to normal CM formula to confirm that they are CM allergic. 'pHF tolerant, CM-allergic' infants (those that tolerated the pHF challenge but reacted to the CM challenge) will be randomised to receive either a free pHF or eHF diet (1:1 ratio) in a blinded manner for one year. Those that reacted to the pHF challenge ('pHF-reactive, CM-allergic' infants) do not need a CM challenge to confirm CM-allergy (reacting to pHF confirms CM allergy) and will be randomised for desensitisation by a blinded Oral Immunotherapy (OIT) protocol with either pHF or eHF (1:1 ratio), in order to be able to be freely fed with the respective formula after OIT. At the end of the pHF/eHF intervention, all infants will undergo a double-blind, placebo-controlled food challenge (DBPCFC) to CM which is the primary outcome of the trial, it will determine whether CMA has resolved and will uncover any differences in CM tolerance between the study groups.

There will be a two-stage internal pilot to assess the feasibility of recruitment. The first stage will last for 13 months from the date that the first site is opened to recruitment. At the end of that time, the following criteria will be assessed, and the study will continue unaltered if they are *all* met:
1) At least 20% of total sample size achieved (41 of the required 206 infants recruited)
2) At least 30% consent rate
3) Less than 20% drop-out rate

If fewer than 41 participants are recruited, ways to improve recruitment will be sought taking into consideration how much the recruitment falls short of the target: e.g. increasing number of recruiting sites, recruiting via additional pathways. If recruitment is significantly below expectations (less than 10% of the total required), terminating the trial will be considered.

If the consent rate is less than 30%, information collected on the reasons for non-consent will be used to identify any aspects amenable to change. If declining consent is predominantly due to parents not favouring this particular method of feeding after having full understanding of it, terminating the trial will be considered.

If drop-out rate is between 20-30%, appropriate actions will be taken: e.g. improve training of the researchers that interact with parents, improve training of parents, reassess the services of external contributors, reassess logistics for study product provision to parents, etc. If drop-out rate is over 30% and the main reason is inherently non-amenable to intervention (e.g. infants do not favour the study product and are not eating sufficient amounts, parents feel that the adverse events are not worth the effort, etc), terminating the trial will be considered.

The pilot will continue, and the next decision point will be after 25 months of recruitment. If at that time >60% of the required sample is recruited (124 participants), the trial will continue unchanged. If fewer than 124 participants are recruited (60%), ways to improve recruitment will be sought taking into consideration how much the recruitment falls short of the target: e.g. increasing number of centres, improving consent process to increase patient understanding, recruiting via additional pathways. If

recruitment is significantly below expectations (less than 50% of the total required - <103 infants), terminating the trial will be considered.

5 TRIAL SETTING AND SELECTION OF CENTRES / CLINICIANS

5.1 Selection of Centres/Clinicians

Criteria for the selection of centres will include:

- NHS Hospitals in the UK providing paediatric allergy care.
- Sufficient research capacity comprised of staff, time and facilities to undertake the trial, including patient screening and recruitment, randomisation, storage of trial product, collection and provision to the CTU of all required data, collection of research samples, identification and management of adverse events including notification to the CTU within protocol defined timeframes, identification and provision of information to the CTU of all protocol breaches.
- All staff contributing to the trial must have valid certified GCP training throughout the conduct of the trial. Requirements of the Sponsor are that renewal of GCP must occur every 3 years and the certificate should be provided to the CTU.
- Willingness to participate.

Final decisions on site selection will be determined by the Trial Management Group and will be described in the supplementary document 'DREAM Site Suitability Assessment'.

Initiation of centres will be undertaken in compliance with relevant LCTC SOPs. Centres fulfilling the criteria will be selected to be recruitment centres for the DREAM trial and will be opened to recruitment upon successful completion of all global (e.g. REC and HRA) and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to the CTU as detailed in the trial 'greenlight' checklist.

Participating centres will be listed in the DREAM Participating Centres log, maintained separately to the protocol.

6 STUDY POPULATION

6.1 Inclusion Criteria

The participant must fulfil *all* of the following criteria to be randomised in the study. Eligibility will be assessed in a staged manner:

6.1.1 Visit 1 Inclusion Assessments

1. Infant aged 6 to 12 months, inclusive.
2. Convincing medical history of *IgE-mediated* allergic reaction following ingestion of cow's milk formula, as determined by trial physician.
3. Infant fed with formula, either exclusively or mixed with breastfeeding.
4. Weight of at least 7.5kg.
5. Written informed consent by parent/legal guardian prior to completing any study-related procedure.
6. Titre of cow's milk-specific IgE in serum, equal or higher to 2 kU/L (collected at visit 1, confirmed prior to visit 2/3), at inclusion **or** wheal reaction of equal or over 5mm to SPT* to CM at inclusion

6.1.2 Visit 2/3 Inclusion Assessments

7. Positive result in the challenge to pHF (V2) **or** positive result in the challenge to CM (V3)

* SPT to whole, fresh milk

6.2 Exclusion Criteria

Any of the following will exclude someone from the study. Eligibility will be assessed in a staged manner:

6.2.1 Visit 1 Exclusion Assessments

1. Unequivocal history of severe anaphylaxis to CM in the past requiring more than one dose of adrenaline.
2. Doctor diagnosis of *non IgE-mediated* allergy to cows' milk or cows' milk formula (eosinophilic esophagitis, gastritis, gastroenteritis, FPIES, enteropathies and proctocolitis). *Onset or worsening of pre-existing eczema due to CM consumption is not an exclusion criterion*.
3. Any significant clinical condition that may interfere with patient's safety or the study outcomes. These diseases include, but are not limited to, cardiovascular disease, malignancy, hepatic disease, renal disease, haematological disease, neurological disease, immunological and endocrine disease.
4. Requirement for continuous or frequent (monthly or more) intermittent use of oral corticosteroids for other conditions.
5. Requirement for pharmacotherapy for any other clinical condition, if it could interfere with the patient's safety or the study outcomes.
6. Parents or guardians, who, by investigator judgment, are unlikely to comply with the study protocol for any reason (language barrier, communication issues, inability to understand procedures, etc).
7. History of overnight hospitalisation (only A&E attendances not included) for wheeze and/or bronchiolitis on more than one occasion.
8. Currently participating in another clinical trial that may interfere with the patient's safety or the study outcomes.

6.2.2 Visit 2/3 Exclusion Assessments

9. *Severe* anaphylaxis (anaphylaxis refractory to a single dose of intramuscular adrenaline) during challenge to pHF **or** CM.

6.3 Co-enrolment Guidelines

Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the DREAM trial this must first be discussed with the CTU who will contact the Chief Investigator Professor Nikolaos Papadopoulos.

7 PARTICIPANT TIMELINE, ASSESSMENTS AND PROCEDURES

	V_1 Screening visit	V_2 phf challenge	V_3 CM challenge [1]	V_4 1st OIT Visit [2]	V_5 2nd OIT Visit [2]	V_6 3rd OIT Visit [2]	TC1 Telephone call 1 [1]	V_7 Mid-study assessment	TC2 Telephone call 2 [3]	V_8 1st part DBPCFC to CM	V_9 2nd part DBPCFC to CM
ACTIVITY		3-21 Ds from V1	2-28 Ds from V2	2-6 Ws from V2	4-6 Ws from Randomisation (V4) [4]	8-12 Ws from Randomisation (V4) [4]	12 Ws (+/- 2) from Randomisation (V3)	24 Ws (+/- 2) from Randomisation (V3 or V4)	36 Ws (+/- 2) from Randomisation (V3 or V4)	48 Ws (+/- 2) from Randomisation (V3 or V4)	1-4 Ws from V8
Informed consent signed	X										
Assessment of eligibility	X	X	X								
Confirmation of eligibility			X	X							
Demographics & review of medical history and diet [5]	X										X
Assessment of Adverse events				X	X	X	X	X	X	X	X
Physical Examination, current medical history & vital signs [6]	X	X	X	X	X	X		X		X	X
Skin Prick Testing [7]	X									X	
Blood samples for antigen specific IgE [8]	X									X	
Blood samples for safety markers [9]	X										
Blood samples for storing [10]	X							X		X	
Buccal samples for storing [11]		X						X		X	
Provide stool sample containers		X	(X)			X		X			
Collection of stool samples for storing [12]			X	X				X		X	
Randomisation [13]			(X)	X							
Dispensing of randomised study product for home [14]			(X)	X	X	X					
Provide diary and instructions			(X)	X	X	X		X		X	
Collect and review Diary					X	X		X		X	X
Oral Immunotherapy (OIT)				X	X	X					
Oral Challenge and follow-up call		X	X							X	X
Telephone questions [15]							X		X		

[1] Only applicable to participants with a negative reaction to pHF at V2.

[2] Only applicable to participants with a positive reaction to pHF V2.

[3] Telephone call 2 will take place for all participants 36 weeks (+/- 2w) after randomisation.

[4] There must be at least 4 weeks between each of the OIT visits (V4, V5 and V6).

[5] *For visit 1:* Date of birth, birth weight, gestation time, gender, parity, race, number of siblings, family history of allergic disease (eczema-atopic dermatitis, Allergic rhinoconjunctivitis, asthma, food allergy) and other epidemiological characteristics. Details of any personal history of disease with focus on asthma, wheeze, urticaria and angioedema, atopic dermatitis, food allergies, and drug allergies. Concomitant medication.
For visit 9: Details of any personal history of disease with focus on asthma, wheeze, urticaria and angioedema, atopic dermatitis, food allergies, and drug allergies. Concomitant medication

[6] Weight, length, EASI score for eczema & history of wheeze. Safety assessments: General physical examination with chest auscultation, Peripheral arterial pulse, heart rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation.

[7] SPT for CM using whole, fresh milk, egg, House Dust Mite mix, cat dander, 6 grass pollen mix.

[8] Antigen-specific IgE to the following Antigens: CM, casein, alpha lactalbumin, beta lactoglobulin.

[9] Full blood count; Liver function tests, Urea, creatinine.

[10] Blood samples will be collected for storing, only from participants whose parents have provided consent for this additional sampling.

[11] Buccal samples will be collected for storing before the challenge starts, only from participants whose parents have provided consent for these additional samplings.

[12] Stool samples must be taken as close to the visit 3 (pHF negative participants) or visit 4 (pHF reactive participants), visit 7, and visit 8 date as possible, prior to the start of the challenge, and only from participants whose parents have provided consent for these additional samplings.

[13] Online randomisation as per the protocol.

[14] Provide the patient with formula, and make arrangements with Sharp to continue provision at patients home.

[15] The following will take place at telephone call 1 and 2:

1. Parents will be asked if they have any questions
2. They will be asked to confirm they are happy to continue with the trial
3. They will be asked if there was any problem with provision of the trial formula
4. They will be asked if they have been using the trial formula as advised
5. They will be reminded of the trial formula expiration and advised to discard any formula that has expired or exceeded the shelf life.
6. They will be asked if their child has had any allergic episode where they needed to use an EpiPen, or any other adverse events
7. They will be asked whether they have attended any unplanned visits and why;
8. They will be reminded to fill in the diary and if they have enough copies of the diary
9. They will be reminded of the date of their next visit
10. They will be asked whether their child has been introduced to any new foods

() Will take place, dependent on eligibility.

OIT Visits

Telephone calls

DBPCFCs

8 RECRUITMENT AND RANDOMISATION

8.1 Participant Identification

The following recruitment pathways will be used to identify potential participants for the DREAM trial. Other strategies will be considered if recruitment needs support, including Manchester-specific pathways of FARSITE and GP ScriptSwitch/pop-up.

8.1.1 Bounty

Bounty holds an extensive registry of infants-children, their age and other characteristics, with parental consent to contact. The following process will be undertaken approximately every 6 months (i.e. a total of six times) to parents of 5-11-month-old infants, thus reaching different individuals each time (as every six months, the pool of 5-11-month-old infants is renewed):

1. Emails will be sent out by Bounty to members of their register who are within a proximity of a participating site and are identified as parents/persons with parental responsibility of 6-12 month-old infants. Letters may also be sent in the future to aide recruitment if few responses are received.
2. The emails (and letters) will contain information about the trial and a link to an online survey. Conducting the survey via telephone may be considered for those that do not have internet access.
3. The survey will contain questions about the health of the infants, including potential milk-allergic and other symptoms. It will also include questions about the contact details of the parents.
4. Survey results (online and telephone) will be assessed by trained and delegated members of the research team at the University of Manchester, who will decide which infants are approached about the study, based on the inclusion/exclusion criteria. They will provide details to the local hospital who will invite the infant for a screening visit.
5. The decision of whether each patient will be invited will be recorded and kept along with reasons for those who are not invited.

8.1.2 Specialist Clinics, databases and other points of care

8.1.2.1 Clinics

1. For new patients seen in clinic with a presumed reaction to cow's milk and/or cow's milk products', parents will be given a brief information leaflet about the trial.
2. They will be given sufficient time to consider the information prior to being invited to a screening visit, which will take place at least 24 hours later.
3. Posters will also be displayed in clinics.

8.1.2.2 Databases

1. Clinic databases at participating sites will be searched by delegated members of the clinical teams at sites to identify potentially eligible patients.
2. Invitation letters and brief information leaflets will be posted to parents of potential participants, asking them to contact the researchers to discuss the trial.

3. This will be followed up with a phone call from a member of the local clinical care team within 15 days if there has been no contact.

