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Synopsis

Desensitisation to cow's milk, following partially or extensively hydrolysed formulae feeding regimens, in infants with allergy to cow's milk: the DREAM RCT Synopsis (The DREAM study)

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Abstract

Background: Immunoglobulin E-mediated (immediate) cow's milk allergy is one of the most frequent food allergies in infants, with a significant adverse impact on quality of life. There is no satisfactory treatment for cow's milk allergy, and guidelines recommend milk avoidance, feeding with 'hypoallergenic' formulas (extensively hydrolysed formulas), emergency management of accidental reactions and waiting for the allergy to resolve spontaneously. Currently, the only potentially curative regimen is oral immunotherapy, that is, exposing patients to increasing doses of cow's milk using a strictly controlled dose schedule. However, milk immunotherapy is not used in clinical practice due to risk of reactions. DREAM's intention was to explore whether oral immunotherapy with a partially hydrolysed cow's milk formula would be able to provide a safe and effective means of oral immunotherapy for milk-allergic infants.

Limitations: The trial was affected by a serious breach that led most of the participants to receive partially hydrolysed formula, even if randomised to extensively hydrolysed formula. It also ended prematurely due to unsatisfactory recruitment, and the main outcomes were not reached.

Methods: DREAM was a two-arm, parallel-group, double-blind randomised controlled trial. Eligible patients were infants aged 6–12 months with convincing medical history of *immunoglobulin E-mediated* allergy to cow's milk formula. Inclusion criteria included a titre of cow's milk-specific immunoglobulin E equal or higher to 2 kU/l, or wheal equal or over 5 mm to skin prick test to milk. Additionally, for the infants to be randomised, they needed to have a positive result to an open oral challenge either to partially hydrolysed formula or to milk. Participants were randomised to extensively hydrolysed formula or partially hydrolysed formula with a 1 : 1 ratio. Following randomisation, participants commenced free-feeding with the blinded product (or strict dose-based oral immunotherapy if they

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were not tolerant of the blinded product). The main outcome was the result of a double-blind, placebo-controlled food challenge to cow's milk at the end of 1 year of free-feeding (or of dose-based immunotherapy) to establish if infants had become tolerant. As the trial was discontinued early on account of poor recruitment, no infant progressed to the double-blind, placebo-controlled food challenge.

Results: Out of 16 randomised participants who underwent an initial partially hydrolysed formula challenge, only 1 (6.25%) reacted to it (95% confidence interval 00.0 to 19.6). Hence, 93.75% of the allergic infants randomised in the trial tolerated partially hydrolysed formula. All fifteen infants that were found to be partially hydrolysed formula-tolerant also received partially hydrolysed formula free-feeding at home, on account of the serious breach. As per the trial's criteria, these infants (and all randomised participants) were shown to be allergic to cow's milk via either a positive open challenge to it (for the 15 partially hydrolysed formula-tolerant infants) or a positive open challenge to partially hydrolysed formula (for the single partially hydrolysed formula-reactive infant).

Conclusions: Partially hydrolysed formula was tolerated by the majority of well-characterised and confirmed cow's milk-allergic infants in the DREAM trial.

Future work: Our findings demonstrate that partially hydrolysed formula holds promise as a potential oral immunotherapy medium in free-feeding oral immunotherapy regimens in future research. Further trials designed on the premise of partially hydrolysed formula oral immunotherapy are needed.

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A plain language summary of this synopsis is available on the NIHR Journals Library Website https://doi.org/10.3310/GJGG7715.

Introduction

The DREAM trial aimed to assess a new treatment for immunoglobulin E (IgE)-mediated (immediate) cow's milk allergy (CMA) in infancy. CMA is one of the most frequent food allergies in infants;[1–7] British Society for Allergy and Clinical Immunology (BSACI) guidelines recommend cow's milk (CM) avoidance, feeding with 'hypoallergenic' formulas [extensively hydrolysed formulas (eHFs)], emergency management of accidental reactions and waiting for spontaneous resolution.[8] Feeding with processed CM products (the Milk Ladder) is also supported, but this approach is non-standardised. The only potentially curative regimen is oral immunotherapy (OIT) to CM, that is, feeding CM to patients on a strict medically supervised dosing schedule, which is not part of routine care due to increased risk of reactions.[9–13] OIT to milk, in particular, is well recognised to be associated with risks.[14] Thus, patients with IgE-mediated CMA are currently advised to strictly avoid CM and may need to carry an adrenaline autoinjector,[15] which, on occasion, fails to prevent mortality.[16] Furthermore, evidence shows that a number of patients will not achieve 'spontaneous' resolution of CMA as early as previously believed,[17–20] with evidence supporting a poorer prognosis, especially for more 'severe' allergic children.[17,18,21,22] This necessitates a reassessment of our current approach of withholding interventions in anticipation of spontaneous resolution. OIT is the most promising of these options, as recently has been seen for other foods such as peanut.[23,24]

We proposed that free-feeding with a partially hydrolysed formula (pHF), a more 'allergenic' formula than the current standard of care (eHF), could help resolve CMA. We designed a clinical trial where CMA infants would be randomised into pHF (active product) or eHF (standard care) feeding for a year and would then be assessed for CMA resolution via a double-blind, placebo-controlled food challenge (DBPCFC). Infants would be stratified by initial pHF reactivity, and those who could not tolerate pHF free-feeding initially would first be desensitised via a short dose-based OIT regimen. The trial flow chart can be seen in *Figure 1*.

Objectives and outcomes

The **primary objective** was to determine whether 1 year of feeding with pHF is more efficacious than with eHF as a treatment for 6- to 12-month-old infants with IgE-mediated CMA.

The **secondary objectives** were:

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

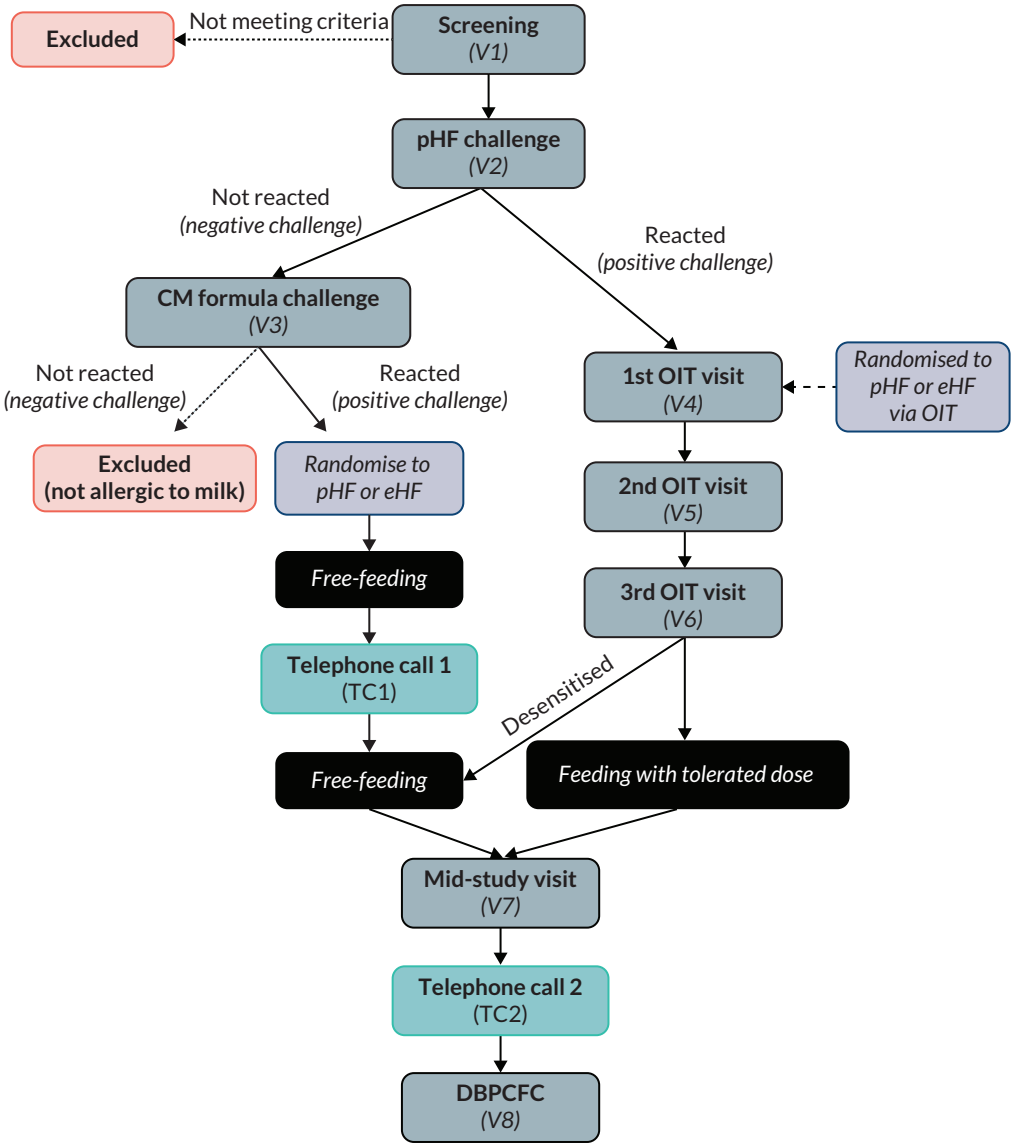

FIGURE 1 Trial flow chart. CM, cow's milk; DBPCFC, double-blind placebo controlled food challenge; eHF, extensively hydrolysed formula; OIT, oral immunotherapy; pHF, partially hydrolysed formula; TC, telephone call; V1, visit 1; V2, visit 2.

