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Desensitisation regimens in milk allergy

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Registration date 08/01/2021	**Overall study status** Stopped	[_] Statistical analysis plan [X] Results
Last Edited 30/12/2025	**Condition category** Other	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
Cow's milk allergy (CMA) occurs when proteins in cow's milk are recognised as a foreign substance by the body and the immune system reacts to them by developing allergic symptoms. One type of CMA is caused by the immunoglobulin E antibody (called IgE). With this type of CMA, symptoms can appear within minutes of consuming cow's milk or up to 2 hours afterwards. CMA is one of the most common food allergies in infants but there is no standardised way to treat it. Current guidelines suggest complete avoidance of all products containing cow's milk and waiting for the allergy to resolve spontaneously. The 'Milk Ladder' is also supported, which involves slowly reintroducing processed milk and dairy products back into the baby's diet but the Milk Ladder is not always suitable for all babies with cow's milk allergy.
The aim of this study is to assess the use of a partially hydrolysed (pHF) milk formula (which means that the milk protein is partially broken down) and also a fully hydrolysed (eHF) milk formula, for desensitisation to cow's milk in children with CMA.

Who can participate?
Infants aged 6-12 months old, who have an allergy to cow's milk and are fed with formula milk.

What does the study involve?
Participating infants will be given one of the milk formulas to be fed freely or will follow a strictly controlled schedule (oral immunotherapy). The hospital staff will not know who receives which formula. After 1 year of feeding, the infants will take part in a 'food challenge' where they will be given a food that contains cow's milk on one day and on a different day (either before or after), the same food will be given but it would not contain any cow's milk (placebo), and they will be monitored for any allergic reactions. The hospital staff will not know which food contains cow's milk. This is to determine whether 1 year of feeding with pHF milk is more effective than feeding with eHF milk in treating infants with moderate-severe CMA.

What are the possible benefits and risks of participating?
The control (eHF) and intervention (pHF) formulas are widely used as a supplement to or substitute for breastfeeding. Few side effects are expected from feeding with these formulas compared to normal formulas but for children with CMA there is a chance that they may experience anaphylaxis, rash, worsening of eczema or asthma. These reactions are commonly expected in patients with CMA.
The research team are well experienced in managing allergic reactions and will be able to treat

any that might occur. They will also provide parents with training to help identify any reactions and advise what they should do if they ever happen. The child's doctor will also prescribe adrenaline autoinjectors (allergy pen) for use at home if it is ever needed. Bruising may be experienced following blood tests and blood sample collections, but they will be minor and should clear-up after a few days. It is hoped that the results of this study will help doctors and patients in the future decide how they should or should not treat infants with CMA.

Where is the study run from?
Liverpool Clinical Trials Centre (UK)

When is the study starting and how long is it expected to run for?
July 2019 to December 2025

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
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Contact information

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
279786

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 47599, IRAS 279786

Study information

Scientific 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 (the DREAM study)

Acronym
DREAM

Study objectives
The primary hypothesis is that 1 year of feeding with pHF will be more efficacious than with eHF in the treatment of 6-12-month-old infants with IgE-mediated CMA.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 09/02/2021, London-Central Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ; +44 (0)207 104 8221; londoncentral.rec@hra.nhs.uk), ref: 20/LO/1254

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Cow's milk allergy

Interventions
DREAM is a parallel-group, double-blind, randomised, normal-care-controlled study that will evaluate the efficacy and safety of partially hydrolysed milk formula (pHF) fed to infants with moderate/severe CMA, in comparison to the current gold standard of feeding with extensively hydrolysed formula (eHF). Infants who can tolerate pHF from the start will be fed freely, whereas infants who cannot, will be fed through an oral immunotherapy (OIT) schedule.