8.1.2.3 Patient Identification Centres (PICs)

1. Potentially eligible patients will be identified at Patient Identification Centres (PICs) during routine clinic visits.
2. PIC site staff will introduce the study to parents of potentially eligible patients and, if interested and with their agreement, potential patients will be appropriately referred to the recruiting site.
3. The study will also be promoted using posters and information leaflets.

8.1.2.4 Other points of care

The study will be promoted by healthcare workers (clinicians, nurses, dietitians, etc.) who are assessing these children, and at participating sites where children present for emergency management of allergic reactions. When healthcare staff identify a potential candidate, they will provide them with information about the trial and advise them to call the researchers if interested. The study will also be promoted with posters/leaflets at these sites.

8.1.3 Trial promotion and advertisements

The trial will be advertised through newsletters and social media accounts of Anaphylaxis Campaign, Allergy UK, and other relevant organisations. The trial will also be promoted through the trial website and social media.

8.2 Screening Logs

A screening log will be maintained for the following groups of patients and returned to the LCTC on a regular basis, as this will provide important information for monitoring purposes:

- Patients who are identified as proceeding in section 8.1.1.
- All patients identified in section 8.1.2
- All patients assessed for eligibility but not randomised in visits 3 and 4

The screening log will capture which patients have been screened for the trial but assessed as ineligible, and those considered eligible and approached for consent but for whom consent was not obtained; reasons (all per patient) for non-inclusion will be recorded. Reasons for declining to participate will be asked routinely but it will be made clear that parents/persons with parental responsibility do not have to provide a reason unless happy to do so.

Screening logs will contain information on consented and non-consented patients. The data for those who are non-consented is considered fully anonymous to all individuals outside of the patient's usual clinical care team. Sites will maintain their own trial register linking patients screening and/or randomisation numbers to their identifiers. Under no circumstances will this log be returned to the LCTC.

Parents with a potentially eligible child will be invited to take part in the DREAM trial. If they are interested, parents and their infants will be invited to attend VISIT 1 (Screening Visit) and will be provided with a Parent Information Sheet and Consent form (PISC).

8.3 Informed Consent

Parents and those persons with parental responsibility may give consent for the patient to take part in DREAM; hereafter throughout this protocol they shall be referred to as 'parent(s)'. Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Written informed consent is required for all patients participating in LCTC coordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Informed consent must be obtained prior to any trial related procedures taking place.

8.3.1 Prospective Informed Consent Process

The Principal Investigator will ensure that written and informed consent is sought by any appropriately trained and delegated medical staff, and research nurses if local site policy allows. Proxy consent from the parents must be obtained prior to each infant participating in the trial and undergoing any study-specific procedures. This consent will be sought after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment, the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted.

The Parent Information Sheet and Consent (PISC) forms, describing in detail the trial treatment, procedures and risks will be approved by a Research Ethics Committee (REC) and the parent will be asked to read and review the document. Upon reviewing the document, the person seeking consent will explain the research study to the parent. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason, without this affecting future care. The parent will be given opportunity to ask any questions that may arise, and time to consider the information prior to agreeing to participate. A contact point where further information about the trial may be obtained will be provided on the PISC.

The parent will then sign and date the consent form if they agree to their infant participating in the trial. Both the person obtaining consent and the parent must personally sign and date the form at the same time, with the researcher completing their signature **after** the parent. Signing of the trial-specific consent form is the only method for valid consent for trial participation. Verbal consent, either in person or over the phone, is not acceptable in the DREAM trial. Consent provided on a generic consent form (i.e. not the REC-approved DREAM consent form) or by signature of any other document, for example the patient medical notes, is also not acceptable.

A copy of the signed PISC will be given to the parent for their records. The original copy will be filed in the Investigator Site File (ISF), a copy filed in the participant's medical notes and a further copy should be sent to the CTU via secure email or post within 7 days of completion, and separately to pseudonomised trial documents. A record of the consent process must also be documented in the participant's medical notes.

The right of a parent to refuse consent for the infant to participate in the trial without giving reasons will be respected. After the infant has entered the trial, the clinician will remain free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis.

Similarly, the parent remains free to withdraw the infant at any time from the protocol treatment and trial follow-up without being subject to any resulting detriment, by revoking the informed consent (see section 8.11.2 for further details). The rights and welfare of the patients will be protected by emphasising to their parents that the quality of medical care will not be adversely affected if they decline for their infant to participate in this study.

8.4 Enrolment/Baseline

8.4.1 Screening Visits and Confirmations of Eligibility

Informed consent will be obtained before proceeding with any study investigations.

8.4.1.1 VISIT 1 (Screening Visit)

Visit 1 will last up to 2-3 hours. In this visit, each participant's eligibility will be checked against the **inclusion and exclusion criteria** (see sections 6.1.1 and 6.2.1). Evidence for the participant's eligibility will be collected and recorded in the patient's medical records.

Participants will undergo the following assessments:

1. Obtain informed consent: See section 8.3.

2. Demographics & full medical history and diet: Date of birth, birth weight, gestation time, gender, parity, race, number of siblings, family history of allergic disease (eczema-atopic dermatitis, Allergic rhinoconjunctivitis, asthma, and food allergy) and other epidemiological characteristics. Details of any personal history of disease with focus on asthma, urticaria and angioedema, atopic dermatitis, food allergies, and drug allergies. Concomitant medication.

3. Physical Examination, current medical history & vital signs: Weight, length, EASI Score & history of wheeze. The following will be confirmed to be normal and a statement to this effect recorded in the medical notes: general physical examination with chest auscultation, Peripheral arterial pulse, heart rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation.

4. Skin prick tests: will be conducted for cows' milk using whole, fresh milk, egg, House dust mite mix, cat dander, 6 grass pollen mix.

5. Blood sample for antigen-specific IgE to the following antigens: IgE levels to CM (CM-IgE), Alpha lactalbumin (ALA-IgE), beta lactoglobulin (BLG-IgE), and casein (Cas-IgE).

6. Safety blood tests: The following will be confirmed to be normal and a statement to this effect recorded in the medical notes:

- **Haematology:** Full blood count
- **Biochemistry:** Liver function tests; Urea; creatinine.

7. Collection of blood samples for storing: These will be collected only where **consent** has been provided and processed and stored locally until transferred to the central laboratory.

8. Assessment of eligibility: All laboratory results will be reviewed prior to proceeding to VISIT 2 (Open Challenge to pHF). A medically qualified doctor authorised on the site Delegation Log will compare the results against the inclusion/exclusion criteria (see sections 6.1.1 and 6.2.1) and will indicate if they are met. Confirmation of eligibility will be recorded in the patient's **medical notes** and on the Eligibility CRF by the delegated clinician.

8.4.1.2 VISIT 2 (Open Challenge to pHF)

Visit 2 will take place min: 3 days, max: 21 days after visit 1. Participants will be monitored by a delegated clinician, supported by delegated nurse(s), and will remain in the department for up to 8 hours, as appropriate. In rare cases and if they experience severe anaphylaxis, they may need to be hospitalised overnight, as per the clinical judgment of the clinician.

Participants will undergo the following assessments:

1. Physical Examination, current medical history & vital signs: Weight, length, EASI Score & history of wheeze. The following will be confirmed to be normal and a statement to this effect recorded in the medical notes: General physical examination with chest auscultation, Peripheral arterial pulse, heart rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation.

2. Collection of buccal samples for storing: These will be collected only where **consent** has been provided, before the start of the challenge and stored locally until transferred to the central laboratory.

3. Open challenge to pHF: as per the trial SOPs. Results of the challenge must be recorded in the **participant's medical notes**.

4. Reassessment of eligibility: A medically qualified doctor authorised on the site Delegation of Authority and Signature Log must confirm full eligibility of the patient for patients with a positive result at this challenge (see section 6). A record of this confirmation must be made in the patient's medical notes and appropriate CRF.
   In the event of weight loss during the trial screening period, randomisation may be postponed until the required weight is achieved, providing all other inclusion criteria are met and visits fall within the required timeframes.

- **Participants with a *negative* result at this challenge will proceed to VISIT 3 (Open Challenge to CM Formula).**
- **Participants with a *positive* result at this challenge will skip visit 3, and will proceed directly to VISIT 4 (OIT Visit 1).**

Provide stool sample containers for the next visit: Provide eligible participants with containers for the collection of stool samples at home. Parents should take samples as close to the visit 3 (pHF tolerant participants) or visit 4 (pHF reactive participants) dates as possible, prior to the start of the challenge, and only from participants whose parents have provided **consent** for these additional samplings.

5. Follow up communication: A follow-up communication (phone/email) will take place within 48 hours to check for late AEs. Any late symptoms should be recorded in the **participant's medical notes**, and the clinician should assess if they are possibly associated with the challenge and record this in the participant's medical notes and transcribed onto the CRFs.

8.4.1.3 VISIT 3 (Open Challenge to CM Formula)

Visit 3 will take place min:2 days, max:4 weeks after visit 2. Participants will be monitored by a delegated clinician, supported by a delegated nurse(s) and will remain in the department for up to 8 hours, as appropriate. In rare cases and if they experience severe anaphylaxis, they may need to be hospitalised overnight, as per the clinical judgment of the clinician.

Participants will undergo the following assessments:

1. Physical Examination, current medical history & vital signs: Weight, length, EASI Score & history of wheeze. The following will be confirmed to be normal and a statement to this effect recorded in the medical notes: General physical examination with chest auscultation, Peripheral arterial pulse, heart rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation.

2. Collect stool samples: These will be collected only where **consent** has been provided and stored locally until transferred to the central laboratory.

3. Open challenge to CM Formula: as per the trial SOPs. Results of the challenge must be recorded in the **participant's medical notes**.

4. Reassessment and confirmation of eligibility: A medically qualified doctor authorised on the site Delegation of Authority and Signature Log must confirm full eligibility of the patient (see section 6). A record of this confirmation must be made in the patient's medical notes and appropriate CRF.
   In the event of weight loss during the trial screening period, randomisation may be postponed until the required weight is achieved, providing all other inclusion criteria are met and visits fall within the required timeframes.

5. Allocation to a randomised treatment (if meeting criteria as follows) see section 8.5 for randomisation procedures:

   - **Participants with a *negative* result at this challenge will not be randomised; they will not proceed any further in the trial.**
   - **Participants with a *positive* result at this challenge will be randomised *and* will skip visits 4, 5 and 6, *and* will proceed directly to VISIT 7 (Mid Trial Visit).**

6. Prescribe adequate amount of allocated study product for home: Complete study prescription for the pharmacy/unblinded team to dispense the allocated study product to ***randomised participants***. An adequate number of tins should be prescribed to supply the participant with enough formula to last until further product is received at home. Pharmacy/unblinded team will also complete appropriate accountability logs and the Sharp product request form to request further product for home delivery using the appropriate request form.

7. Providing diary and instructions for use: Give ***randomised participants*** diaries and instructions for filling in.

8. Provide stool sample containers for the next visit: Provide eligible participants with containers for the collection of stool samples at home. Parents should take samples as close to visit 7 as possible, and only from participants whose parents have provided **consent** for these additional samplings.

9. Follow up communication: A follow-up communication (phone/email) will take place for all challenge participants regardless of whether they were randomised within 48 hours. Any late symptoms should be recorded in the **participant's medical notes**, and the clinician should assess if they are possibly associated with the challenge and record this in the participant's medical notes and transcribed onto the CRFs.

8.5 Randomisation Procedures

Participants will be randomised to receive either normal care (eHF) or the intervention (pHF) in a 1:1 ratio once:

a. Fully informed written consent/proxy consent has been obtained.
b. Eligibility criteria have been fulfilled as confirmed by a medically qualified doctor.
c. Baseline assessments have been completed.

Participants will be randomised at visit 3 or 4 using a secure (24-hour) web-based randomisation programme controlled centrally by the LCTC. A personal login username and password, provided by the LCTC, will be required to access the randomisation system; designated research staff will be issued with their personal login and password upon completion of training in the use of the system.

When the system requirements (consent, eligibility and baseline assessments at visits 1, 2 and 3) are confirmed, a unique study number (randomisation number) will be displayed on a secure webpage and an automated email confirmation will be sent to the authorised randomiser, PI and Trial Manager – this will not contain the treatment allocation. A separate email containing the treatment allocation will be sent to members of the pharmacy department or appropriate unblinded staff members responsible for dispensing the study formula, and Sharp. It is the responsibility of the PI or delegated research staff to inform the pharmacy department at their centre prior to randomisation to ensure there is sufficient supply of the study treatments.

Randomisation: web access https://ctrc.liv.ac.uk/Randomisation/DREAM

If there are any problems with the randomisation systems contact the LCTC on 0151 795 8781 or via email on DREAM@liverpool.ac.uk

(Note that the LCTC is open from 0900 – 1700, Monday – Friday, excluding public holidays and University of Liverpool closure days.)

In the event of a randomisation system failure, the centre should contact the coordinating team in CTU (Monday to Friday between 9:00 to 17:00 excluding bank holidays and University of Liverpool closure days) to try to resolve the problem. If the problem cannot be resolved the coordinating CTU will perform central randomisation and randomise the participant using the back-up randomisation system. The back-up randomisation system is an exact replica of the live system but is based on a standalone PC at CTU.

8.6 Who is Blinded to Allocations

Parents of participants, LCTC staff (excluding statistical team members as appropriate) and all members of the site research teams managing trial participants will be blinded to treatment allocations.