5. To characterise participants' reactivity to pHF.

The **primary outcome** is whether the infant is characterised as CM protein-tolerant as per the result of a DBPCFC which would take place 12 months after randomisation [randomisation takes place at visit 4 (V4) for pHF-reactive infants and visit 3 (V3) for pHF-tolerant infants].

The **secondary outcomes** were:

1. the dose at which reactivity occurs in the DBPCFC
2. the maximal wheal size of skin prick test (SPT) to CM
3. specific IgE levels to CM, casein, alpha-lactalbumin and beta-lactoglobulin
4. Eczema Area and Severity Index (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 (AEs) 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 (V8).

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Methods for data collection and analysis – diagram of research pathway

DREAM was a two-arm, parallel-group, double-blind randomised controlled trial. Eligible patients were infants aged 6–12 months with convincing medical history of *IgE-mediated* allergic reaction following ingestion of CM formula, as determined by a trial physician. To be recruited, infants were required to be fed with formula (either exclusively or mixed with breastfeeding) and have a titre of CM-specific IgE in serum, equal or higher to 2 kU/l or wheal reaction of equal or over 5 mm to SPT to CM at inclusion. Additionally, the infants needed to have a positive result to either pHF or CM in the trial challenges and be at least 7.5 kg at the time of randomisation.

Infants were not eligible if they had unequivocal history of severe anaphylaxis to CM in the past requiring more than one dose of adrenaline; doctor diagnosis of *non-IgE-mediated* allergy to CM or CM formula [eosinophilic esophagitis, gastritis, gastroenteritis, food protein-induced enterocolitis syndrome (FPIES), enteropathies and proctocolitis]; any significant clinical condition that may interfere with patient's safety or the study outcomes; a requirement for continuous or frequent (monthly or more) intermittent use of oral corticosteroids for other conditions; a requirement for pharmacotherapy for any other clinical condition, if it could interfere with the patient's safety or the study outcomes; or a history of overnight hospitalisation for wheeze and/or bronchiolitis on more than one occasion. Infants were ineligible if their parents or guardians were unlikely to comply with the study protocol for any reason, if they were currently participating in another trial that may interfere with their safety or the study outcomes or if another infant in the same household was currently participating in the study. Additionally, if the infant developed severe anaphylaxis during the challenges to pHF or CM, they were not eligible to be randomised for the trial.

Patients were randomised to eHF or pHF with a 1 : 1 ratio using a secure (24-hour) web-based randomisation programme. Randomisation lists were generated with random variable block sizes, stratified by site and initial tolerance to pHF. The randomisation list was produced by an independent statistician, who was not otherwise involved in the DREAM study.

Following randomisation, participants commenced free-feeding or dose-based OIT, followed by free-feeding with the allocated product. Initial product was dispensed by the hospital pharmacy with additional product dispensed to participants' homes. Parents of participants, staff at the Clinical Trials Unit (except statisticians and data managers as appropriate) and all members of the research teams managing participants were blinded to treatment allocation.

The primary outcome was CM-protein tolerance according to the result of a DBPCFC at 12 months after randomisation. Secondary outcomes were the dose at which reactivity occurs in the DBPCFC; the maximal wheal size of SPT to CM; specific IgE levels to CM, casein, alpha-lactalbumin and beta-lactoglobulin; EASI scores for eczema; wheeze; doctor diagnosis of other food allergies; height; weight and AEs.

The original planned sample size for DREAM was 206 patients. This allowed for 20% attrition. Eighty-two infants per group were required to detect a difference in the proportion of infants who became tolerant from 0.35 in the eHF group to 0.6 in the pHF group (odds ratio of 2.786), using a two-group chi-squared test with 90% power and a two-sided 5% significance level. Due to poor recruitment, it was agreed with the funder to reduce the statistical power to 80%, requiring 62 infants per group and a total sample size of 156 after inflating for 20% attrition.

There was a two-stage internal pilot planned to assess feasibility of recruitment. The first stage, after 13 months of recruitment, required that at least 20% of the total sample size was achieved, at least 30% consent rate and < 20% dropout rate. The second stage was planned for after 25 months of recruitment required that at least 60% of the total sample size was achieved, but this stage was never reached, as the trial was stopped prematurely by the funder due to poor recruitment.

Further details on inclusion/exclusion criteria and other protocol aspects can be seen at *Appendix 1*.

Statistical analysis

The planned statistical analysis as outlined in the protocol was to present binary outcomes (including the primary outcome) in terms of relative risk and analyse using logistic regression adjusted for stratification factors along with a sensitivity analysis using a chi-squared test for consistency with the sample size calculation and subgroup analyses for initial tolerance to pHF. Continuous data were to be presented as means and standard deviations and analysed using two-sample t-tests (or if data were skewed as medians and ranges and analysis using Mann–Whitney U-tests). Baseline characteristics and AEs were also to be presented descriptively split by treatment group.

As the study was stopped prematurely and there were only 16 participants randomised at this time, the planned analysis could not be completed. A statistical analysis plan was prepared, focusing on descriptive presentation of results, where possible. There was no formal comparison of outcomes performed. The plan and other relevant documents are kept by the Liverpool Clinical Trials Centre, University of Liverpool.

Results summary

DREAM opened to recruitment on 30 August 2022 and was closed prematurely on 18 October 2023. Sixteen infants were randomised to eHF (n = 8) or pHF (n = 8). The Consolidated Standards of Reporting Trials flow diagram can be seen in *Figure 2*. All participants commenced feeding with the allocated product, but due to the serious breach (outlined in detail in the challenges section), participants in the eHF arm were unintentionally switched to pHF when they received shipments at home (n = 7 participants affected).

Baseline demographics and clinical characteristics were relatively well balanced between the treatment groups (*Table 1*).