Potential infants will be identified by their usual care teams at recruiting sites and Patient Identification Centres (PICs). The pregnancy and parenting club, Bounty, will also send invitation letters and information leaflets to parents of infants aged 5-11 months (to allow for processing time) who are registered in the Bounty database and have given consent to contact for research. Parents who receive these invitations will be directed to a short online survey to fill in. Infants deemed potentially eligible based on these replies will be invited to take part in a screening visit. The trial will recruit for 3 years and each infant will be in the trial for 1 year.

VISIT 1: At visit 1 (screening visit) the parent will provide legal written informed consent to participate. Patients with a history of CMA will be reviewed to see if they meet specific criteria for moderate/severe CMA (e.g Skin Prick Test result to CM of ≥5mm or a CM-specific IgE blood value of ≥2 kU/l). Those who meet all inclusion criteria and no exclusion criteria will proceed to visit 2, which is a pHF food challenge.

Parents will also be asked whether they consent to the collection of some blood, stools and buccal swab samples for future research (optional part of the trial). These samples will be collected at three timepoints during the trial. The family can still be recruited to DREAM without agreeing to this additional option.

One to two phone calls will also take place throughout the trial during which nurses will ask a number of questions to check-up on the participant and if parents have any questions. Each telephone call will last about 5 minutes, and will take place twice for the participants on the free feeding arm, and once for the participants on the OIT arm (as these will remain engaged with the researchers during the OIT module, hence less phone communication will be needed).

VISIT 2: If participants do not react at the pHF challenge at visit 2 this means that they are either not truly allergic to cows milk or they are allergic to cows milk but they can tolerate pHF. To

clarify this, these participants will go to visit 3 which is an open challenge to cows milk to confirm if they are allergic to cows milk or not. If, on the other hand, participants do react to the pHF challenge at visit 2, that means that they are milk-allergic and are also allergic to pHF as well. These participants do not need to undergo a milk challenge at visit 3 to confirm milk allergy, so they will skip visit 3 and will go straight to the OIT module (visit 4) where they will be randomised.

VISIT 3: Only participants who did not react to the pHF challenge at visit 2, will attend visit 3. Visit 3 entails an open challenge to cows milk to confirm whether these participants are indeed allergic to cows milk. Participants who do not react to this challenge will be confirmed to not be milk allergic and will not proceed any further in the trial. Those who do react will be confirmed to be milk allergic, will continue with the trial, and because they will have already tolerated pHF from the challenge at visit 2, will be allowed to have pHF freely at home. They will be randomised at this visit (visit 3) and given blinded product (pHF or eHF) to have freely at home. They will skip the OIT module because they can already tolerate pHF freely, therefore, they do not need immunotherapy, and will go straight to visit 7.

VISIT 4: Participants that reacted to the pHF challenge at visit 2 will attend this visit (and will have skipped visit 3 as they do not need a CM challenge to confirm CM-allergy - reacting to pHF confirms CM allergy). These participants will be randomised to pHF or eHF at this visit (visit 4) and start on a blinded OIT module that includes 3 visits. During each visit the participants will be given increasing doses of their allocated formula in order for them to start tolerating increasingly higher doses.

VISIT 5: This is the second visit of the OIT module. Participants on the OIT module will be given increasing doses of pHF in order for them to start tolerating increasingly higher doses.

VISIT 6: This is the third visit of the OIT module. Participants on the OIT module will be given increasing doses of pHF in order for them to start tolerating increasingly higher doses.

Telephone call 1: Participants on the free-feeding arm will receive telephone call 1 to check-up on the participant and check if the parents have any questions.

VISIT 7: All participants will attend this visit (both free-feeding and OIT participants) in order to review the diaries, provide new diaries, do a clinical examination and collect blood samples, stool samples and buccal swabs to be stored for future research.

Telephone call 2: All participants will receive telephone call 2 to check-up on the participant and check if the parents have any questions.

VISIT 8: All participants will attend this visit that includes day 1 of a Double-blind placebo-controlled food challenge to cows milk-containing product or placebo. This will be either the active or placebo day.