Nutricia will provide matched pHF and eHF tins with blinded labelling. The formulas themselves will not be processed for blinding and will be altered in no way from the original market-approved products. This means that the products will not be exactly identical, but they are similar and it is expected that unless the parents actively go to great lengths to break the blind, the blinding will be preserved.

Nutricia will also label tins with unique tin numbers. When Nutricia send tins to Sharp, they will also provide a tin allocation list detailing which tins are eHF and which are pHF. The unblinded statistician at LCTC will also receive this list.

When Sharp send tins to pharmacies or appropriate unblinded staff, they will also provide a tin allocation list detailing which of the received tins are eHF and which are pHF.

When pharmacy or unblinded staff dispense initial tins to participants, they will record which tin numbers have been dispensed. Similarly, when Sharp send additional tins to participants, they will record which tin numbers have been provided.

8.7 Schedule for Follow-up

8.7.1 Oral ImmunoTherapy (OIT) Visits

Participants will undergo several increasing doses of their allocated formula during each OIT visit. Please see study OIT SOP.

8.7.1.1 VISIT 4 (OIT Visit 1)

Visit 4 will be conducted 2-6 weeks after visit 2 (these participants skipped visit 3) and will take up to 8 hours.

Participants will undergo the following assessments:

1. Confirm eligibility to continue participation.

2. Allocation to randomised treatment: Participants attending visit 4 (these are the participants with a positive result to VISIT 2 (Open Challenge to pHF) will be randomised (see section 8.5).

3. Collect stool samples: These will be collected only where **consent** has been provided and stored locally until transferred to the central laboratory.

4. Physical Examination, current medical history & vital signs to be assessed prior to OIT schedule: Weight, length, EASI Score & history of wheeze. The following will be confirmed to be normal and a statement to this effect recorded in the medical notes: General physical examination with chest auscultation, Peripheral arterial pulse, heart rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation.

5. OIT dose escalation schedule: will be conducted as per the trial OIT SOPs. Results of the OIT must be recorded in the **participant's medical notes**.

6. Prescribe allocated study product for home: Complete study prescription for the pharmacy/unblinded team to dispense an adequate amount of the allocated study product. An adequate number of tins should be prescribed to supply the participant with enough formula to last until the next visit (or until further product is received at home if no further OIT visits are required). Pharmacy/unblinded team will complete appropriate accountability logs and, if necessary, the Sharp product request form to request further product for home delivery using the appropriate request form.

7. Provide diary and instructions for use: Give participants diary and instructions for filling in.

8. Record AEs: Any AEs occurring from this visit must be recorded in the participant's medical notes and on the AE Log (see section 10).

8.7.1.2 VISIT 5 (OIT Visit 2)

Visit 5 will be conducted 4-6 weeks after randomisation (visit 4) and will take up to 8 hours. Note that there must be at least 4 weeks between each OIT visit (visits 4, 5, and 6).

Participants will undergo the following assessments:

1. Confirm continuation of participation.

2. Physical Examination, current medical history & vital signs to be assessed prior to OIT schedule: Weight, length, EASI Score & history of wheeze. The following will be confirmed to be normal and a statement to this effect recorded in the medical notes: general physical examination with

chest auscultation, Peripheral arterial pulse, heart rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation.

3. Unplanned visits: Any unplanned visits since the last visit and the reason for the visit, will be captured.

4. Collect diary from previous visit: Collect completed diary pages from previous visit and review. Any AEs will be recorded in the participant's medical notes and on the AE Log.

5. OIT dose escalation schedule: will be conducted as per the trial OIT SOPs. The participant will escalate to higher doses than the previous visit. Results of the OIT must be recorded in the **participant's medical notes**.

9. Prescribe allocated study product for home: Complete study prescription for the pharmacy/unblinded team to dispense an adequate amount of the allocated study product. An adequate number of tins should be prescribed to supply the participant with enough formula to last until the next visit (or until further product is received at home if no further OIT visits are required). Pharmacy/unblinded team will complete appropriate accountability logs and, if necessary, the Sharp product request form to request further product for home delivery using the appropriate request form.

6. Providing diary and instructions for use: Give participants diary and instructions for filling in.

7. Record AEs: Any AEs occurring from this visit must be recorded in the participant's medical notes and on the AE Log (see section 10).

The participants will be advised to continue dosing at home after this visit, with doses slightly lower to the one they managed to tolerate at this visit, as per the trial OIT SOPs.

8.7.1.3 VISIT 6 (OIT Visit 3)

Visit 6 will be conducted 8-12 weeks after randomisation and will take up to 8 hours. Note that there must be at least 4 weeks between each OIT visit (visits 4, 5, and 6).

Participants will undergo the following assessments:

1. Confirm continuation of participation.

2. Physical Examination, current medical history & vital signs to be assessed prior to OIT schedule: Weight, length, EASI Score & history of wheeze. The following will be confirmed to be normal and a statement to this effect recorded in the medical notes: general physical examination with chest auscultation, Peripheral arterial pulse, heart rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation.

3. Unplanned visits: Any unplanned visits since the last visit and the reason for the visit, will be captured.

4. Collect diary from previous visit: Collect completed diary pages from previous visit and review. Any new AEs will be recorded in the participant's medical notes and on the AE Log and any previous AEs will be followed-up and marked as resolved if appropriate.

5. OIT dose escalation schedule: will be conducted as per the trial OIT SOPs. The participant will escalate to higher doses than the previous visit. Results of the OIT must be recorded in the **participant's medical notes**.

6. Prescribe adequate amount of allocated study product for home: Complete study prescription for the pharmacy/unblinded team to dispense the allocated study product to ***randomised participants***. An adequate number of tins should be prescribed to supply the participant with enough formula to last until further product is received at home. Pharmacy/unblinded team will also complete appropriate accountability logs and the Sharp product request form to request further product for home delivery using the appropriate request form.

7. Provide diary and instructions for use: Give participants diary and instructions for filling in.

8. Record AEs: Any AEs occurring from this visit must be recorded in the participant's medical notes and on the AE Log (see section 10).

9. Provide stool sample containers for the next visit: Provide parents with containers for the collection of stool samples at home. Parents should take samples as close to visit 7 as possible, and only from participants whose parents have provided **consent** for these additional samplings.

The participants will be advised to continue dosing at home after this visit, with doses close to the one they managed to tolerate, or feed freely, as per the trial OIT SOPs.

8.7.2 Telephone Calls

There will be two telephone calls as below:

- **Telephone call 1:** Telephone call 1 is for participants who do not undergo OIT. It will take place 12 weeks (+/- 2w) after randomisation. There will be no telephone call 1 for participants undergoing OIT as these participants will remain engaged with the researchers through the OIT visits.

- **Telephone call 2:** Telephone call 2 will take place for all participants 36 weeks (+/- 2w) after randomisation.

The following will take place for telephone call 1 and 2:

1. Parents will be asked if they have any questions;
2. They will be asked to confirm they are happy to continue with the trial;
3. They will be asked if there was any problem with provision of the trial formula;
4. They will be asked if they have been using the trial formula as advised;
5. They will be reminded of the trial formula expiration and advised to discard any formula that has expired or exceeded the shelf life.

6. They will be asked if their child has had any allergic episode where they needed to use an EpiPen, or any other adverse events;
7. They will be asked whether they have attended any unplanned visits and why;
8. They will be reminded to fill in the diary and asked if they have enough copies of the diary;
9. They will be reminded of the date of their next visit;
10. They will be asked whether their child has been introduced to any new foods.

8.7.3 Mid-Trial Visit

8.7.3.1 VISIT 7 (Mid Trial Visit)

Visit 7 will be conducted 24 weeks (+/- 2 weeks) from randomisation and will last up to two hours. Adherence to treatment will be checked by the research team by reviewing the diary. AEs will be reviewed and recorded **in the participant's medical notes**.

Participants will undergo the following assessments:

1. Continuation of participation will be reconfirmed.

2. Physical Examination, current medical history & vital signs: Weight, length, EASI Score & history of wheeze. The following will be confirmed to be normal and a statement to this effect recorded in the medical notes: general physical examination with chest auscultation, Peripheral arterial pulse, heart rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation.

3. Collection of Buccal samples, blood samples and stool samples for storing: These will be collected only where **consent** has been provided, and stored locally until transferred to the central laboratory.

4. Unplanned visits: Any unplanned visits since the last visit and the reason for the visit, will be captured.

5. Collect diary from previous visit: Collect completed pages from previous visit and review. Any new AEs will be recorded in the participant's medical notes and on the AE Log and any previous AEs will be followed-up and marked as resolved if appropriate.

6. Provide diary and instructions for use: Give participants diary and instructions for filling in.

7. Provide stool sample containers for the next visit: Provide parents with containers for the collection of stool samples at home. Parents should take samples as close to visit 8 at possible, prior to the start of the challenge, and only from participants whose parents have provided **consent** for these additional samplings.

8. Record AEs: Any AEs occurring from this visit must be recorded in the participant's medical notes and on the AE Log (see section 10).

9. Record any new foods: Any new foods that have been introduced since the start of the study must be recorded in the participant's medical notes and appropriate CRF.

8.7.4 Double-blind Placebo Controlled Food Challenge (DBPCFC)

8.7.4.1 VISIT 8 (DBPCFC Day 1)

Visit 8 will be conducted 48 weeks (+/- 2 weeks) from randomisation. This visit entails Day 1 of the DBPCFC, to CM product as per the trial DBPCFC SOPs. Participants will be monitored by a delegated clinician, supported by delegated nurse(s) and will remain in the department for up to 8 hours, as appropriate. In rare cases and if they experience severe anaphylaxis, they may need to be hospitalised overnight, as per the clinical judgment of the clinician.

Participants will undergo the following assessments:

1. Confirm continuation of participation.

2. Physical Examination, current medical history & vital signs: Weight, length, EASI Score & history of wheeze. The following will be confirmed to be normal and a statement to this effect recorded in the medical notes: general physical examination with chest auscultation, Peripheral arterial pulse, heart rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation.

3. Skin prick tests: will be conducted for cows' milk using whole, fresh milk, egg, House Dust Mite mix, cat dander, 6 grass pollen mix.

4. Blood sample for Antigen-specific IgE to the following Antigens: IgE levels to CM (CM-IgE), Alpha lactalbumin (ALA-IgE), beta lactoglobulin (BLG-IgE), and casein (Cas-IgE).

5. Collection of Buccal samples, blood samples and stool samples for storing: These will be collected only where **consent** has been provided, before the start of the challenge and stored locally until transferred to the central laboratory.

6. Challenge Day 1: Will be conducted as per the trial DBPCFC SOPs. Results of the DBPCFC must be recorded in the **participant's medical notes**.

7. Collect diary from previous visit: Collect completed diary pages from previous visit and review. Any new AEs will be recorded in the participant's medical notes and on the AE Log and any previous AEs will be followed-up and marked as resolved if appropriate.

8. Provide diary and instructions for use: Give participants diary and instructions for filling in.

9. Record AEs: Any AEs occurring from this visit must be recorded in the participant's medical notes and on the AE Log (see section 10).

10. Request for any unused tins to be returned at the next visit: Ask parents to return any unused tins at the next visit.

11. Follow up communication: A follow-up communication (phone/email) will take place within 48 hours, as per the SOPs. Any late symptoms should be recorded in the participant's medical notes, and the clinician should assess if they are possibly associated with the challenge and record this in the participant's medical notes and transcribed onto the CRFs.

8.7.4.2 VISIT 9 (DBPCFC Day 2)

Visit 9 will be conducted 1-4 weeks from visit 8. This visit entails Day 2 of the DBPCFC to CM, as per the trial DBPCFC SOPs. Participants will be monitored by a delegated clinician, supported by delegated nurse(s), and will remain in the department for up to 8 hours, as appropriate. In rare cases and if they experience severe anaphylaxis, they may need to be hospitalised overnight, as per the clinical judgment of the clinician.

Participants will undergo the following assessments:

1. Confirm continuation of participation.

2. Physical Examination, current medical history & vital signs: Weight, length, EASI Score & history of wheeze. The following will be confirmed to be normal and a statement to this effect recorded in the medical notes: general physical examination with chest auscultation, Peripheral arterial pulse, heart rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation.

3. Collect diary from previous visit: Collect completed diary pages from previous visit and review. Any new AEs will be recorded in the participant's medical notes and on the AE Log and any previous AEs will be followed-up and marked as resolved if appropriate.

4. Demographics & review of medical history and diet: Details of any personal history of disease with focus on asthma, wheeze, urticaria and angioedema, atopic dermatitis, food allergies, and drug allergies. Concomitant medication

5. Challenge Day 2: Will be conducted as per the trial DBPCFC SOPs. Results of the DBPCFC must be recorded in the **participant's medical notes**. Unblinding of the challenge will take place as per the SOPs.

6. Record AEs: Any AEs occurring from this visit must be recorded in the participant's medical notes and on the AE Log (see section 10).

    - **DBPCFC negative: Participants with a negative result to both days of the DBPCFC will be provided with advice for re-introduction of milk into the diet.**
    - **DBPCFC positive: Participants with a positive result to either day of the DBPCFC should be provided with clinical advice for ongoing CMA management at the clinician's discretion.**

7. Collect any unused tins from parents: Collect any returned tins for destruction. Record returns and destruction in the appropriate accountability log.