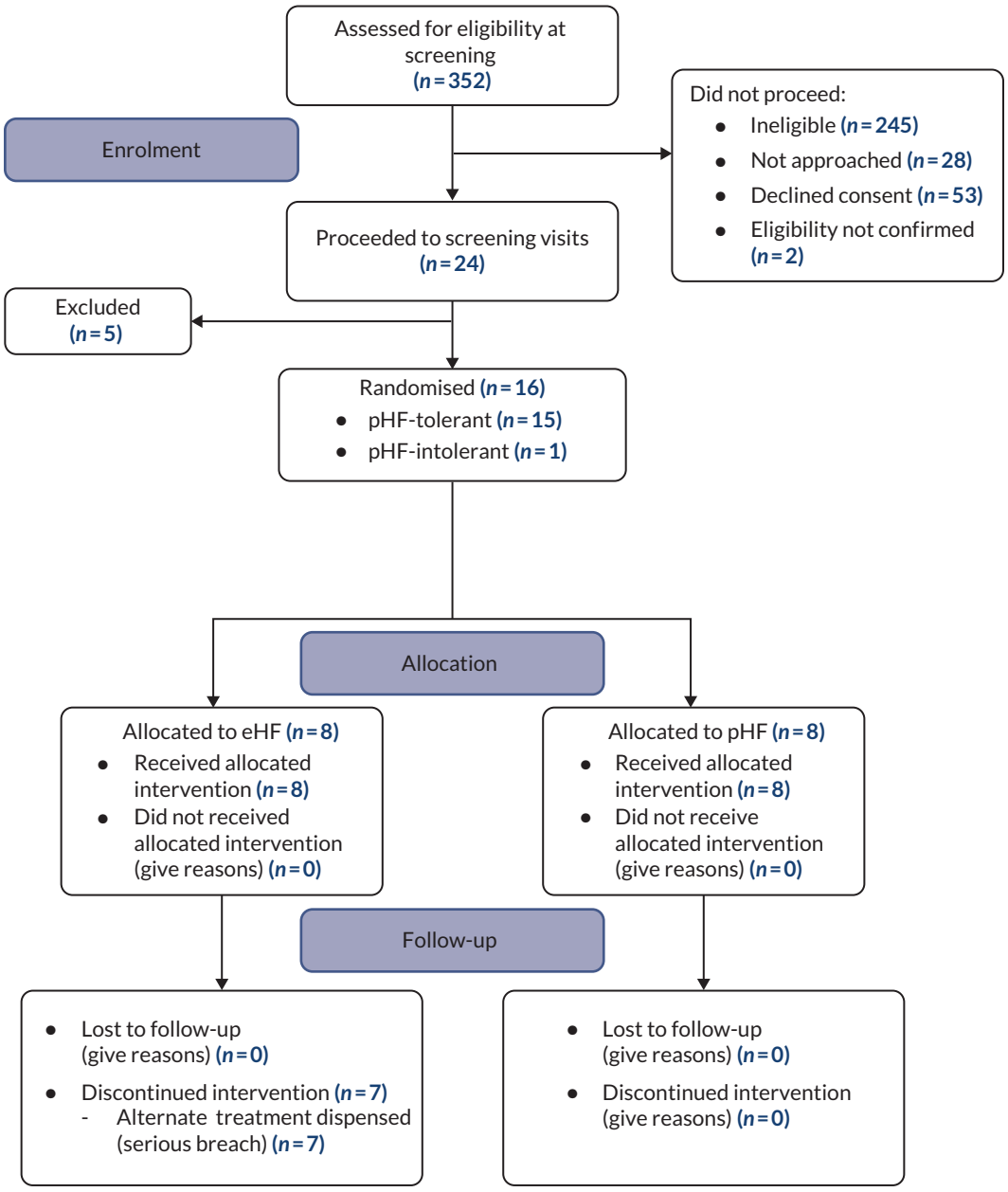

FIGURE 2 Consolidated Standards of Reporting Trials flow diagram.

The mean and median age at first screening was 10 months, which was closer to the end of the recruitment window rather than the start. Most infants were male (11 infants – 68.8%). Many patients (14 infants – 87.5%) had been diagnosed with both atopic dermatitis and other IgE food allergies; almost half (7 infants – 43.8%) had a diagnosis of urticaria and angioedema (*Table 2*).

Median/mean weight was 8.45/8.46 kg, respectively, with minimum weight being 7.5 kg as per the inclusion criterion; mean height was 71.31 cm, and median was 71.00 cm (*Table 3*).

Allergy diagnostic testing median/mean wheal sizes for SPT using fresh milk were 8.5/9.69 mm, respectively, with a minimum of 4 mm, while the median/mean values for commercial milk extract were smaller (7.5/7.75 mm, respectively, with a minimum of 2 mm) (*Table 4*).

The CM IgE median/mean values were 4.39/16.39 kU/l, respectively; while these values for alpha-lactalbumin were 1.06/2.35 kU/l, for beta-lactoglobulin were 0.62/3.65 kU/l and for casein were 1.99/11.85 kU/l, respectively (*Table 5*).

TABLE 1 Demographic details

	Randomised patients			Patients who attended V1 but were not randomised
	Intervention: pHF	Control: eHF	Total	
Age at first screening (months)				
N	8	8	16	8
Mean (SD)	10.00 (1.51)	10.00 (1.93)	10.00 (1.67)	8.25 (3.45)
Median (IQR)	9.50 (2.50)	10.00 (2.00)	10.00 (2.50)	9.00 (3.50)
Range (minimum–maximum)	(8.00–12.00)	(6.00–12.00)	(6.00–12.00)	(1.00–12.00)
Missing	0	0	0	0
Gender: *n* (%)	(*N* = 8)	(*N* = 8)	(*N* = 16)	(*N* = 8)
Female	3 (37.5%)	2 (25%)	5 (31.3%)	3 (37.5%)
Male	5 (62.5%)	6 (75%)	11 (68.8%)	4 (50%)
Missing	0	0	0	1

IQR, interquartile range V1, visit 1.

TABLE 2 Medical history

	Randomised patients			Patients who attended V1 but were not randomised
	Intervention: pHF	Control: eHF	Total	
	(*N* = 8)	(*N* = 8)	(*N* = 16)	(*N* = 8)
Asthma	0	1 (12.5%)	1 (6.3%)	1 (12.5%)
Wheeze	0	1 (12.5%)	1 (6.3%)	1 (12.5%)
Urticaria and angioedema	6 (75%)	1 (12.5%)	7 (43.8%)	6 (75%)
Atopic dermatitis	7 (87.5%)	7 (87.5%)	14 (87.5%)	3 (37.5%)
Doctor-diagnosed food allergies	7 (87.5%)	7 (87.5%)	14 (87.5%)	5 (62.5%)
Drug allergies	0	1 (12.5%)	1 (6.3%)	1 (12.5%)
Other diseases	4 (50%)	1 (12.5%)	5 (31.3%)	2 (25%)
None	0	0	0	0
Not known	0	0	0	0

TABLE 3 Physical exam

	Randomised patients			Patients who attended V1 but were not randomised
	Intervention: pHF	Control: eHF	Total	
Weight (kg)				
N	8	8	16	8
Mean (SD)	8.65 (0.74)	8.27 (0.54)	8.46 (0.66)	7.59 (3.20)
Median (IQR)	8.75 (1.20)	8.30 (0.73)	8.45 (1.00)	8.90 (1.80)
Range (minimum–maximum)	(7.50–9.60)	(7.50–9.10)	(7.50–9.60)	(0.00–9.90)
Missing	0	0	0	0
Height (cm)				
N	8	8	16	8
Mean (SD)	71.13 (2.47)	71.50 (1.20)	71.31 (1.89)	61.63 (25.04)
Median (IQR)	71.50 (3.50)	71.00 (1.00)	71.00 (1.50)	70.00 (5.50)
Range (minimum–maximum)	(67.00–74.00)	(70.00–74.00)	(67.00–74.00)	(0.00–74.00)
Missing	0	0	0	0
EASI score				
N	8	7	15	3
Mean (SD)	9.75 (14.29)	1.87 (1.68)	6.07 (10.95)	1.43 (1.91)
Median (IQR)	2.95 (16.80)	1.80 (3.40)	1.80 (5.00)	0.70 (3.60)
Range (minimum–maximum)	(0.00–37.10)	(0.00–4.40)	(0.00–37.10)	(0.00–3.60)
Missing	0	1	1	5

IQR, interquartile range; SD, standard deviation.
a EASI score: a score of 0 indicates clear or no eczema, 0.1–1.0 indicates almost clear, 1.1–7 indicates mild disease, 7.1–21 indicates moderate disease, 21.1–50 indicates severe disease and > 51 indicates very severe disease.

IQR, interquartile range; SD, standard deviation.

Most infants had a family history of atopic dermatitis (62.5%) and allergic rhinoconjunctivitis (75%), and only 4 (25%) were with family history of food allergy (*Table 6*).

Only 1 of the 16 randomised participants [6.25%; 95% confidence interval (CI) 0.0 to 19.6] reacted in the initial pHF challenge and went into the dose-based OIT pathway. All other patients tolerated pHF and were able to be fed freely following randomisation.

A total of 91 non-serious adverse events (non-SAEs) were reported over the duration of the trial (*Tables 7* and *8*), 16 occurred while receiving eHF and the other 75 assumed to be while receiving pHF (we cannot be certain when the affected participants by the breach switched treatment, but these events occurred either: (1) in participants randomised to receive pHF or (2) after pHF shipments had been sent to participants allocated to eHF). Eighty-eight events were considered mild (16 eHF; 72 pHF), two moderate (both pHF) and one severe (pHF).

There were three SAEs, none of which was assessed as related to the study product (*Table 9*).

There were 34 protocol deviations that in their vast majority ($n = 31$) related to non-collection of samples to store for future research (minor deviations), whereas 2 events were related to not collecting diaries (major deviations) (*Table 10*).