VISIT 9: All participants will undergo this visit that includes day 2 of the double-blind placebo-controlled food challenge to cows milk-containing product or placebo. This will be the alternate day to Day 1 (active or placebo day). This will be the last visit of the trial which will confirm if the participants have outgrown their milk allergy or they are still allergic. After this visit, all participants will be followed up further by their GP as part of their normal care and no additional follow up will take place as part of the trial.

Intervention Type

Other

Primary outcome(s)
CM tolerance assessed using a double-blind, placebo-controlled food challenge (DBPCFC) at 12 months after randomisation (randomisation will take place at V2 for pHF-reactive infants and V3 for pHF-tolerant infants)

Key secondary outcome(s))
Current secondary outcome measures as of 18/10/2021:

1. The dose at which reactivity occurs in the DBPCFC, measured using the DBPCFC at 12 months after randomisation
2. The maximal wheal size of skin prick test to cows' milk, measured by a skin prick test at visit 1 and visit 8
3. Specific IgE levels to cows' milk casein, a-lactalbumin and b-lactoglobulin, measured by a blood test at visit 1 and visit 8
4. Eczema Area and Severity Index (EASI) measured using the EASI questionnaire at visits 1, 2, 3, 4, 5, 6, 7, 8, 9
5. Wheeze (during last 12 months, use of systemic steroids, hospitalizations), from medical history of wheeze collected at visits 1, 2, 3, 4, 5, 6, 7, 8, 9
6. Doctor diagnosis of other food allergies, from medical history of allergies taken at visit 1 and visit 9
7. Height measured with locally available equipment at visits 1, 2, 3, 4, 5, 6, 7, 8, 9
8. Weight measured with locally available equipment at visits 1, 2, 3, 4, 5, 6, 7, 8, 9
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)

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Previous secondary outcome measures:

1. The dose at which reactivity occurs in the DBPCFC, measured using the DBPCFC at 12 months after randomisation
2. The maximal wheal size of skin prick test to cows' milk, measured by a skin prick test at visit 1 and visit 8
3. Specific IgE levels to cows' milk casein, a-lactalbumin and b-lactoglobulin, measured by a blood test at visit 1 and visit 8
4. Eczema Area and Severity Index (EASI) measured using the EASI questionnaire at visits 1, 2, 3, 4, 5, 6, 7, 8, 9
5. Wheeze (during last 12 months, use of systemic steroids, hospitalizations), from medical history of wheeze collected at visits 1, 2, 3, 4, 5, 6, 7, 8, 9
6. Doctor diagnosis of other food allergies, from medical history of allergies taken at visit 1 and visit 9
7. Height measured with locally available equipment at visits 1, 2, 3, 4, 5, 6, 7, 8, 9
8. Weight measured with locally available equipment at visits 1, 2, 3, 4, 5, 6, 7, 8, 9

Completion date
30/12/2025

Eligibility

Key inclusion criteria
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 7.5 kg
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)

Added 17/05/2022:
*5 mm to either whole, fresh milk, or commercial milk extract

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
6 months

Upper age limit
12 months

Sex
All

Total final enrolment
16

Key exclusion criteria
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). Worsening of pre-existing eczema due to CM consumption is not an exclusion criterion. Added 17/05/2022: 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

Added 17/05/2022: 9. Another infant from the same household is currently participating in the study

Visit 2/3 Exclusion Assessments:
10. Severe anaphylaxis (anaphylaxis refractory to a single dose of intramuscular adrenaline) during challenge to pHF or CM

Date of first enrolment
30/08/2022

Date of final enrolment
30/06/2025

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
NHS Lothian
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Sponsor information

Organisation
Manchester University NHS Foundation Trust

ROR
https://ror.org/00he80998

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research; Grant Codes: 17/60/44

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be included in the subsequent results publication

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		30/12/2025	30/12/2025	No	No
HRA research summary			28/06/2023	No	No
Study website		11/11/2025	11/11/2025	No	Yes