8. Follow up communication: A follow-up communication (phone/email) will take place within 48 hours, as per the SOPs. Any late symptoms should be recorded in the participant's medical notes, and the clinician should assess if they are possibly associated with the challenge and record this in the participant's medical notes and transcribed onto the CRFs.

8.8 Procedures for assessing Efficacy

8.8.1 Efficacy assessment 1- Double blind food challenge

The DBPCFC to a specialised CM formula-based meal, provided by REACTA biotech, will take place at the end of the trial (V8 and V9). Briefly, this entails one day when the infants will be given a specialised CM-containing product in ascending doses, and one day where they will be given doses of a similar but non-CM-containing product (placebo). The challenge will be deemed positive if sufficient objective allergic symptoms are seen. Participants will be characterised according to their challenge outcome as CM protein-allergic (reaction on CM day but no reaction on placebo day), CM protein-tolerant (do not react on either the CM or the placebo day), or inconclusive (reacted in placebo day, did not finish challenge, etc). DBPCFC is the gold standard in the diagnosis of IgE-mediated food allergy and inherently entails use of placebo which minimises the potential for bias. This is not a proxy marker, but a well-established procedure used to rigorously characterise allergic individuals, and will be performed according to guidance provided to sites.

8.8.2 Other efficacy assessments

1. The dose at which reactivity occurs in the DBPCFC will be recorded in the participant's medical notes and will be used to assess changes in the tolerance threshold of participants who will react to the DBPCFC (Positive challenge – still CM allergic participants).
2. The maximum wheal size of the Skin prick test to milk by calculating the longest wheal diameter [60] between visits 1 and 8 will be recorded and can be used as a proxy to asses changes in CM sensitisation in participants.
3. The titres of specific IgE levels to cows' milk casein, a-lactalbumin and b-lactoglobulin between visits 1 and 8 will be assessed by CAP FEIA [61] locally at the sites, will be recorded and can be used as a proxy to asses changes in CM sensitisation in participants.
4. EASI scores for eczema will be recorded at all face-to-face visits to assess changes in eczema activity.
5. Information on wheeze episodes, wheeze-related use of systemic steroids, and wheeze-related hospitalisations during last 12 months (in the first visit) and since the last visit (all other occasions) will be recorded at all face-to-face visits to assess differences between the study product-randomised arm and the routine care-randomised arm.
6. Information for physician-diagnosed allergies to other foods will be recorded on visits 1 and 9, to assess differences in the development of allergies to non-CM foods between participants.

8.9 Procedures for Assessing Safety

Safety will be assessed by the PI or delegated research staff actively monitoring and reporting all adverse events during the Active Monitoring Period (see section 10.1).

8.9.1 Safety Assessments

- At each trial visit, the following will be confirmed to be normal: general physical examination with chest auscultation, Peripheral arterial pulse, heart rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation. In case any abnormality is observed, any further actions, including continuation, should be based on clinical judgement and GCP.

- Haematology and biochemistry blood tests will be confirmed as normal at visit 1. In case any abnormality is observed, any further actions, including continuation, should be based on clinical judgement and GCP.
- Weight and height will be measured in kg and cm with locally available equipment and recorded in the participant's medical notes during all visits to assess development of the infants.

8.10 Other Assessments

8.10.1 Special Assays or Procedures

Parents of participants will be asked if they consent to providing buccal samples, stool, and blood samples for future mechanistic research. All mechanistic samples will be sent to the University of Manchester once per year. All samples will remain the responsibility of the originating centre until a representative from the central laboratory has completed the relevant section of the Sample Transfer Log CRF. The samples will be collected and stored/managed as per the trial Laboratory manual. The Trial Manager will arrange for the appropriate shipment of the samples to the University of Manchester central laboratory.

8.10.1.1 Buccal Samples

Buccal samples will be collected by the use of a sponge, which will collect participant saliva. The saliva will be wrung from the sponge into a collection tube and stored at -80˚C at the site until the time of the next annual shipment to the University of Manchester central lab.

8.10.1.2 Stool Samples

Stool samples will be collected (at least one stool sample container) and stored at -80˚C at the site until the time of the next annual shipment to the University of Manchester central laboratory.

8.10.1.3 Blood Samples

Blood samples in at least a gold-top serum sample vacutainer and a purple-top EDTA vacutainer -if phlebotomy is succesful within the first few attempts and enough blood is collected- will be collected via standard phlebotomy and stored at at -80˚C at the site until the time of the next annual shipment to the University of Manchester central laboratory. If phlebotomy is unsuccessful and/or not enough blood is collected due to difficulty in collecting blood in infants/babies, there will not be multiple attempts, in order to reduce the burden on the participants.

8.11 Treatment Discontinuation and Participant Discontinuation / Withdrawal

In consenting to the trial, parents agree to all trial activities including administration of trial treatment, follow-up assessments/visits and data collection. Every effort should be made to facilitate the completion of these for every recruited participant. If it is not possible to complete these activities (or it is deemed inappropriate) the reasons why should be documented. The following sub-sections describe the different levels of discontinuation/withdrawal.

8.11.1 Premature Discontinuation of Trial Treatment

Participants may be discontinued from trial treatment for reasons including, but not limited to:

a. Parent-led, i.e. request by the parent.
b. Intercurrent illness preventing further treatment.
c. Unacceptable toxicity, e.g. participants experience a severe anaphylaxis to the challenge or to the intervention product.
d. Clinician-led:
    - Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion.
    - Reasons of non-adherence or non-compliance with treatment or other trial procedures.
    - Participant meets an exclusion criterion (either newly developed or not previously recognised), e.g. they are diagnosed with non-IgE hypersensitivity to CM at any point in the trial (eczema excluded).

Discontinuation from the trial treatment does not mean discontinuation of the trial altogether. If a parent wishes to withdraw their infant from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up and **participation in the DBPCFC**. The remaining trial procedures, follow up assessment/visits and data collection should be completed as indicated in the protocol (unless consent is specifically withdrawn, see section 8.11.2). The Premature Discontinuation CRF must be completed for participants who withdraw from trial treatment.

8.11.2 Participant Withdrawal from Follow-up

Parents are free to withdraw their infant from follow-up at any time without providing a reason, though a reason should be recorded if one is given. Those who wish to withdraw from further follow-up will have the data collected up to the point of that withdrawal included in the analyses. The participant will not contribute further data to the study, except for safety information, and the LCTC should be informed via email and via completion of a Withdrawal CRF to be returned to the LCTC **within 7 days**.

If parents express a wish to withdraw their infant from follow up, the research team at site should ascertain if this is for all elements of trial follow-up, or if, for example, data from routine assessments can still be collected for the trial.

In the case of ongoing adverse events, participants should be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the patient's condition becomes stable. Any SAEs will be notifiable to the LCTC via processes detailed in section **Error! Reference source not found.** even if a participant has withdrawn from follow up.

8.11.3 Participant Withdrawal from Optional Activities

Parents are free to withdraw their child from the activities that are optional to the study at any time, without providing a reason and without it affecting their or their child's participation in the study. The optional activities include:

- The collection of samples for future research, to be transferred, along with a copy of the complete consent form to the central lab.
- Allowing information or results arising from this study to be used in future healthcare and/or medical research, providing that confidentiality is maintained.

If parents express a wish to withdraw their infant from optional activities, the LCTC should be informed via email and via completion of a Withdrawal CRF to be returned to the LCTC **within 7 days**, to ensure that their data is not processed.

8.11.4 Patient Transfers

If a participant moves from the area, every effort should be made for the participant to be followed-up at another recruiting trial centre, and for this trial centre to take over responsibility for the participant.
A copy of the completed participant CRFs and consent form should be provided to the new centre. The participant remains the responsibility of the original centre until the new site PI has signed the Transfer CRF.

Any changes to participant address details must be notified to Sharp as soon as possible by a member of the research team, in order to ensure correct delivery of milk formula.

If participant transfer to another recruiting centre is not possible, then the participant would be considered withdrawn.

8.12 Missed visits and Loss to Follow-up

Participants will be followed-up until a maximum of 54 weeks post-randomisation. A participant will be considered as lost to follow-up if they fail to return for visits 4, 8 or 9 and is not contactable by the site research team, or if they have transferred to a centre that is not participating in DREAM.

If a participant fails to attend/facilitate a required study visit the following actions must be taken:

- Site will attempt to contact the parent and reschedule the missed visit (be conscious of acceptable windows for collecting valid data) and advise the parent on the importance of maintaining the assigned visit schedule.
- Before a participant is deemed to be lost to follow up, site research staff will make every effort to regain contact with the parent. These efforts should be recorded in the patient medical notes.
- If the participant continues to be unreachable, they should be considered withdrawn from the study with a primary reason of lost to follow up and this should be recorded on the appropriate CRF.

In the case of a missed assessment visit, the scheduled measurements at the next visit should be carried out as planned and the lost data due to the missed visit will be considered as missing values.

8.13 Trial Closure

The end of the trial is defined to be the date on which data for all participants are locked and data entry privileges are withdrawn from the trial database. However, the trial may be closed prematurely by the Funder on the recommendation of the Trial Steering Committee (TSC), who are advised by the Independent Data and Safety Monitoring Committee (IDSMC).

Individual sites may be closed to recruitment prior to their intended recruitment end date if the Trial Management Group (TMG) have concerns about their capacity or capability to deliver the trial, or for operational reasons whereby resources are better used at sites with better capacity to recruit.

At the point of closure to recruitment all sites will be required to undertake closedown activities which include but are not limited to:

- A review of their Investigator Site File (ISF)
- A count of all completed CRFs, parent diaries and completed data queries
- PIs will also be required to sign-off the CRF for each participant, any changes to the data, a closedown checklist, and their site delegation log.

Site and closure activities will be centrally coordinated and conducted in accordance with LCTC processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to REC.
- Reconciliation of returned/disposed trial-related materials.
- All site data entered onto the study database, discrepancies raised, and satisfactory responses received.
- Quality Control checks of the Investigator Site Files, Pharmacy Files (where applicable) and Trial Master File as appropriate.

9 TRIAL TREATMENT/INTERVENTIONS

9.1 Introduction

This study will randomise the participants in 2 groups.

- The first group is normal care and will receive an approved, already in the market eHF formula which has the indication to be used for milk-allergic infants, such as those participating in the study. There is already significant experience with this formula and is nutritionally complete and widely used for this indication. The management of the infants of this arm in regard to the formula will not differ from routine care.
- The other arm will receive a market-approved, already in the market pHF formula which has the indication to be used for infants with colic and for allergy prevention. There is already significant experience with this formula and is nutritionally complete and widely used for this indication. This formula does not have an indication to be used for milk allergic infants.

Neither of these formulas is an investigational medicinal product and MHRA has confirmed that no Clinical Trial Authorisation (CTA) is needed for this trial (see APPENDICES 1).

The main intervention consists of free feeding with pHF as compared to the standard care of free feeding with eHF. Infants who can already tolerate pHF will start free feeding with pHF or eHF from visit 3 onwards. Those who react initially to pHF (visit 2) will undergo a short OIT module to either pHF or eHF (see Schematic of Trial Design).

The pHF free feeding intervention.

It is expected that most infants randomised to the active intervention (pHF) will be eventually able to be fed freely with pHF either from visit 3 onwards or after the OIT module. pHF formula has been selected for this trial with the following rationale: pHF formulae have lower allergenicity than normal CM, but higher than eHF (normal standard care). Both pHFs and eHFs have been created on the premise that pre-digested proteins have a low allergenicity, and both are generated via enzymatic digestion of CM proteins into smaller fragments [51]. However eHFs are 20 million times less allergenic than normal CM [51] (and they are considered to be hypoallergenic and appropriate for CMA infants), whereas pHFs are about *60 times* less allergenic than CM [51] thus bringing the infant in closer contact with more immunologically active CM protein. Because of this, they are not considered to be 'hypoallergenic' and do not have an indication for CM-allergic infants. Currently their main indication in some European countries is feeding of infants who have a high risk for developing allergy due to positive family history. Nevertheless, pHFs are tolerated by around 50-70% of CMA infants [58, 59], which is reasonable considering that they contain peptides of only <5kD [50] whereas peptides need to be >10kD to be consistently allergenic (e.g. normal CM formula contains proteins in the range of 14-67kD [62]). Therefore, when compared to conventional CM formula, pHFs are expected to be much safer for an allergic infant. Additionally, when compared to eHF (standard care), pHFs are immunologically closer to normal CM, which satisfies the main hypothesis of this trial that exposure of CMA infants to immunologically-active processed CM proteins will expedite/facilitate tolerance.

On the basis of the above, we have identified eHF and pHF formulae available in the market with identical composition apart from the extent of milk protein hydrolysis, making them ideal for comparison purposes. These are marketed by the company Nutricia-Danone, who has agreed to provide them for the trial as study products, free of charge. Pre-existing commercial availability will ensure that the study's conclusions will be directly transferable to clinical practice and that the formulas will be readily available for use by the NHS.