TABLE 4 Skin prick tests

	Randomised patients			Patients who attended V1 but were not randomised
	Intervention: pHF	Control: eHF	Total	
CM wheal diameter using whole fresh milk (mm)				
N	8	8	16	7
Mean (SD)	8.63 (2.88)	10.75 (4.43)	9.69 (3.77)	6.29 (4.82)
Median (IQR)	7.50 (2.50)	11.50 (7.00)	8.50 (5.50)	6.00 (10.00)
Range (minimum–maximum)	(6.00–15.00)	(4.00–17.00)	(4.00–17.00)	(0.00–12.00)
Missing	0	0	0	1
Commercial milk extracts wheal diameter (mm)				
N	8	8	16	7
Mean (SD)	7.38 (2.83)	8.13 (4.09)	7.75 (3.42)	4.86 (4.85)
Median (IQR)	7.00 (4.50)	8.00 (5.00)	7.50 (4.50)	5.00 (10.00)
Range (minimum–maximum)	(3.00–11.00)	(2.00–15.00)	(2.00–15.00)	(0.00–10.00)
Missing	0	0	0	1
Egg wheal diameter (mm)				
N	6	6	12	7
Mean (SD)	4.00 (3.41)	4.83 (3.31)	4.42 (3.23)	1.14 (2.27)
Median (IQR)	4.50 (7.00)	4.50 (5.00)	4.50 (6.00)	0.00 (2.00)
Range (minimum–maximum)	(0.00–8.00)	(0.00–9.00)	(0.00–9.00)	(0.00–6.00)
Missing	2	2	4	1
House dust mite mix wheal diameter (mm)				
N	8	8	16	7
Mean (SD)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Median (IQR)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Range (minimum–maximum)	(0.00–0.00)	(0.00–0.00)	(0.00–0.00)	(0.00–0.00)
Missing	0	0	0	1
Cat dander wheal diameter (mm)				
N	8	8	16	7
Mean (SD)	1.00 (1.93)	2.13 (2.53)	1.56 (2.25)	0.57 (0.98)
Median (IQR)	0.00 (1.50)	1.00 (4.50)	0.00 (3.50)	0.00 (2.00)
Range (minimum–maximum)	(0.00–5.00)	(0.00–6.00)	(0.00–6.00)	(0.00–2.00)
Missing	0	0	0	1
Six-grass pollen wheal diameter (mm)				
N	8	8	16	7
Mean (SD)	0.38 (1.06)	0.00 (0.00)	0.19 (0.75)	0.00 (0.00)
Median (IQR)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Range (minimum–maximum)	(0.00–3.00)	(0.00–0.00)	(0.00–3.00)	(0.00–0.00)
Missing	0	0	0	1

TABLE 5 Antigen-specific IgE tests

	Randomised patients			Patients who attended V1 but were not randomised
	Intervention: pHF	Control: eHF	Total	
CM IgE (kU/l)				
N	8	7	15	6
Mean (SD)	19.98 (33.49)	12.29 (22.37)	16.39 (28.12)	5.09 (8.21)
Median (IQR)	4.60 (19.59)	3.56 (4.82)	4.39 (17.24)	1.72 (5.08)
Range (minimum–maximum)	(1.62–100.00)	(0.93–62.80)	(0.93–100.00)	(0.00–21.30)
Missing	0	1	1	2
Alpha-lactalbumin IgE (kU/l)				
N	7	6	13	6
Mean (SD)	3.19 (5.13)	1.38 (1.62)	2.35 (3.89)	0.77 (1.10)
Median (IQR)	1.34 (4.20)	0.86 (1.24)	1.06 (1.24)	0.41 (0.12)
Range (minimum–maximum)	(0.11–14.30)	(0.10–4.50)	(0.10–14.30)	(0.00–3.00)
Missing	1	2	3	2
Beta-lactoglobulin IgE (kU/l)				
N	7	6	13	5
Mean (SD)	3.94 (6.12)	3.31 (2.88)	3.65 (4.72)	2.26 (4.17)
Median (IQR)	0.61 (9.41)	3.00 (6.03)	0.62 (6.03)	0.58 (0.31)
Range (minimum–maximum)	(0.35–15.40)	(0.10–6.87)	(0.10–15.40)	(0.00–9.71)
Missing	1	2	3	3
Casein IgE (kU/l)				
N	7	6	13	6
Mean (SD)	19.63 (36.70)	2.77 (3.92)	11.85 (27.50)	4.92 (8.73)
Median (IQR)	1.99 (26.59)	1.52 (2.64)	1.99 (4.99)	1.05 (4.92)
Range (minimum–maximum)	(0.50–100.00)	(0.10–10.40)	(0.10–100.00)	(0.00–22.30)
Missing	1	2	3	2

IQR, interquartile range; SD, standard deviation.

TABLE 6 Family history

	Randomised patients		
	Intervention: pHF	Control: eHF	Total
	(*N* = 8)	(*N* = 8)	(*N* = 16)
Eczema-atopic dermatitis	6 (75%)	4 (50%)	10 (62.5%)
Allergic rhinoconjunctivitis (hay fever)	6 (75%)	6 (75%)	12 (75%)
Asthma	5 (62.5%)	3 (37.5%)	8 (50%)
Food allergy	1 (12.5%)	3 (37.5%)	4 (25%)
None	0	1 (12.5%)	1 (6.3%)
Not known	0	0	0

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TABLE 7 Non-SAEs

	Control: eHF		Intervention: pHF		Total	
Non-SAEs	**Events, *n***	**Patients, *n* (%)**	**Events, *n***	**Patients, *n* (%)**	**Events, *n***	**Patients, *n* (%)**
Allergic reaction	0	0	6	5 (33.3%)	6	5 (31.3%)
Bronchial infection	1	1 (12.5%)	1	1 (6.7%)	2	2 (12.5%)
Chest infection	0	0	2	1 (6.7%)	2	1 (6.3%)
Conjunctivitis	0	0	2	1 (6.7%)	2	1 (6.3%)
Cough	0	0	1	1 (6.7%)	1	1 (6.3%)
Croup	0	0	2	2 (13.3%)	2	2 (12.5%)
Diarrhoea	0	0	3	2 (13.3%)	3	2 (12.5%)
Eczema flare	0	0	8	2 (13.3%)	8	2 (12.5%)
Eye angioedema	0	0	1	1 (6.7%)	1	1 (6.3%)
Fall	0	0	2	1 (6.7%)	2	1 (6.3%)
Fever	2	2 (25%)	7	3 (20%)	9	5 (31.3%)
Flu symptoms	0	0	1	1 (6.7%)	1	1 (6.3%)
Gastric reflux	0	0	1	1 (6.7%)	1	1 (6.3%)
Hand, foot and mouth disease	0	0	1	1 (6.7%)	1	1 (6.3%)
Hay fever	0	0	1	1 (6.7%)	1	1 (6.3%)
Heat stroke	0	0	1	1 (6.7%)	1	1 (6.3%)
Infected bite (animal)	1	1 (12.5%)	0	0	1	1 (6.3%)
Loose stool	0	0	1	1 (6.7%)	1	1 (6.3%)
Post-vaccination symptoms	0	0	1	1 (6.7%)	1	1 (6.3%)
Rash	0	0	2	1 (6.7%)	2	1 (6.3%)
Red swollen eye	1	1 (12.5%)	0	0	1	1 (6.3%)
Skin infection	0	0	3	1 (6.7%)	3	1 (6.3%)
Sore throat	0	0	1	1 (6.7%)	1	1 (6.3%)
Teething	2	1 (12.5%)	5	1 (6.7%)	7	2 (12.5%)
Tonsillitis	1	1 (12.5%)	1	1 (6.7%)	2	2 (12.5%)
Toothache	1	1 (12.5%)	1	1 (6.7%)	2	1 (6.3%)
Upper respiratory infection	2	2 (25%)	5	4 (26.7%)	7	6 (37.5%)
Urticaria	2	1 (12.5%)	7	2 (13.3%)	9	3 (18.8%)
Viral illness	2	2 (25%)	1	1 (6.7%)	3	3 (18.8%)
Vomiting	0	0	7	3 (20%)	7	3 (18.8%)
Vomiting and diarrhoea	1	1 (12.5%)	0	0	1	1 (6.3%)
Total	**16**	**6 (75%)**	**75**	**9 (60%)**	**91**	**11 (68.8%)**

Note
Participants affected by the serious breach are included in the eHF column if they experienced the respective AE before home supply started for them, and in the pHF column if they experienced it after home supply started.

TABLE 8 Non-SAEs by severity

		Control: eHF		Intervention: pHF		Total	
Non-SAEs	Severity	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)
Allergic reaction	Mild	0	0	5	4 (26.7%)	5	4 (25%)
	Severe	0	0	1	1 (6.7%)	1	1 (6.3%)
Bronchial infection	Mild	1	1 (12.5%)	1	1 (6.7%)	2	2 (12.5%)
Chest infection	Mild	0	0	2	1 (6.7%)	2	1 (6.3%)
Conjunctivitis	Mild	0	0	2	1 (6.7%)	2	1 (6.3%)
Cough	Mild	0	0	1	1 (6.7%)	1	1 (6.3%)
Croup	Mild	0	0	1	1 (6.7%)	1	1 (6.3%)
	Moderate	0	0	1	1 (6.7%)	1	1 (6.3%)
Diarrhoea	Mild	0	0	2	2 (13.3%)	2	2 (12.5%)
	Moderate	0	0	1	1 (6.7%)	1	1 (6.3%)
Eczema flare	Mild	0	0	8	2 (13.3%)	8	2 (12.5%)
Eye angioedema	Mild	0	0	1	1 (6.7%)	1	1 (6.3%)
Fall	Mild	0	0	2	1 (6.7%)	2	1 (6.3%)
Fever	Mild	2	2 (25%)	7	3 (20%)	9	5 (31.3%)
Flu symptoms	Mild	0	0	1	1 (6.7%)	1	1 (6.3%)
Gastric reflux	Mild	0	0	1	1 (6.7%)	1	1 (6.3%)
Hand, foot and mouth disease	Mild	0	0	1	1 (6.7%)	1	1 (6.3%)
Hay fever	Mild	0	0	1	1 (6.7%)	1	1 (6.3%)
Heat stroke	Mild	0	0	1	1 (6.7%)	1	1 (6.3%)
Infected bite (animal)	Mild	1	1 (12.5%)	0	0	1	1 (6.3%)
Loose stool	Mild	0	0	1	1 (6.7%)	1	1 (6.3%)
Post-vaccination symptoms	Mild	0	0	1	1 (6.7%)	1	1 (6.3%)
Rash	Mild	0	0	2	1 (6.7%)	2	1 (6.3%)
Red swollen eye	Mild	1	1 (12.5%)	0	0	1	1 (6.3%)
Skin infection	Mild	0	0	3	1 (6.7%)	3	1 (6.3%)
Sore throat	Mild	0	0	1	1 (6.7%)	1	1 (6.3%)
Teething	Mild	2	1 (12.5%)	5	1 (6.7%)	7	2 (12.5%)
Tonsillitis	Mild	1	1 (12.5%)	1	1 (6.7%)	2	2 (12.5%)
Toothache	Mild	1	1 (12.5%)	1	1 (6.7%)	2	1 (6.3%)
Upper respiratory infection	Mild	2	2 (25%)	5	4 (26.7%)	7	6 (37.5%)
Urticaria	Mild	2	1 (12.5%)	7	2 (13.3%)	9	3 (18.8%)
Viral illness	Mild	2	2 (25%)	1	1 (6.7%)	3	3 (18.8%)
Vomiting	Mild	0	0	7	3 (20%)	7	3 (18.8%)
Vomiting and diarrhoea	Mild	1	1 (12.5%)	0	0	1	1 (6.3%)

continued

This synopsis should be referenced as follows:
Guibas G, Brayshaw E, Brown M, Moitt T, Raptis G, Roberts G, *et al*. Desensitisation to cow's milk, following partially or extensively hydrolysed formulae feeding regimens, in infants with allergy to cow's milk: the DREAM RCT Synopsis (The DREAM study) [published online ahead of print February 25 2026]. *Efficacy Mech Eval* 2026. https://doi.org/10.3310/GJGG7715

TABLE 8 Non-SAEs by severity (*continued*)

		Control: eHF		Intervention: pHF		Total	
Non-SAEs	Severity	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)
Total	Mild	16	6 (75%)	72	6 (40%)	88	8 (50%)
Total	Moderate	0	0	2	2 (13.3%)	2	2 (12.5%)
Total	Severe	0	0	1	1 (6.7%)	1	1 (6.3%)

Note
Where patients have experienced more than one AE and more than one severity, they have been reported in the most severe category.

Discussion

Reflections on the project: challenges faced and limitations

This was a trial with significant strengths. DREAM was supported by a NIHR grant, and the Trial Management Group (TMG) included several experienced clinicians and researchers; the trial was robustly supported by an experienced NHS trust and Clinical Trials Unit. Several large trusts were intending to participate in the trial and had contributed to drafting a thorough and detailed protocol during setup. However, there were also a number of challenges.

COVID

The COVID pandemic and subsequent lockdowns took place while the trial was in setup and impacted the trial, as it did in many other trials. Although setup did continue during the lockdowns and progress was made, it is likely that the rate of progress was slower due to local capacity, prioritisation of COVID and other urgent research and slower communications overall during the lockdowns.

Poor recruitment of sites

DREAM struggled to recruit the number of sites planned; 12 sites were planned to take part in the trial at start, but at the point of termination, 7 had joined.

A concern was discrepancies in the understanding of what trial processes should be attributed to research costs and which to NHS treatment costs; hence, a major contribution to poor adoption of the protocol by sites was the Schedule of Events Cost Attribution Tool (SoECAT). The sponsoring site had completed the SoECAT according to standard of care procedures at that trust. Unfortunately, standard of care varied across sites. Only one SoECAT can be completed per trial. This led to the original costing model not being applicable to all potential sites. It was unclear what the escalation route was under these circumstances regarding SoECAT issues or whether there could be flexibility in applying SoECATs when this was the case. There was significant time lost in renegotiating costings with sites to fit within their standard of care pathways, and the budget allocations were revisited and reconsidered to this end. Due to the timing of the trial and pressures of COVID recovery plans, a number of sites decided not to initiate this trial on account of the SoECAT issue.

Another point that some sites were concerned about was the 2-day DBPCFC, which was the primary outcome of the trial. The points raised had to do with the process being personnel-heavy and therefore difficult to accommodate in a busy ward and expectations by some sites that this process would be covered by research rather than NHS costs, as originally assigned. In order to deal with the former point, and with the agreement of Efficacy and Mechanism Evaluation and the sponsor, the 2-day DBPCFC was changed to a single-day DBPCFC with a substantial amendment, to become less demanding on the sites. In regard to the DBPCFC itself being allocated as NHS cost, during the trial planning it was considered that as DBPCFC is the golden standard in the diagnosis of IgE-mediated food allergy,[25,26] it would be appropriate that this is allocated as a treatment cost.

Overall, it appeared that some sites felt that the research funding did not wholly reflect the cost of certain rigorous procedures, and this likely has had an adverse effect in site recruitment. On reflection, albeit the SoECAT's purpose is to clarify these issues, there appears to be considerable discrepancies where certain processes may be perceived and allocated differently by distinct sites; allocations that are not in keeping with a site's specific view could make them less likely to participate. It would appear that in the DREAM trial, a 'one size fits all' SoECAT was not practical; therefore, involving all the key partners in budget

TABLE 9 Line listing of SAEs

SAE number	Treatment allocation	Diagnosis	Onset date	Serious criteria	Severity	eHF Relatedness: Site assessment	eHF Relatedness: MR assessment	eHF Relatedness: Expectedness	pHF Relatedness: Site assessment	pHF Relatedness: MR assessment	pHF Relatedness: Expectedness	Most likely cause, if unrelated (principal investigator assessment)	Outcome
1	pHF	Chest infection	26 June 2023	Required hospitalisation	Moderate	Unrelated	Unrelated	Not expected	Unrelated	Unrelated	Not expected	Viral infection	Resolved
2	pHF	Anaphylaxis to CM exposure	21 August 2023	Required hospitalisation	Severe	Unrelated	Unrelated	Expected	Unrelated	Unrelated	Expected	Patient's original condition	Resolved
3	pHF	Infected chickenpox	15 October 2023	Required hospitalisation	Severe	Unlikely	Unrelated	Not expected	Unlikely	Unrelated	Not expected	Infected chickenpox	Resolved

MR, medical review.

TABLE 10 Protocol deviation summary

		Intervention: pHF		Control: eHF	
		Events, *n*	Participants, *n* (%)	Events, *n*	Participants, *n* (%)
Protocol deviation		18	6 (75%)	16	8 (100%)
Major deviation		1	1 (12.5%)	1	1 (12.5%)
	PD26	1	1 (12.5%)	1	1 (12.5%)
Minor deviation		17	6 (75%)	15	8 (100%)
	PD22[a]	0	0 (0%)	1	1 (12.5%)
	PD25	17	6 (75%)	14	8 (100%)

a Blood test not performed in V1; protocol does not mention use of previous clinical samples for this. Reason given – 'Prev samples obtained. Difficulty obtaining samples a Screening visit-safety bloods prioritised'.

Note
PD22 – Blood tests for IgE not carried out.
PD25 – Samples for future research not collected.
PD26 – Diaries not filled in or collected.

This synopsis should be referenced as follows: Guibas G, Brayshaw E, Brown M, Moitt T, Raptis G, Roberts G, *et al*. Desensitisation to cow's milk, following partially or extensively hydrolysed formulae feeding regimens, in infants with allergy to cow's milk: the DREAM RCT Synopsis (The DREAM study) [published online ahead of print February 25 2026]. *Efficacy Mech Eval* 2026. https://doi.org/10.3310/GJGG7715

allocation early, in order to identify and resolve 'standard of care' discrepancies, could potentially help fine-tune the budget and support site recruitment.

Poor recruitment of participants.
Fourteen sites were invited to participate in the clinical trial, 12 as part of initial Health Research Authority application, and an additional 2 as part of an amendment. Of those 14, 4 then declined, and 1 had no capacity. Nine sites agreed to participate. Seven sites were open to recruitment, and only three eventually managed to randomise patients. Southampton University joined the clinical trial shortly before it was terminated, with little time available to recruit. Two sites opened to recruitment from the start of the study, and recruited for a longer period, but also struggled to recruit (*Table 11*).