The OIT module. OIT trials are numerous and it is now well established that CM OIT can facilitate CMA resolution with success range up to 90% [2, 63]. It is therefore reasonable to expect that an OIT regimen to pHF could help pHF-reactive participants tolerate pHF free feeding. Although a pHF OIT regimen has not been used in a trial up to now, given the above-described immunological characteristics of pHF we also expect that such a regimen would be considerably safer than normal CM OIT, which is known to cause frequent reactions [15, 32-35, 39, 64]. CM OIT protocols consist of hospital visits where escalating doses of CM are given to the patient, while in-between visits the patient eats daily at home the dose reached at the previous hospital visit. Our OIT protocol reflects this well-established pattern insofar as we have made provisions for three up-dosing hospital visits (V4, V5 and V6) with approximately one month in-between them for home dosing. This OIT module was introduced to ensure that both pHF–reactive and pHF-tolerant children can participate in this study, as excluding the former would have made the trial less representative of the general CMA population. Additionally, pHF-tolerant infants may have a different immunological status than pHF–reactive ones and may be more likely to outgrow their allergy by default; therefore, only recruiting pHF-tolerant infants could have biased the study. The OIT module ensures that the majority of pHF-reactive infants will also be able to participate, and eventually be fed pHF.

The normal care (control) group. The control group will be fed with eHF, either directly or following a 'dummy' OIT with eHF. This is the routine normal care for milk allergy in infants.

9.2 Study Formulae

9.2.1 Formulation, Packaging, Labelling, Storage and Stability

9.2.1.1 Extensively Hydrolysed Formula (eHF)

Generic name: Pepti - Nutricia
Supply and distribution: Danone Nutricia will supply the milk formula which will be distributed by Sharp.
Packaging: 800g or 400g tins
Labelling: Tins will be labelled by Danone Nutricia in English and in compliance with Annex 13 of the Good Manufacturing Practice (GMP). Each tin will be labelled and used for DREAM study use only.
Storage: The tins have been packaged in a protective atmosphere and will be kept tightly sealed and stored in a dry and cool area (5-25˚C, not refrigerated).
Stability: Each tin has an unopened shelf-life of 18 months from manufacture. Once opened, the product must be consumed within 28 days. Opened tins must be resealed and stored a cool, dry area (5-25˚C, not refrigerated). Any product leftover after 28 days of opening, must be destroyed.

9.2.1.2 Partially Hydrolysed Formula (pHF)

Generic name: HA - Nutricia
Supply and distribution: Danone Nutricia will supply the milk formula which will be distributed by Sharp.
Packaging: 800g or 400g tins
Labelling: Tins will be labelled by Danone Nutricia in English and in compliance with Annex 13 of the Good Manufacturing Practice (GMP). Each tin will be labelled and used for DREAM study use only.
Storage: The tins have been packaged in a protective atmosphere and will be kept tightly sealed and stored in a dry and cool area (5-25˚C, not refrigerated).

Stability: Each tin has an unopened shelf-life of 18 months from manufacture. Once opened, the product must be consumed within 28 days. Opened tins must be resealed and stored a cool, dry area (5-25˚C, not refrigerated). Any product leftover after 28 days of opening, must be destroyed.

9.2.2 Manufacture and Distribution

The study formula will be manufactured in batches and will be shipped to Sharp for storage and distribution. Pharmacy or delegated site staff will receive an initial supply of blinded eHF, pHF, and open label pHF and non-hydrolysed formula.
Sites will monitor local stock levels and request additional supply from Sharp, as necessary, using the appropriate request form.
Upon dispense, pharmacy/unblinded team will request further supply of the allocated study product for delivery direct to the participant's home, using the appropriate request form. Allow 5-7 days for delivery to participant homes.
Sites will make further requests for direct delivery to participant homes as required, ensuring there are no interruptions to the intervention. Parents may advise site staff if more or less product is required.

9.2.3 Preparation, Dosage and Administration of Trial Treatment/s

Dosage Free-Feeding: Dosage will be at the discretion of the parents, following a gradual introduction.
Dosage OIT: Dosage will be advised by the delegated treating clinician at each OIT visit.
Preparation: Per 100 ml ready to feed, 90 ml of boiled water at 40˚C (preferably) + 3 levelled scoops. Prepared food must be consumed within 2 hours. Any unfinished feeds must be discarded.

RISK mitigation Measures summary

- Parents will be prescribed two adrenaline autoinjector devices to have at all times, and will be advised to have appropriate antihistamine medications with them at all times to use if needed.
- Parents will be offered training to ensure that they are able to identify and manage reactions and to use the medications appropriately.
- Parents will be advised to observe the infants for at least 1 hour post-feeding, when most allergic reactions may take place.
- Following a successful pHF challenge or OIT module, free-feeding will be introduced in a gradual manner, over the next week.
- Parents will be instructed to reduce the feeding dose in both the Free-feeding and OIT-feeding arm at home if the infant is ill, to reduce the chance of a reaction.
- The infants who will undergo the OIT module will be instructed to receive a lower dose at home than the maximum dose they tolerated at their latest OIT visit, to minimise the chances of a reaction.
- For all OIT infants, it will be advised that they have routine care (eHF) formula at home to use for their normal everyday feeding, while undergoing the OIT module.
- Breastfeeding is allowed freely.

9.2.4 Dose Modifications and management of Toxicity

Home dosing will be carried out at home either through free feeding or dose-feeding.

1. Free-feeding participants will be fed the randomised trial product at various and variable non-predefined doses.
2. Dose-feeding participants will be advised to not exceed a predefined dose within a given time. This dose will be defined by the previous OIT visit they attend and therefore will change after every OIT visit.

All participants on home dosing will be advised to reduce the feeding dose when infants are unwell.

9.2.5 Specific restrictions

None.

9.2.6 Accountability Procedures for Trial Treatment/s

The PI is responsible for the management of trial treatment to be used for the trial. The trial products should be stored in the original packaging, in a locked, secure storage facility with access limited to those individuals authorised to dispense or administer the trial product.

Initial supply of the trial product will be to the site Pharmacy or suitable alternative. The site Pharmacists or other unblinded staff are responsible for dispensing stock to an appropriately secure area for more immediate access by the research teams. Pharmacists or unblinded staff must release the allocated trial product with the shortest shelf-life first. No trial product supplied for this trial must be used for any other purpose.

Accountability logs will be maintained by the PI, pharmacist, or delegated research team member, which will include a signed account of all the tins received from the distributor, the tins dispensed and any tins that have been returned and destroyed. Expired tins can be destroyed as per local Trust standard procedures.

Inventory will be reconciled at the end of the trial, and only once LCTC have given site authorisation on behalf of the Sponsor, remaining unused tins maybe disposed of directly by the Pharmacy or unblinded teams.

9.2.7 Assessment of Compliance with Trial Treatment/s

Compliance to trial treatment and dosage will be assessed through the completion of participant diaries. These will be collected periodically at different timepoints throughout the trial.

9.3 DBPCFC

9.3.1 Formulation, Packaging, Labelling, Storage and Stability

Generic name: Milk Challenge Meal (MCM)
Supply and distribution: Reacta Biotech Ltd. will supply the MCMs (active and placebo) for the DBPCFC via a third-party distributor.
Packaging: MCMs will be supplied in sealed, food-contact compliant and tamper evident containers, which will be packed into dose boxes and trial-specific packages.
Storage: MCM kits will be stored in a dry and cool area prior to reconstitution.

Stability: The shelf life of MCM at ambient temperature (≤25˚C) will be determined. Once reconstituted, the shelf-life of MCM is 24 hours when stored at 2-8˚C.

9.3.2 Preparation, Dosage and Administration of Trial Treatment/s

The DBPCFC product will be prepared for the DBPCFC visits by appropriately trained and delegated staff, according to the Trial's DBPCFC SOPs.

9.3.3 Dose Modifications

Dose modifications during the DBPCFC will be done according to the Trial's DBPCFC SOPs.

9.3.4 Specific restrictions

None.

9.3.5 Accountability Procedures for Trial Treatment/s

The PI is responsible for the management of challenge products to be used for the trial. The challenge products should be stored in the original packaging, in a locked, secure storage facility with access limited to those individuals authorised to dispense or administer the trial product.

Supply of the challenge product will be to the appropriate research contact at site. A research team member delegated by the PI is responsible for reconstituting the challenge products as per the trial Challenge SOPs and/or instructions provided in each kit.

Accountability logs will be maintained by the research team member, which will include a signed account of challenge kits received from the distributor, the kits that have been administered and any kits that have been destroyed. Expired kits can be destroyed as per local Trust standard procedures.

9.4 Unblinding

N.B Allocation must not be routinely revealed to LCTC personnel. Unblinding will generally be discouraged while the trial is ongoing.

Simply ceasing feeding with the trial product is a viable option for the participant's care, it should only be necessary for unblinding to occur in exceptional circumstances, e.g. to enable appropriate ongoing care following cessation of feeding with the trial product. Unblinding must be discussed with the PI (or appropriate delegate approved by the PI) prior to occurring.

Once approved, site personnel should request the unblinding from the local site pharmacy or unblinded staff (N.B. the PI is responsible for ensuring that all research personnel are aware of contact details for obtaining details of the treatment allocation).

As soon as possible thereafter, the Trial Manager at LCTC should be contacted confirming unblinding has taken place and an unblinding CRF should be completed and returned to LCTC. A copy of this should be placed in the patient's medical notes and a copy stored in the investigator site file.

Any participant, for whom randomised allocation is unblinded for any reason will continue to be followed up and assessed at the end of the study for the intention to treat analysis.

9.5 Concomitant Medications/Treatments

There are no specifically prohibited medications in relation to the study.

9.6 Dose Modifications

Doses will vary according to participant preference (free feeding arm) and tolerance level (OIT arm), as described in the OIT SOP.

10 SAFETY REPORTING

10.1 Time Period for Active Monitoring of Safety Events

The “active monitoring” of all safety events experienced by trial participants will be from randomisation until 48 hours after visit 9.

Any additional information on selected adverse events related to the initial challenges, will be captured in the Challenge Form (see sections 8.4.1.2 and 8.4.1.3). Expected adverse events during the challenges will not be included in the adverse events log, but rather in the challenge logs.

Any safety events occurring *after* the end the active monitoring period that meet the definition of **serious** (see section 10.3) must continue to be reported by sites to the LCTC in accordance with the timeframes and procedures described in section 10.9.

Upon becoming aware of a serious adverse event (SAE/Related SAE/RUSAE), the investigator or other delegated member of the site team must report this to the LCTC **within 24 hours**.

10.2 Terms and Definitions

Table 1: Terms and Definitions of Safety Events

Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users, or other persons whether or not related to the investigational product.
Related Adverse Event (Related AE)	An AE which resulted from administration of any of the research procedures – i.e. assessed as “probably”, “possibly” or “almost certainly” related to the trial procedures (see section 10.5).
Serious Adverse Event (SAE)	An adverse event which meets the definition of “serious” (see section 10.3).
Related Serious Adverse Event (Related SAE)	An adverse event which meets the definition of “serious” (see section 10.3). A SAE which is assessed to be “probably”, “possibly” or “almost certainly” related to the trial procedures (see section 10.5).
Related Unexpected Serious Adverse Event (RUSAE)	A Related SAE which is not expected, i.e. not consistent with the known effects of the trial procedures (see section 10.5).

10.3 Assessment of Seriousness

The assessment of seriousness of safety events should be performed by an appropriately delegated, medically qualified member of the site research team.

A safety event (whether or not assessed as related to the trial) is assessed as serious if it:

- Results in death;
- Is life-threatening (i.e. the investigator considers the event places the subject at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have cause death);

- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation);
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions);
- Consists of a congenital anomaly or birth defect (in offspring of trial participants, or their partners, regardless of time of diagnosis), or
- Is otherwise considered medically significant by the investigator.

10.4 Severity of Adverse Events

All adverse events should be assessed for severity. The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions in the table below:

Table 2: Definitions of Severity Grading

Mild	Does not interfere with routine activities
Moderate	Interferes with routine activities
Severe	Impossible to perform routine activities

N.B. A distinction is drawn between **serious** and **severe** AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria in section 10.3. Hence, a severe AE need not necessarily be a Serious Adverse Event.

10.5 Relationship to Trial Treatment

The assessment of causality should be made by the investigator responsible for the care of the participant using the definitions in ***Error! Reference source not found.***.

Table 3: Definitions of Causality

Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

If any doubt about the causality exists, the local investigator should inform the study coordination centre who will notify the CI. In the case of discrepant views on causality between the investigator and others,

the opinion of the treating investigator will never be downgraded, and the REC will be informed of both points of view.

10.6 Assessment of Expectedness

The Chief Investigator for the DREAM trial is responsible for determining whether a safety event is expected or unexpected. There is no requirement for a reporting investigator to make an assessment of expectedness.
An event will be considered 'unexpected' if it is not listed within the current and approved protocol (see section 10.6.1) for the study at the time of the event's onset. The nature, severity, or frequency of the event should be considered – if this is not consistent with that described for the type of event in the protocol the event should be assessed as unexpected.

10.6.1 Reference Safety Information (RSI)

The RSI in DREAM is detailed in Table 4: Expected Events

Table 4: Expected Events

Event
Anaphylaxis
Urticaria
Exacerbation of eczema
Allergic reaction
Acute bronchospasm (asthma)

10.7 Notes on Adverse Event Inclusions and Exclusions

The following events must be recorded for the purposes of the trial:

- An exacerbation of a pre-existing illness.
- An increase in frequency or intensity of a pre-existing episodic event/condition.
- A condition (even though it may have been present prior to the start of the trial) detected after trial treatment.
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment.
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event).
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention.
- Injury or accidents.

Do not record:

- Medical or surgical procedures - the condition which leads to the procedure is the adverse event.
- Pre-existing disease or conditions present before treatment that do not worsen.
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery*.
- Overdose of medication **without signs or symptoms****
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

** Elective surgery is cited here as example of an event that is not reportable as an AE.*

** See also section 10.12.1. *If overdose occurred with resulting signs and symptoms that met the protocol criteria for AEs or /SAEs/ then they should be reported accordingly. This bullet is to note that though overdose of medication without signs or symptoms may be excluded from AE reporting this may still require investigation to ensure the protocol and regulatory requirements are met e.g. for IMP management and administration to ensure participant safety.*

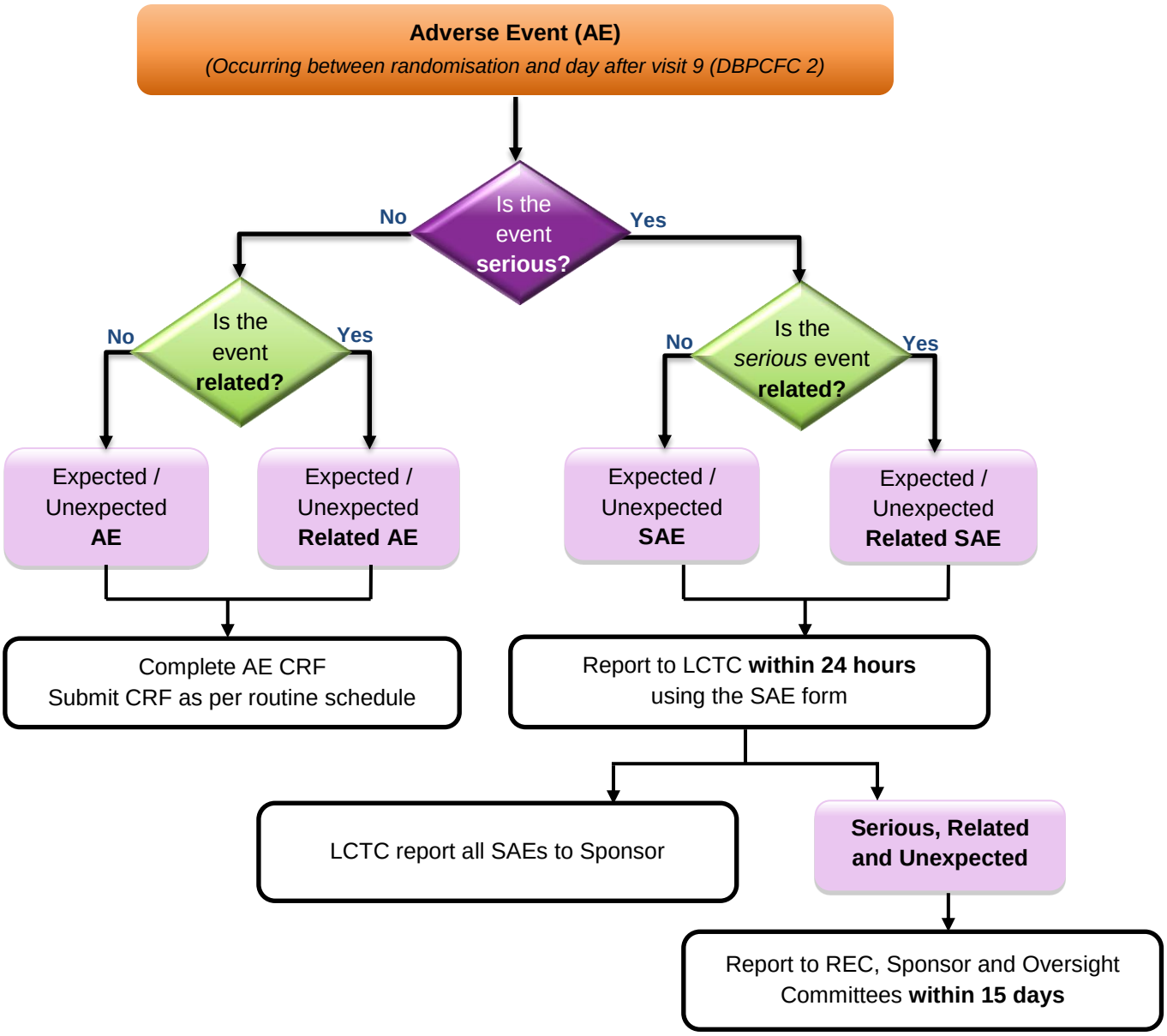
10.8 Notification of Deaths

If the research team become aware of the death of a participant (whether related to the trial or not) this should be notified to the LCTC using SAE form within **24 hours** of becoming aware.

10.9 Reporting Procedures

All safety events that are recorded for the study should be reported following the procedures detailed below. The occurrence of a safety event may come to the attention of research staff during routine study visits, from the participant's notes, directly from the parent or by other means. Note that reporting procedures vary dependent on the nature of the incident (i.e. "serious" events are to be reported to LCTC in an expedited manner). Any questions concerning adverse event reporting should be directed to the LCTC in the first instance. A flowchart is given below to aid in determining reporting procedures for different types of adverse events.

10.9.1 Flowchart for Reporting Requirements of Adverse Events



10.9.2 Reporting Safety Events

All safety events (whether or not assessed as serious / related / expected) should be recorded on an AE form; multiple events can be recorded on one form.

Safety events that are assessed as "serious" must **also** be recorded in more detail on an SAE Form; a single form is used for each individual event (i.e. a single diagnosis), though multiple symptoms can be recorded. Each SAE should have a corresponding record on the participant's AE form.

Additional information should be provided on a follow-up form and sent to LCTC within 5 days if the serious event has not resolved at the time of the report.

SAE Forms collect data regarding the nature of event, date of onset, severity, corrective therapies given, outcome and causality; all serious events reported to LCTC will be reviewed by the CI or authorised delegate and assessed for causality and expectedness.

10.10 Follow-up After Adverse Events

All AEs should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting SAEs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes:

- resolved;
- resolved with sequelae (specifying with additional narrative);
- not resolved/ongoing;
- ongoing at final follow-up;
- fatal or unknown.

10.11 Safety Reporting Responsibilities – Investigator

The PI is responsible for ensuring all safety events that are observed or recorded during the study are reported to LCTC, regardless of their relationship to trial treatment. It is the responsibility of the PI/Co-Investigator (medically qualified person) as recorded on the Delegation Log, to assess the seriousness and causality of events.

All safety events must be recorded on an AE form and transferred to LCTC **within 7 days of the site team becoming aware of the event**.

Safety events that meet the definition of “serious” must be reported in more detail to the LCTC on an SAE form and reported **immediately and in no circumstances later than 24 hours from becoming aware,** where they will be appropriately processed.

The SAE form should be completed by an appropriately delegated member of the research team; the assessments of seriousness and causality must be performed by an appropriately medically qualified person. Minimum reporting information must be provided in initial reports for all studies.

Minimum information required for reporting:

- Sponsor study number
- One identifiable coded subject
- One identifiable reporter
- One SAE
- A causality assessment
- A description of circumstances

N.B. In the absence of a delegated medically qualified person the form should be completed and signed by an alternative member of the research site trial team and submitted to the LCTC. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the LCTC. The initial report shall be followed by detailed follow-up reports as appropriate.

Safety events should be reported to the site R&D team in accordance with local policy.

10.11.1 Reporting an Initial or Follow-Up SAE

The investigator should ensure the actions below are completed for all reportable SAEs:

i. Research sites should telephone the appropriate trial manager / data manager on telephone number **0151 795 8781** to advise that an SAE report has been submitted as soon as possible.

ii. **The SAE form should be transferred SECURELY to lctcsafe@liverpool.ac.uk (within 24 hours).**

iii. The responsible investigator must notify their R&D department of the event (as per standard local governance procedures).

iv. The patient must be identified by trial number, age or month and year of birth and initials **only**. The patient's name **must not** be used on any correspondence.

v. SAEs must be subsequently followed up in line with the processes below:
   a. Follow up must continue until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised.
      N.B. Follow-up may continue after completion of protocol treatment if necessary.
   b. Follow-up information is noted on a new SAE form to be transferred securely to the LCTC as soon as more information becomes available.
   c. Tick the appropriate box on the new SAE form to identify the type of report; this is dependent on resolution status of the SAE e.g. follow-up / final.

vi. Extra, annotated information and/or copies of anonymised test results may be provided separately.

Patient safety incidents that take place in the course of research should be reported to the National Reporting and Learning System (NRLS) by each participating NHS Trust in accordance with local reporting procedures.

10.11.2 Maintenance of Blinding

Systems for reporting safety events assessed as "serious" and "related" (i.e. Related SAEs and RUSAEs), should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial. SAE forms allow reporting investigators to make an assessment of causality without having to unblind the participant; breaking the blind will only take place where information about the participant's trial treatment is clearly necessary for the appropriate medical management of the participant.

Cases that are considered serious, unexpected and possibly, probably or almost certainly related to one of the trial therapies (i.e. possible RUSAEs) would have to be unblinded at the LCTC prior to reporting to onward reporting.

Unblinding procedures are detailed in section 9.4.

10.12 Safety Reporting Responsibilities – LCTC

The trial Sponsor, Manchester University NHS Foundation Trust, have delegated to LCTC the duty of onward reporting of safety events to REC. SOPs will be followed to ensure appropriate reporting as detailed below.

All "serious" safety events will be forwarded to the CI or authorised delegate by LCTC within 24 hours of receiving the minimum information from site.

The CI or authorised delegate will review information provided by site and for all events assessed as "related" will provide an assessment of "expectedness".

Safety events that are assessed as "serious", "related" and "unexpected", i.e. RUSAEs, will be onward reported by LCTC to the ethics committee **within 15 days** of the LCTC first becoming aware of the event.

Additionally, RUSAEs will be reported to the trial Sponsor, PIs of participating sites, and relevant product manufacturer, Nutricia or Sharp.

A list of all safety events recorded for the trial will also be reported annually by LCTC to the ethics committee and IDSMC.

Any concerns raised by the TSC or IDSMC or inconsistencies regarding safety reporting noted at a given site may prompt additional training at sites, with the potential for the LCTC to carry out site visits if there is suspicion of unreported AEs or SAEs in patient case notes. Additional training will also be provided if there are unacceptable delays in safety reporting timelines.

10.12.1 Overdose

The trial product for all arms is food, hence no toxicity is expected. However, an overdose may occur in the OIT arm. If a participant has a large amount of the trial product, there is an increased chance of an allergic reaction. Parents will be well informed of this risk and they will have the necessary medication and training to recognise and treat an allergic reaction. The risk will further be mitigated by parents in the OIT arm being advised to use routine care formula to give to the infant as add-on to the trial formula if the infant is still hungry after having the maximum allowed dose of trial formula.

10.12.2 Safety reports

Safety reports will be generated during the course of the trial which allows for monitoring of safety events, including reporting rates and safety events across sites. The LCTC will prepare Annual Progress Reports (APRs) containing a list of all SAEs for submission to the REC. If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all participating centres will be notified.

10.13 Contact Details and Out-of-hours Medical Cover

All local PIs should ensure to delegate at least one other appropriately trained (in the study and in GCP) medically qualified doctor for assessment of adverse events, safety reporting and making medical decisions in their absence.

The CI or delegate are able to provide medical advice in relation to participation during office hours, using the contact details listed at the beginning of this document.

Emergency and out-of-hours medical care will be in line with usual NHS arrangements and local standard practice. All parents will be provided with a copy of the PISC which includes information about their child's participation and contact details for the local research team who may be contacted if necessary.

11 STATISTICAL CONSIDERATIONS

11.1 Introduction

Separate statistical analysis plans for interim and final analyses will be developed prior to any comparative analyses. The main features of these analyses are included here in the protocol.

11.2 Method of Randomisation

Participants will be equally randomised to eHF or pHF (1:1 ratio) using a secure (24-hour) web-based randomisation programme, controlled centrally by LCTC to ensure allocation concealment. Randomisation lists will be generated using block randomisation with random variable block length, stratified by site and initial tolerance to pHF. The lists will be produced by an independent statistician (who is not otherwise involved in the DREAM study) at LCTC.

11.3 Sample Size calculation

We have set high inclusion thresholds for SPTs/IgE, to recruit infants with a low chance to 'spontaneously' outgrow CMA (that is, to outgrow CMA while they are under normal care-eHF feeding, as is the case for our control group). Therefore, although population-based studies report a high rate of up to 75% spontaneous CMA resolution [5, 65, 66], in patients meeting our strict criteria only 37% developed tolerance by age four in one study [29] and only 20-30% by 3 years of age in three other studies [30, 67, 68]. We therefore expect spontaneous resolution (for the 'normal care' group) to be ~30% and allowed for 35% (closest to the highest reported) to ensure that the study will be sufficiently powered even in the worst-case scenario.

Regarding the expected resolution rate for the active intervention (pHF) group, to date there is no study using pHF for free feeding and there is no evidence for an expected rate. Although CM OIT has a success rate of 65%-90% [36-42] our study differs from CM OIT in that we are not giving normal CM but a less allergenic form (and therefore one would expect lower rates of CMA resolution in our trial due to exposure to less CM proteins); on the other hand, our trial also differs from CM OIT in that we are not giving the OIT product in small doses but in large quantities (freely), and therefore one would expect higher rates of resolution in our trial due to exposure to more protein. In any case, to power our study reliably we assume that the resolution rate for the intervention group should be at the lower end of the reported rates for CM OIT (65%). To ensure that the study will be sufficiently powered even in the worst-case scenario, we calculated the power on an expected 60% size effect for the pHF group. Indeed, a study where processed CM (baked milk) was used for desensitisation returned a size effect of 60% [53], further indicating that this would be an appropriate effect size.