The following two tables demonstrate that out of 352 pre-screenings carried out to identify potentially eligible patients who could be approached, only 106 (30.1%) were thought to be potentially eligible to approach (*Tables 12* and *13*).

The main reason for ineligibility to approach that affected 65.04% of those deemed ineligible was found to be *not convincing medical history of IgE reaction to* CM (*Tables 14* and *15*).

Of the 106 potential recruits who were found eligible to approach, 78 (73.6%) were approached and attended screening visit 1 (V1); of the remaining 28 potential recruits who did not attend V1, most (17–60.71%) were excluded because they could not arrange a visit within the required time frame (*Tables 16* and *17*).

Of the 78 potential recruits who attended V1, 54 declined to give consent; most of them (29–67.4%) did not give a reason (*Tables 18* and *19*).

Of the remaining 24 participants who did consent, 6 were found to be ineligible for randomisation, mostly due to not meeting the IgE/SPT criteria (2–33%) and having a negative CM challenge (2–33% – *Tables 20* and *21*).

Of the remaining 18 eligible participants, 16 were randomised; the 2 remaining participants were not randomised, as the trial was terminated before they reached that point.

Overall, these numbers suggest that a main drop-off point was pre-screening, where 65% of pre-screened potential participants were thought to not have a history suggestive of IgE-mediated allergy to milk; hence, several patients appear to have been previously misdiagnosed as being IgE-milk allergic. Although immediate CMA is known to affect 1.8–7.5% of infants,[1–7] estimates vary because of differences in study design, diversity in study populations, geographical variability[7,27] and variety in clinical manifestations, including several infants presenting with non-allergic urticaria. Also, many studies are now nearly two decades old[17] and have not used DBPCFC to set the diagnosis (the gold standard of diagnosis). This has likely overestimated the prevalence of CMA. The pre-screening by our team did show that for most patients thought to have an immediate milk allergy, this was likely not the case. For any clinical trial intent on recruiting IgE-mediated milk-allergic infants, it should be kept in mind that the pool of presumed allergic patients likely includes a large percentage of patients who – when their history gets under further scrutiny – are found to be unlikely to suffer from this particular condition. The trial appears to have been affected by this, including the BOUNTY recruitment, albeit not similarly at all sites. The reasons why only few of the sites that were open to recruitment managed to recruit/randomise are unclear. It could be that the setting at these sites was more conducive to recruiting milk-allergic infants, highlighting both the variability in the capacity of sites to recruit particular patient populations, and also the importance of the site's engagement.

Other learning points in regard to patient recruitment involve timelines. The recruitment window was intentionally small in order to facilitate starting the trial within infancy, a key hallmark of the trial; however, the recruitment even of infants that were within this window was felt to be challenging, as illnesses and work/child care obligations of the parents in a harsh economic environment affected their ability to bring the infants for V1. Of those infants that were potentially eligible but did not attend V1, about 60% (17 infants) were due to inconvenient timescales; this age window also coincides with plans to return to work for some parents, further compounding the issue of the small recruitment window. Notwithstanding these issues, the 'window of immunologic susceptibility' is shown to be within infancy,[28,29] and it would, therefore, be more appropriate for OIT to start around that time. Feeding starting in infancy as first-line management was a key premise of the DREAM trial and a main strength, which was felt to be too central for the trial to alter to ease up recruitment; this would have likely adversely impacted the results. Practical issues in recruiting *infant* participants within a small recruitment window should be thoroughly considered for future trials. Considering higher reimbursement for parents should also be a consideration,

TABLE 11 Timescale of site recruitment

Site code	Site	Date site opened to recruitment	Date site closed to recruitment	Date of first randomisation	Date of last randomisation	Total randomised
1	Manchester University NHS Foundation Trust	6 September 2022	18 October 2023	7 December 2022	26 September 2023	5
2	The Newcastle upon Tyne Hospitals NHS Foundation Trust	30 August 2022	18 October 2023	1 February 2023	21 August 2023	8
3	University Hospital Southampton NHS Foundation Trust	31 July 2023	18 October 2023	–	–	0
5	James Paget University Hospitals NHS Foundation Trust	27 October 2022	18 October 2023	–	–	0
6	Sandwell Hospital and West Birmingham NHS Trust	24 February 2023	18 October 2023	–	–	0
7	University Hospitals Bristol NHS Foundation Trust	19 May 2023	18 October 2023	–	–	0
8	NHS Greater Glasgow and Clyde	27 February 2023	18 October 2023	22 May 2023	4 October 2023	3

TABLE 12 Screening summary by centre

Site number	Site name	Date last screened	Total screenings (*N*), *N*	Potentially eligible (a), *n* (%)	Approached and attended screening V1 (b), *n* (%)	Consented (c), *n* (%)	Eligibility confirmed (d), *n* (%)	Randomised (e), *n* (%)
1	Royal Manchester Children's Hospital	13 October 2023	45	30 (66.7)	17 (56.7)	6 (35.3)	5 (83.3)	5 (100.0)
2	Great North Children's Hospital	2 October 2023	203	38 (18.7)	33 (86.8)	11 (33.3)	10 (90.9)	8 (80.0)
3	University Hospital Southampton NHS Foundation Trust	29 September 2023	15	5 (33.3)	5 (100.0)	2 (40.0)	0 (0)	0 (0)
5	James Paget University Hospitals NHS Foundation Trust	10 August 2023	14	8 (57.1)	6 (75.0)	0 (0)	0 (0)	0 (0)
6	Sandwell and West Birmingham Hospitals NHS Trust	27 September 2023	52	9 (17.3)	4 (44.4)	0 (0)	0 (0)	0 (0)
7	Bristol and Weston NHS Foundation Trust	16 August 2023	8	4 (50.0)	4 (100.0)	0 (0)	0 (0)	0 (0)
8	NHS Greater Glasgow and Clyde	22 September 2023	15	12 (80.0)	9 (75.0)	5 (55.6)	3 (60.0)	3 (100.0)
			352	**106 (30.1)**	**78 (73.6)**	**24 (30.8)**	**18 (75.0)**	**16 (88.9)**

This synopsis should be referenced as follows: Guibas G, Brayshaw E, Brown M, Moitt T, Raptis G, Roberts G, *et al*. Desensitisation to cow's milk, following partially or extensively hydrolysed formulae feeding regimens, in infants with allergy to cow's milk: the DREAM RCT Synopsis (The DREAM study) [published online ahead of print February 25 2026]. *Efficacy Mech Eval* 2026. https://doi.org/10.3310/GJGG7715

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TABLE 13 Calculating percentages

Percentages	Equation
Per cent considered potentially eligible	a/N
Per cent approached	b/a
Per cent consent provided	c/b
Per cent eligibility confirmed after screening	d/c
Per cent randomised	e/d

TABLE 14 Reasons for ineligibility

Site number	Site name	Ineligible patients	A (*N*)	B (*N*)	C (*N*)	D (*N*)	E (*N*)	G (*N*)	H (*N*)	I (*N*)	L (*N*)	M (*N*)	N (*N*)	P (*N*)
1	Royal Manchester Children's Hospital	15	3 (20%)	11 (73.33%)	0	0	1 (6.67%)	1 (6.67%)	0	0	0	0	0	0
2	Great North Children's Hospital	165	17 (10.3%)	134 (81.21%)	3 (1.82%)	0	3 (1.82%)	0	3 (1.82%)	5 (3.03%)	3 (1.82%)	1 (0.61%)	1 (0.61%)	0
3	University Hospital Southampton NHS Foundation Trust	10	4 (40%)	3 (30%)	1 (10%)	0	0	0	2 (20%)	0	0	0	0	1 (10%)
5	James Paget University Hospitals NHS Foundation Trust	6	2 (33.33%)	0	2 (33.33%)	1 (16.67%)	0	0	0	0	1 (16.67%)	0	0	0
6	Sandwell and West Birmingham Hospitals NHS Trust	43	1 (2.33%)	12 (27.91%)	3 (6.98%)	2 (4.65%)	0	0	23 (53.49%)	1 (2.33%)	1 (2.33%)	0	0	0
7	Bristol and Weston NHS Foundation Trust	4	0	0	0	0	2 (50%)	0	2 (50%)	0	0	0	0	0
8	NHS Greater Glasgow and Clyde	3	0	0	1 (33.33%)	0	0	0	2 (66.67%)	0	0	0	0	0
		246	**27 (10.98%)**	**160 (65.04%)**	**10 (4.07%)**	**3 (1.22%)**	**6 (2.44%)**	**1 (0.41%)**	**32 (13.01%)**	**6 (2.44%)**	**5 (2.03%)**	**1 (0.41%)**	**1 (0.41%)**	**1 (0.41%)**