A two-group chi-squared test with a 0.05 two-sided significance level will have 90% power to detect the difference between a proportion of 0.35 in the eHF group and a proportion of 0.60 in the pHF group (odds ratio of 2.786) when the sample size in each group is 82. Allowing for 20% attrition, a total of 206 patients will be randomised.

11.3.1 Feasibility (attaining recruitment targets)

1st Recruitment pathway – Feasibility study

We have conducted an ethically-approved feasibility study regarding the 1st recruitment pathway (Bounty), to get insight about**: i.** the potential number of surveys that will be filled in and submitted by parents; and **ii.** The number of infants that will be eligible for the next step (Hospital screening visit–V1).

Email contact details are currently available from Bounty for the catchment area of the study partners for roughly **35,000** infants between 6-12 months of age. Postal details for those with no email address are also available for roughly **11,000** infants, for a total of about **46,000** infants. To reach these infants Bounty will send e-mails (and letters if appropriate) approximately every 6 months (six times overall in the three-year recruitment period); therefore, throughout the whole recruitment period we will reach a total population of 46,000 x 6 = **276,000** infants of appropriate age for the study. Assuming that 2% of them have immediate CMA, this means that throughout the study we will have access to 5,520 age-appropriate infants with CMA through Bounty alone.

We have conducted a feasibility study in order to get insight about the actual numbers of potentially eligible infants that we will be able to invite to V1 from this population. For the feasibility study we sent out 8000 emails containing a link to the online DREAM recruitment survey to parents of 6-12-month-old infants identified by Bounty in cities where we will be recruiting.
The results of the feasibility study were as follows:

i. **30%** of parents (2349/8000) opened and read the email containing the survey link.
ii. **4.5%** of those (103/2349), filled in and submitted the survey.
iii. **17.5%** of those (18/103), were deemed to be eligible for an invite to the screening visit- V1.

The above evidence furnished by the feasibility study has informed the Bounty recruitment pathway as follows: We expect that: **i.** 30% of the parents reached through Bounty will open their mail **(82,800** out of 276,000); **ii.** 4.5% of those will fill in and submit the survey (**3726** out of 82,800); and **iii.** 17.5% of those (652 out of 3726 infants) will be eligible for the screening visit –V1 from the 1st pathway.

Assumptions from all pathways

After being screened at V1, potential participants need to meet the inclusion criteria to proceed to the free feeding (or the OIT module). **The assumptions for this stage are as follows: i.** We assume that no more than **25%** of the infants screened at V1 will meet the IgE or SPT inclusion criteria (conservative estimation). These infants will continue to the next step (pHF challenge-V2). **ii.** We expect that **~33%** of these infants will react to pHF at the pHF challenge–V2 [59], and will therefore be recruited as 'pHF–reactive, CM protein-allergic'. **iii**. From the remaining infants (those not reacting to pHF) we assume that **50%** will react to CM in the milk challenge–V3, and will therefore be recruited as 'pHF–tolerant, CM protein-allergic' (conservative assumption, as for this age range and these specific IgE levels, clinical reactivity is over 90% [69]).

The above conservative assumptions suggest that, for 206 infants to proceed to free feeding/OIT module, we need **1241 infants** to be reviewed at the screening visit-V1. 652 infants will reach V1 from the first recruitment pathway (Bounty). The remaining infants will be invited to V1 through the other recruitment pathways.

11.4 Interim Monitoring and Analyses

Accumulating data will be presented at regular intervals (at least annually) for review by an IDSMC. These analyses will be performed at the Clinical Trials Unit. The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community.

11.5 Analysis Plan

The trial will be analysed using the International Conference on Harmonisation E9 guidelines and reported using the 'Consolidation Standard of Reporting Trials' (CONSORT) guidelines.

The analyses of primary and secondary outcomes will use the principle of intention to treat, based on all the randomised participants, as far as is practically possible. A p-value of 0.05 or less will be used to declare statistical significance for all analyses and results will be presented with 95% confidence intervals. Baseline characteristics will be presented but no comparisons will be undertaken, rather the clinical importance of any imbalance will be noted.

Binary data (including the primary outcome of the proportion of patients who are no longer allergic to CM protein) will be reported in terms of relative risk and analysed using logistic regression, adjusted for the stratification factors (site and initial tolerance to pHF). There will be a secondary analysis of the primary outcome using a chi-squared test for consistency with the sample size calculation. There will also be two subgroup analyses of the primary outcome, the first will include patients who initially tolerated pHF and the second will include patients who did not initially tolerate pHF.

Continuous data will be presented as means and standard deviations and analysed using two-sample t-tests (if data is skewed, medians and ranges will be presented, and analysis will be by Mann Whitney U tests). All related AEs and serious adverse events SAEs reported by the clinical investigator will be presented, identified by treatment group, but no formal comparisons will be made across the treatment groups.

Missing data will be monitored, and strategies developed to minimise its occurrence, however as much data as possible will be collected about the reasons for missing data and this will be used to inform the handling of missing data.

12 REGULATORY AND ETHICAL APPROVALS

12.1 Statement of Compliance

Statement of compliance: The study will be carried out in accordance with:

- The World Medical Association Declaration of Helsinki
- LCTC Standard Operating Procedures
- Principles of Good Clinical Practice
- The template content is structured consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013)
- UK Policy Framework for Health and Social Care Research

12.2 Ethical Considerations

The study will abide by the principles of the World Medical Association Declaration of Helsinki and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996). The specific ethical considerations are:

12.2.1 Involvement of Infants

In compliance with GCP, parents will be fairly informed of the trial, risks, benefits, and alternatives, asked to ensure they understand how it relates to their infant, and make a voluntary decision about entry. Autonomy, privacy and welfare will be paramount, overriding the research. Parents will be kept informed of findings that might cause them to withdraw, without detriment to on-going care.

12.2.2 Trial-Specific Visits

The trial will involve additional, non-routine visits for participants. These visits are made explicit in the PISC. Every effort will be made by participating centres to schedule these visits at the convenience of the participants, within the expected time window. Reasonable travel expenses (up to £20) will be reimbursed for participants attending VISIT 7 (Mid Trial Visit).

12.2.3 Additional Tests

Additional, non-routine blood and skin prick tests will be carried out during trial visits for diagnostic and safety purposes. These tests will be carried out by experienced personnel and made explicit in the PISC.

12.2.4 Additional Samples

Additional blood, stool and buccal samples will be collected for the purpose of future mechanistic research. Provision of these samples are optional to the trial and will not affect trial participation. These additional samples will be made explicit in the PISC and parents of participants will be asked to provide consent for the collection of theses samples.

12.3 HRA Approval

DREAM will come under the Health Research Authority (HRA) Approvals process as part of the initial REC submission and will follow the HRA processes for submission of amendments to REC and the HRA.

12.4 Ethical Approval

Favourable ethical opinion will be obtained from a REC and global governance approval from HRA prior to the trial being initiated at LCTC.

Prior to opening a site to recruitment, LCTC will ensure that local governance approval has been obtained: for sites in England and Wales, this will be a confirmation of “Capacity & Capability”; for sites in Scotland and Northern Ireland, this will be R&D Approval.

12.5 Protocol Deviation and Serious Breaches

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and ethical e.g. REC, requirements are handled based on their nature and severity.

Non-Serious Breaches
Protocol deviations and other non-serious breaches of GCP, etc. will be managed according to local site and LCTC procedures as appropriate. They will be reported to trial oversight committees.

Serious Breaches
A breach of the protocol or GCP is ‘serious’ if it meets the regulatory definition of being “likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial”. This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential/suspected serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a ‘serious’ breach of GCP or protocol and therefore requires expedited reporting to the REC.

In determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants, the Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDSMC and TSC). In determining whether or not the breach is likely to significantly affect the scientific value of the trial, the Sponsor may seek advice from the Trial Statistician. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of ‘serious’ and is subject to expedited reporting to REC.

Breaches confirmed as ‘serious’ will be reported to the REC within 7 days by the Sponsor (or delegate) and notified to the TMG, IDSMC and TSC at their next meeting.

Any requests for additional information from the Sponsor, TMG, TSC, IDSMC, or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

Incidence of protocol non-compliance are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

12.6 Trial Discontinuation

In the event that the DREAM trial is prematurely discontinued, participants will not receive any further trial treatment and will return to their local standard care.

13 DATA MANAGEMENT AND TRIAL MONITORING

Details of the monitoring to be carried out for the DREAM study are included in the DREAM Trial Monitoring Plan.

Trial Oversight Committees related to the monitoring of the trial are detailed in section 15.4.

13.1 Source Documents

In order to resolve possible discrepancies between information appearing in the case report form (CRF) and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF.

Source data is defined as: “All information in original records and certified copies of original records of 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). (ICH E6, 1.51).

Source documents are defined as: “Original documents, data, and records” (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).

Documents will be considered source documents only for data where no prior record exists and is recorded directly in the bespoke document, e.g. food diaries. These must be **photocopied** and retained at site before mailing the original wet-ink copies to LCTC.

Date(s) of conducting informed consent process, including date of provision of patient information, randomisation number, and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient’s medical record chronologically.

13.2 Data Capture Methods

Participant CRF folders will be provided to sites for local completion by members of the research team trained and delegated the duty. Study staff named at each site will enter data from source documents corresponding to a participant’s visit onto the relevant CRF in the participant’s folder. The CRF is the primary data collection instrument for the study so all data requested on the CRF **must** be recorded and all missing data must be explained. Any corrections should be made in accordance with GCP. All missing data must be explained using the acronyms in *Table 5: Missing Data Acronyms*:

Table 5: Missing Data Acronyms

“**N/D**” not done	Procedure not done
“**N/A**” not applicable	Item is not applicable to the individual case

"**N/K**" not known	Data item is unknown
"**N/R**" not recorded	Data item has not been recorded on source data

If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE-OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

A copy of all CRFs should be retained at site and the originals should be posted to LCTC.

Participant diaries are source documents and should be **photocopied by sites** in order to retain a copy at site before posting the originals to LCTC.

Copies of completed CRFs and participant diaries must be sent to the LCTC **separately from the completed PISC** in order to preserve pseudonymisation and maintain confidentiality.

Data from CRFs and diaries will be entered into the trial databases by LCTC. The trial databases are built and maintained by LCTC using standard, secure, clinical trial database software.

All trial-specific documents, other than the signed consent form, will refer to participants using only participant numbers and participant initials. Participants' names and any other identifying details will not be included.

13.3 Monitoring

13.3.1 Central Monitoring

Data stored at the LCTC will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the LCTC from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log).

Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to the LCTC. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database.

Centres will also submit monthly logs documenting the number of patients screened, eligible and randomised.

If centres do not remain engaged with the trial, then they may be closed to recruitment and additional centres identified.

There are a number of monitoring features in place at the LCTC to ensure reliability and validity of the trial data, to be detailed in the TMP, maintained separately from this protocol.

13.3.2 Clinical Site Monitoring

In order to perform their role effectively, the Trial Manager, Data Manager and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient records, laboratory reports, appointment books, etc. Since this affects the patient's confidentiality, this fact is included on the PISC.

In agreeing to participate in this study, a PI grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. The purposes of site monitoring visits include, but are not limited to:

- assessing compliance with the trial protocol;
- discussing any emerging problems that may have been identified prior to the visit;
- checking CRF and query completion practices.

13.4 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.

CRFs will be labelled with the patient's initials and unique trial screening and/or randomisation number. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

To enable verification that appropriate informed consent is obtained, copies of the parents signed informed consent forms will be supplied to the LCTC by recruiting centres, which requires that name data will be transferred to the LCTC. This transfer of identifiable data is disclosed in the PISC.

The LCTC will preserve the confidentiality of participants taking part in the study and The University of Liverpool is registered as a Data Processor with the Information Commissioners Office. All documentation received at LCTC, which includes direct identifiers such as names (e.g. consent forms) will be stored securely and separately to all other pseudonymised participant data (e.g. CRFs).

Centres will ensure other trial documents are not posted in the same envelope as the consent form as there is a risk to patient confidentiality.

Sharp are responsible for the distribution of the trial milk formula to recruiting centres and participants homes; therefore they will be required to receive contact details including name, address and telephone details.

13.5 Quality Assurance and Control

QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded, and reported in compliance with applicable regulatory requirements. To assure protocol compliance, ethical standards, regulatory compliance, and data quality, as a minimum, the following will occur:

- The Trial Manager at LCTC will verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual site.

- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the site to be eligible to be initiated.
- Data will be evaluated for compliance with protocol and accuracy in relation to source documents.
- The study will be conducted in accordance with procedures identified in the protocol.
- Independent oversight of the trial will be provided by the IDSMC and independent members of the TSC.
- The types of materials to be reviewed, who is responsible, and the schedule for reviews may be specified or referenced in other documents.
- Types and mechanisms of training of staff for the study should be specified.
- The PI and other key staff from each centre will attend site initiation training, coordinated by the LCTC, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG is to monitor screening, randomisation and consent rates between centres.
- The process for consent, recruitment and randomisation will be evaluated for compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan.