TABLE 15 Details on reasons of ineligibility

A	Infant not aged 6–12 months inclusive at V1
B	Not convincing medical history of IgE-mediated allergic reaction following ingestion of CM formula, as determined by trial physician
C	Infant not fed with formula, either exclusively or mixed with breastfeeding
D	Weight of < 7.5 kg
E	No titre of CM-specific IgE in serum, equal or higher to 2 kU/l [collected at V1, confirmed prior to visit 2 (V2)/3], at inclusion **nor** wheal reaction of equal or over 5 mm to SPT* to CM at inclusion (* 5 mm to either whole, fresh milk or commercial milk extract)
F	Negative result in the challenge to pHF (V2), and negative result in the challenge to CM (V3)
G	Unequivocal history of severe anaphylaxis to CM in the past requiring more than one dose of adrenaline
H	Doctor diagnosis of non-IgE-mediated allergy to CM or CM formula (eosinophilic esophagitis, gastritis, gastroenteritis, FPIES, enteropathies and proctocolitis)
I	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
J	Requirement for continuous or frequent (monthly or more) intermittent use of oral corticosteroids for other conditions
K	Requirement for pharmacotherapy for any other clinical condition, if it could interfere with the patient's safety or the study outcomes
L	Parents or guardians, who, by investigator judgement, are unlikely to comply with the study protocol for any reason (language barrier, communication issues, inability to understand procedures, etc.)
M	History of overnight hospitalisation (only accident and emergency attendances not included) for wheeze and/or bronchiolitis on more than one occasion
N	Currently participating in another clinical trial that may interfere with the patient's safety or the study outcomes
O	Severe anaphylaxis (anaphylaxis refractory to a single dose of intramuscular adrenaline) during challenge to pHF or CM
P	Another infant from the same household is currently participating in the study

TABLE 16 Reasons for not being approached

Site number	Site name	Patients who were not approached	GCP trained staff not available, *n* (%)	Formula not Halal/Kosher certified, *n* (%)	Unable to arrange a visit within required time frame, *n* (%)	Other, *n* (%)
1	Royal Manchester Children's Hospital	13	0	0	9 (69.23%)	4 (30.77%)
2	Great North Children's Hospital	5	0	0	4 (80%)	1 (20%)
5	James Paget University Hospitals NHS Foundation Trust	2	0	0	0	2 (100%)
6	Sandwell and West Birmingham Hospitals NHS Trust	5	0	1 (20%)	3 (60%)	1 (20%)
8	NHS Greater Glasgow and Clyde	3	0	0	1 (33.33%)	2 (66.67%)
		28	**0**	**1 (3.57%)**	**17 (60.71%)**	**10 (35.71%)**

GCP, good clinical practice.

TABLE 17 Frequency of 'other' reasons for not being approached

Classified other reason	*N* (%)
No response	6 (60.0)
Study stopped	2 (20.0)
Unable to contact	2 (20.0)

TABLE 18 Reasons for declined consent

Site number	Site name	Number of patients declining consent	Does not want trial treatment, *n* (%)	Does not want to take part in research, *n* (%)	Unwilling to give reason, *n* (%)	Patient's parent did not want to continue to next visit, *n* (%)	Other, *n* (%)
1	Royal Manchester Children's Hospital	11	0	0	0	0	11 (100%)
2	Great North Children's Hospital	22	0	0	0	2 (9.09%)	20 (90.91%)
3	University Hospital Southampton NHS Foundation Trust	3	0	0	0	3 (100%)	0
5	James Paget University Hospitals NHS Foundation Trust	6	0	1 (16.67%)	0	0	5 (83.33%)
6	Sandwell and West Birmingham Hospitals NHS Trust	4	0	0	0	0	4 (100%)
7	Bristol and Weston NHS Foundation Trust	4	2 (50%)	1 (25%)	0	0	1 (25%)
8	NHS Greater Glasgow and Clyde	4	0	0	1 (25%)	1 (25%)	2 (50%)
		54	**2 (3.7%)**	**2 (3.7%)**	**1 (1.85%)**	**6 (11.11%)**	**43 (79.63%)**

Note
Percentage calculated using all patients where consent was not obtained (b-c) as the denominator.

TABLE 19 Frequency of 'other' reasons for not consenting

Classified other reason	*N* (%)
Anxious	2 (4.7)
Declined	29 (67.4)
Found ineligible	3 (7.0)
No response	3 (7.0)
Not interested	4 (9.3)
Study closed	1 (2.3)
Does not want to	1 (2.3)

TABLE 20 Reasons for patients becoming ineligible during screening

Site number	Site name	Number of patients not confirming eligibility	D, *N* (%)	E, *N* (%)	F, *N* (%)
1	Royal Manchester Children's Hospital	1	1 (100%)	0	0
2	Great North Children's Hospital	1	0	1 (100%)	0
3	University Hospital Southampton NHS Foundation Trust	2	0	1 (50%)	1 (50%)
8	NHS Greater Glasgow and Clyde	2[a]	0	0	1 (50%)
		6	**1 (16.67%)**	**2 (33.33%)**	**2 (33.33%)**

a One patient missing a reason for eligibility not being confirmed.

Note
Percentage calculated using all patients where consent was not obtained (c-d) as the denominator.

TABLE 21 Legend on reasons for patients becoming ineligible

A	Infant not aged 6–12 months inclusive at V1
B	Not convincing medical history of IgE-mediated allergic reaction following ingestion of CM formula, as determined by trial physician
C	Infant not fed with formula, either exclusively or mixed with breastfeeding
D	Weight of < 7.5 kg
E	No titre of CM-specific IgE in serum, equal or higher to 2 kU/l (collected at V1, confirmed prior to V2/3), at inclusion **nor** wheal reaction of equal or over 5 mm to SPT* to CM at inclusion (* 5 mm to either whole, fresh milk or commercial milk extract)
F	Negative result in the challenge to pHF (V2), and negative result in the challenge to CM (V3)
G	Unequivocal history of severe anaphylaxis to CM in the past requiring more than one dose of adrenaline
H	Doctor diagnosis of non-IgE-mediated allergy to CM or CM formula (eosinophilic esophagitis, gastritis, gastroenteritis, FPIES, enteropathies and proctocolitis)
I	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
J	Requirement for continuous or frequent (monthly or more) intermittent use of oral corticosteroids for other conditions
K	Requirement for pharmacotherapy for any other clinical condition, if it could interfere with the patient's safety or the study outcomes
L	Parents or guardians, who, by investigator judgement, are unlikely to comply with the study protocol for any reason (language barrier, communication issues, inability to understand procedures, etc.)
M	History of overnight hospitalisation (only accident and emergency attendances not included) for wheeze and/or bronchiolitis on more than one occasion
N	Currently participating in another clinical trial that may interfere with the patient's safety or the study outcomes
O	Severe anaphylaxis (anaphylaxis refractory to a single dose of intramuscular adrenaline) during challenge to pHF or CM
P	Another infant from the same household is currently participating in the study
R	Unable to arrange a visit within required time frame (e.g. DNAd and site unable to contact parent)
S	Patient's parent did not want to continue to next visit

in order to support them to attend during a period where they have started going back to work after paternal leave.

Serious breach

A serious breach was identified shortly before the trial was stopped due to poor recruitment that affected the integrity of key data. It was identified in September 2023 that not all participants had continued to receive the allocated treatment once they received home shipments. Seven out of the eight participants allocated to eHF had received at-home pHF instead.

No serious adverse effects had been reported because of this breach, as these participants had all been previously shown to be pHF-tolerant through a challenge. After urgent communications between the cochief investigators, the TMG, the sponsor, the Trial Steering Committee and the Independent Data Management Committee, it was agreed that the trial was unblinded for safety reasons, that delivery of products to parents was ceased and that the participants exit the trial and return to normal care. The patients thus were removed from the trial and went under the responsibility of their respective clinicians in the context of routine care; after being removed from the trial, some patients continued – by the decision of some of the responsible clinicians – with commercial pHF feeding, *outside of the trial*. Appropriate reports were compiled and submitted to the Research Ethics Committee.

Because all participants had received an initial dispense from hospital stock (which was not affected by the serious breach) before home delivery had begun, seven participants had received *both* treatment allocations; hence, it was deemed that there was significant impact to the integrity of the data at this stage. Should the trial have continued to sample size target, the impact could have diminished, but the trial was stopped prematurely due to poor recruitment. In *Table 22*, we present the number of days the participants were on the originally allocated and initially dispensed eHF before they received the erroneous home delivery of pHF; it must be noted that these seven participants might have continued (and likely did) feeding on eHF until the hospital-provided eHF tins were used completely, even after they received pHF at home; hence, the exact number of days that the participants were on either pHF/eHF is difficult to identify accurately.