13.6 Records Retention

The PI at each investigational site must make arrangements to store the essential trial documents including:

- Investigator Site File*
- Pharmacy Site File*
- All relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

**Must include essential documents as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice).*

Trial documents must be stored for the full archiving period of 15 years.

The PI will arrange for confidential destruction of documents at the end of this period upon instruction by the Sponsor or LCTC. The PI is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The LCTC undertakes to store originally completed CRFs for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only. The LCTC will archive the documents in compliance with the principles of GCP. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage by appropriately delegated staff members. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

14 INDEMNITY

DREAM is sponsored by Manchester University NHS Foundation Trust and coordinated by the LCTC in the University of Liverpool.

The Sponsor does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated study, the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

15 ROLES AND RESPONSIBILITIES

15.1 Role of Study Sponsor and Study Funder

The Sponsor of this trial is the Manchester University NHS Foundation Trust. The Sponsor will ensure that clear agreements are reached, documented, and carried out, respecting the dignity, rights, safety and wellbeing of participants and the relationship with healthcare professionals. This will provide for proper design, management, initiation, conduct, monitoring, data collection, data analysis, data protection, financing and reporting of this trial meeting appropriate scientific, legal and regulatory standards. The responsibility for design, conduct, management, data analysis, data interpretation, manuscript writing, and dissemination of results is delegated to the Trial Management Group.

The Funder of this trial is the National Institute of Health Research who are providing financial funding through their Efficacy and Mechanism Evaluation programme. The Funders will assure the quality of the trial, taking the lead in establishing that the research proposal is worthwhile, of high scientific quality, has an appropriate research infrastructure with expert clinical trial management, has the capacity to comply with the principles of GCP and proper use of the funds representing good value for money. The Funder had no role in the design of the trial and will not have any role during its execution, analyses, interpretation of the data, or decision to submit the results for publication.

15.2 Funding and Support in Kind

Funder	Financial and Non-financial Support Given
National Institute for Health Research	Financial funding for all aspects of the trial
Danone Nutricia Research	Limited to the supply of eHF and pHF and provision of information related to the trial product
Reacta Biotech	Limited to the supply of food Challenge Kits and provision of information related to the food

15.3 Protocol Contributors

Name	Affiliations	Contribution to protocol
Nikolaos Papadopoulos	University of Manchester	Inception and design of trial, Grant award, led the writing of this protocol, clinical and scientific arrangements, trial design and conduct
Georgios Gkimpas	University of Manchester	Collaborator from inception, design of trial, contributed to Grant award, protocol development, clinical and scientific arrangements, trial design and conduct
Michaela Brown	LCTC, University of Liverpool	Led statistical arrangements, trial design and conduct
Tracy Moitt	LCTC, University of Liverpool	Protocol development, governance arrangements and trial conduct
Amy Tao	LCTC, University of Liverpool	Protocol development, governance arrangements and trial conduct

Graham Roberts	University Hospital Southampton NHS Foundation Trust	Collaborator from inception, clinical and scientific arrangements, trial design and conduct
Louise Michaelis	The Newcastle upon Tyne Hospitals NHS Foundation Trust	Collaborator from inception, clinical and scientific arrangements, trial design and conduct
Paul Turner	Imperial College Healthcare NHS Trust	Collaborator from inception, clinical and scientific arrangements, trial design and conduct
Jürgen Schwarze	NHS Lothian	Collaborator from inception, clinical and scientific arrangements, trial design and conduct
Paula Williamson	LCTC, University of Liverpool	Collaborator from inception, trial design and conduct
Lynne Regent	Anaphylaxis Campaign	Collaborator from inception, trial design and conduct

15.4 Trial Committees

15.4.1 Trial Management Group (TMG)

A TMG will be formed comprising the CI, other lead investigators (clinical and non-clinical) and members of the LCTC. The TMG will be responsible for the day-to-day running and management of the trial and will meet approximately 12 times a year. Refer to the TMG terms of reference and trial oversight committee membership document for further details.

15.4.2 Trial Steering Committee (TSC)

The TSC will consist of an independent medical expert (chairperson), two independent experts in the field of paediatric allergy and an independent biostatistician. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman.

The ultimate decision for the continuation of the trial lies with the TSC. The TSC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually) (at least annually). Refer to the TSC terms of reference and trial oversight committee membership document for further details.

15.4.3 Independent Data and Safety Monitoring Committee (IDSMC)

The IDSMC consists of an independent medical expert (chairperson) in the field of paediatric health, an independent expert in the field of paediatric allergy, and an independent expert in medical statistics.

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually). Details of the interim analysis and monitoring are provided in section 11.4.

The IDSMC will provide a recommendation to the TSC concerning the continuation of the study. Refer to the IDSMC charter and trial oversight committee membership document for further details.

16 PUBLICATION AND DISSEMINATION

16.1 Publication Policy

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the TMG. Publications shall include a list of participating PIs and collaborators.

The TMG will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected.

All publications shall include a list of the study team, and if there are named authors, these should include the trial's CI, Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least.

The ISRCTN allocated to this trial will be attached to any publications resulting from this trial and members of the TSC and IDSMC should be acknowledged.

Any publications arising from this research will be reviewed appropriately prior to publication. Use of data and distribution of publications will be carried out in accordance with the individual contractual agreements in place.

16.1.1 Authorship

Contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line as members of the DREAM Consortium which will also be named at the manuscript head.

16.2 Dissemination to Key Stakeholders

On completion of the research, a Final Trial Report will be prepared and submitted to the REC. The results of DREAM will be published regardless of the magnitude or direction of effect. Lay summaries of the study findings will be posted to the trial website.

Information will be conveyed to the academia, the research community, the clinicians, and the industry, via several routes:

i. *Publications in peer reviewed journals*. Including the mechanistic component, it is expected that the proposed study will furnish a large body of evidence, which could provide a basis for several manuscripts. This will facilitate rapid knowledge exchange within the scientific community.

ii. *Dissemination through the institutions communication structures*: Evidence will be highlighted via the website of the institutions of the co-applicants, with permanent URLs linking to these publications; results will also be promoted via mailing lists and discussion fora.

iii. *Presentations in scientific meetings:* Findings will be conveyed via presentations in national and international conferences, seminars and workshops; hand-outs and electronic versions of the presentations will also be provided.

iv. *Training of clinicians:* Throughout the study, clinical collaborators will train on all its aspects. Visiting clinicians and other clinical fellows and trainees will also be introduced into these techniques, both during and after the study. This will allow the transfer of knowledge to other institutions and hospitals.

v. *Round table and consensus meetings:* Insofar as the proposed research has the potential to radically alter the guidelines on CMA management, international society meetings will be arranged with the purpose of communicating and discussing the findings; symposia and meetings of opinion leaders will be organised in order for a consensus to be reached; it is expected that the findings could form the basis of improved Practice Parameters and PRACTical ALlergy (PRACTAL) documents.

vi. *Contact with the industry:* This proposal entails co-operation with the industry, as Nutricia-Danone will be supplying the study products (partially hydrolysed and extensively hydrolysed formulae). Industry networking will be expanded throughout and beyond the study via contact with industry representatives and by securing industry support for the promotion of our findings and for further research based on them.

vii. *Patent submission*: Findings with industrial applications will be appropriately exploited through patent submissions and adequate promotion.

viii. *Public promotion:* Upon potential establishment of our protocol as a routine practice option for CMA, we will inform patients in lay language via use of leaflets and by actively pursuing to present and discuss this option on TV and radio broadcasts. The Anaphylaxis Campaign Charity will also assume a very active role in dissemination through its extensive network.

16.3 Data Sharing

All requests for access to the anonymised individual participant data (IPD) will be reviewed by an internal committee at the CTU and discussed with the Chief Investigator in accordance with the CTU policy on data sharing.

17 CHRONOLOGY OF PROTOCOL AMENDMENTS

17.1 Version 1.0 (07/10/2020)

Summary of Amendments		
Section Number	**Section Title**	**Summary of Changes**
N/A	N/A	N/A – Original version, not REC approved

17.2 Version 2.0 (16/12/2020)

Summary of Amendments		
Section Number	**Section Title**	**Summary of Changes**
2	Protocol summary	Addition of randomisation ratio to the summary table
4	Trial Design	Clarification of 1:1 randomisation ratio
8.5	Randomisation Procedures	Clarification of 1:1 randomisation ratio
11.2	Method of Randomisation	Clarification of 1:1 randomisation ratio

17.3 Version 3.0

Summary of Amendments		
Section Number	**Section Title**	**Summary of Changes**
3.4.1	Primary Outcome/Endpoint	Clarification of CM tolerance, characterised as CM protein tolerant.
3.4.2	Secondary Outcome/Endpoint	Addition of safety endpoint as per initial Detailed Research Plan.
6.1	Inclusion Criteria	Clarification of skin prick test to whole, fresh milk. Clarification that onset or worsening of pre-existing eczema is not an exclusion criterion.
7	Participant Timeline, Assessments and Procedures	Change to sampling timepoints: Blood samples will be taken at visit 1, 7 and 8. Stool sample containers will be provided at visits 2, 3, 6, and 7. Parents will take samples will be taken at home and collected at visits 3 or 4, 7 and 8. Clarification of the randomisation timepoints. Addition of telephone follow-up questions, to remind parents of formula expiration dates and shelf-life; and capture the occurrence of any unplanned visits
8.4.1.1	Visit 1 (Screening Visit)	Clarification of skin prick test to whole, fresh milk.

		Removal of SPT to casein, a-lactalbumin and b-lactoglobulin for practical reasons.
8.4.1.2	Visit 2 (Open Challenge to pHF)	Clarification that randomisation may be postponed in the event of weight loss. Addition of the provision of stool sample containers to return stool sample at visit 3 or 4.
8.4.1.3	Visit 3 (Open Challenge to CM Formula)	Addition of the collection of stool samples. Addition of the provision of stool sample containers to return stool sample at visit 7. Clarification that randomisation may be postponed in the event of weight loss. Clarification of the process of prescribing/dispensing study product.
8.7.1	Oral Immunotherapy (OIT) Visits	Clarification that several increasing doses will be carried out at each OIT visit.
8.7.1.1	Visit 4 (OIT Visit 1)	Addition of the collection of stool samples. Clarification of the process of prescribing/dispensing study product.
8.7.1.2	Visit 5 (OIT Visit 2)	Capture the occurrence of any unplanned visits. Clarification of the process of prescribing/dispensing study product.
8.7.1.3	Visit 6 (OIT Visit 3)	Addition of the provision of stool sample containers to return stool sample at visit 7. Capture the occurrence of any unplanned visits. Clarification of the process of prescribing/dispensing study product.
8.7.2	Telephone Calls	Addition of telephone follow-up questions, to remind parents of formula expiration dates and shelf-life; and capture the occurrence of any unplanned visits.
8.7.3.1	Visit 7 (Mid trial Visit)	Capture the occurrence of any unplanned visits. Addition of the provision of stool sample containers to return stool sample at visit 8.
8.7.4.1	Visit 8 (DBPCFC Day 1)	Clarification of skin prick test to whole, fresh milk. Addition of the request to return unused formula at the next visit. Removal of SPT to casein, a-lactalbumin and b-lactoglobulin for practical reasons.
8.7.4.2	Visit 9 (DBPCFC Day 2)	Addition of the unblinding of the DBPCFC. Addition of guidance for reintroducing milk/continuation of CMA management at end of trial. Collection of any unused tins for destruction.
8.10.1.1	Buccal Samples	Addition of further instructions to buccal sample collection process.
8.11.1	Premature Discontinuation of Trial Treatment	Removal of the definition of severe anaphylaxis for consistency with another definition in the protocol, and to allow more clinical freedom to site PIs to

		consider each participant's follow-up based on local routine clinical practice and participant-specific clinical features and findings.
8.11.3	Participant Withdrawal from Optional Activities	Addition of section to clarify the process for participants who wish to withdraw from activities that are optional to the study.
9.2.2	Manufacture and Distribution	Addition of section to clarify the process of requesting further trial formula.
9.3.5	Accountability Procedures for Trial Treatment/s	Removal of the need for an unblinded person locally, as the blinding will be done centrally by Reacta.
10.11	Safety Reporting Responsibilities – Investigator	Removal of the requirement to use medDRA coding.
N/A	Throughout	Correction of typographical errors. Clarification of CM tolerance, characterised as CM protein tolerant. Addition of instruction to document participant results in medical records.

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19 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Documents referenced within the protocol are separately maintained and version controlled. Any of the supplementary documents subject to REC review are submitted as separate version-controlled documents.

APPENDICES

Documents referenced herein as accompanying the protocol that separately updated and version controlled are:

Open Challenge SOP
DBPCFC SOP
OIT SOP
Parent Information Sheet and Consent Form
GP Letter
Invitation Letters
Poster
Information Leaflet
Statistical Analysis Plan
Trial Monitoring Plan
Trial Risk Assessment

Appendix 1: MHRA Notification of no requirement for CTA

Notification that a Clinical Trial Authorisation (CTA) is not required

Dear Prof. Papadopoulos,

Thank you for your email dated 1st February 2017.

I can confirm that your proposal is not a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC and no submission to the Clinical Trials Unit at the MHRA is required.

Kind regards

Clinical Trial Helpline

MHRA

Medicines & Healthcare products
Regulatory Agency