TABLE 22 Number of tins dispensed and times

Treatment	Days on initial product (eHF): from randomisation to dispense at home	Days on alternative product (pHF): from dispense at home to end of trial	Days on product: from randomisation until end of trial
eHF	7	160	167
eHF	2	125	127
eHF	6	16	22
eHF	8	251	259
eHF	111	71	182
eHF	11	82	93
eHF	1	41	42
eHF	14	N/A	14
pHF	N/A	N/A	315
pHF	N/A	N/A	125
pHF	N/A	N/A	58
pHF	N/A	N/A	245
pHF	N/A	N/A	224
pHF	N/A	N/A	79
pHF	N/A	N/A	70
pHF	N/A	N/A	149

N/A, not applicable.

Overall, after the study product was received by and was under the TMG, further logistics relating to storing/distribution to parents appeared to be quite complex. Detailed planning for such logistics should be a key consideration early on in the design of any study dealing with OIT, so that the process can be made as clear and robust as possible.

Changes

Amendments

A number of amendments were discussed and agreed at the TMG, approved by the funder and were submitted to the ethics committee in an effort to tackle issues that had to do mostly with poor recruitment of both sites and of participants.

Overall, six amendments were submitted, excluding an amendment to issue a parent letter to explain the reason for early termination. These included, among several other minor points, the following changes aimed to support recruitment: move weight criterion of at least 7.5 kg from V1 to point of randomisation; randomisation may be postponed if a patient is underweight, provided that all other inclusion criteria are met; addition of two new sites; eligibility may be confirmed by medically trained doctors as well as nurse consultants; condense the DBPCFC visits (last two visits) to a single visit to reduce site excess treatment costs, revisit research costs, and minimise burden on sites and families; Change of Patient Identification Centre (PIC) site to a recruiting site, and addition of PIC site; further addition of a recruiting site; reduction in statistical power from 90% to 80%, thus reducing sample size from 206 to 156 participants.

Change of chief investigator

Due to the original chief investigator, Nikolaos Papadopoulos, not remaining substantively employed by the University of Manchester (UoM) and moving his base abroad during the COVID lockdown, a change of chief investigator took place to Georgios Gkimpas and Louise Michaelis as cochief investigators. While the amendment to this effect was being discussed and put in place between the sponsor, the funder, the UoM and the University Hospitals Newcastle, progress in the setup of the trial was slower, until the new cochief investigators were put in place.

Principal findings and achievements per project outcome

Explanation of limitations regarding trial's outcomes

As the trial was ended prematurely due to poor recruitment, and no participant underwent the DBPCFC that was the main outcome, the primary – tolerance-related – objective could not be pursued; additionally, no secondary objectives related to *tolerance* could be assessed. Analysis for secondary objectives related to *safety* was hindered by the serious breach described above: in short, due to 7/8 patients on the eHF arm having also received pHF as per the breach, comparison of adverse effects between the two arms would have significant limitations; hence, mostly descriptive statistics are presented in the results. Collection and storing of samples took place, but no testing was intended to take place as part of DREAM, and they are also likely affected by the same limitations relating to the serious breach. These samples are intended to be used in separate future research. The secondary objective for which the trial has provided reliable evidence that was not contingent on the DBPCFC and was not significantly affected by the breach is the objective number five, which relates to the 'characterisation of participants' reactivity to pHF'.

Characterisation of participants' reactivity to partially hydrolysed formula

Of the 16 randomised patients who underwent the initial pHF challenge, only 1 (6.25%) reacted (95% CI 00.0 to 19.6). Hence, the results showed that close to 94% of the CMA infants in the DREAM trial tolerated pHF, via an open pHF challenge (and subsequent free-feeding). These infants' CMA status has been rigorously characterised through doctor's diagnosis, positive SPTs **or** positive CM-specific IgE, and a positive open challenge to CM; most of the infants also did react to the early doses of the CM challenge, further confirming their CM allergy. The criteria for an infant to continue to challenge included CM-specific IgE equal or higher to 2 kU/l, **or** SPT wheal equal or over 5 mm to CM. We believe that these criteria allow our population to be considered as less likely to experience spontaneous resolution of CMA. SPT and specific IgE are currently the most reliable tests to indicate persistent milk allergy, although exact predictive cut-off values are not yet established.[5,17,20–22,30–34] In a study of 3- to 15-month-old infants,[18] significant differences in spontaneous resolution were seen between those with CM-IgE levels of < 2 kUA/l and > 2 kUA/l, and between those with CM SPT of < 5 mm and > 5 mm. In another study on children (median age 13 months),[17] 57% of patients with CM-IgE < 2 kU/l had become tolerant by age 4 years, as opposed to a total of 14% for those with > 2 kU/l. In another study,[21] a SPT of > 5 mm identified the majority of children with persistent CMA beyond age 4 years. Other studies also provided similar evidence.[19,35] We, therefore, argue that our population included participants with moderate/severe CM allergy who were less likely to spontaneously outgrow it.

We have shown that the vast majority of these CMA infants tolerated pHF formula. This formula has lower allergenicity than CM but is more allergenic than eHF (normal standard care). Both pHFs and eHFs are generated by cutting down CM proteins into smaller fragments,[36] but eHFs are 20 million times less allergenic than CM,[36] whereas pHFs are only about *60 times* less allergenic.[36] pHF is not considered 'hypoallergenic' and does not have an indication for CM-allergic infants. In this context, providing strong evidence that most moderate/severe allergic infants can freely tolerate this pHF formula – a *non*-hypoallergenic formula – is important: OIT utilising a formula with reduced allergenicity such as pHF could be, in terms of safety, a significant improvement from the use of normal CM. Two systematic reviews have underscored the potential of CM OIT to facilitate CMA resolution,[37,38] but both noted that this remains unrealised due to frequent AEs. pHF's reduced allergenicity holds significant promise to address this safety issue, if it is to be used as an OIT medium, albeit differences in the content of different pHFs need to be taken into consideration. Along these lines, pHFs are immunologically closer to normal CM than eHF (standard care), which suggests that exposure of CMA infants to this formula in an OIT regimen could expedite/facilitate tolerance; it has been shown that regular intake of processed CM favours resolution of CMA;[39,40] indeed, this is also supported by BSACI guidelines, which suggest that the reintroduction of CM may start with less allergenic forms.[8]

Most CMA patients can tolerate processed milk in various forms, for example, up to 83% of CMA children tolerate baked milk.[41–44] In older/smaller trials, it was shown that 50–70% of them could also tolerate pHF.[45–48] There is some literature where pHF has been used for milk-allergic patients;[49] however, evidence does not support that it can be used safely in CMA. Indeed, in a recent trial from the USA,[50] 10 out of 10 well-defined CM-allergic children failed to tolerate a different pHF, prompting the researchers to discontinue their trial. DREAM is the first clinical trial to demonstrate tolerance of a high percentage of robustly characterised allergic infants to pHF. Additionally, DREAM has demonstrated that most of these infants have tolerated *free-feeding* with pHF (as opposed to restrictive dose-based diets), which is the 'normal routine' way of feeding formula to infants and is another significant improvement to strict dose-based OIT. These differences with the American study could well be, as the American authors also suggest, due to population differences (e.g. European vs. USA, temporal differences in milk allergy, etc.) or perhaps differences in the pHF formula used. It could also be relevant to the wide age window of these participants, with most of them being over 3 years old, as opposed to our cohort of infants solely < 12 months old. A possible loss of tolerance to pHF over time has not been explored previously and is worth studying. This further highlights the importance of time-sensitive intervention in the window of immunologic susceptibility in infancy, which was a key feature of the DREAM trial.

Future directions

In this context, DREAM provides important evidence that could support further trials to improve OIT for CMA infants/toddlers from a safety point of view, but also to attempt to further mainstream OIT by allowing a much more convenient and easier-to-use free-feeding regimen. The strengths of the trial, as reported above, have to do with the rigorous characterisation of our allergic population, and with providing strong evidence that the formula was well tolerated. As it is the case for most such trials, a main limitation has to do with the trial's cohort, in that it is unclear whether such widespread tolerance can be expected in CMA children with different characteristics, for example, those with lower IgE/smaller SPT wheals, of different age or from other countries. Also, different composition of pHF – for example, those based on casein versus those on whey or both – are likely to affect tolerance. Another limitation has to do with recording of minor AEs in the context of the serious breach: as per the results presented above, certain minor AEs could be associated with the trial product, but it cannot be unequivocally established whether the participants were on pHF or eHF when they experienced them. However, it was clear through the trial's design that 15 out of 16 participants did tolerate a hospital-based challenge to pHF, up to a final dose of 100 ml (cumulative total dose of 144.1 ml – ascending doses of 0, 1, 3, 10, 30 and 100 ml), which shows that the infants did tolerate well a substantial amount of formula.

Patient and public involvement

The patients/public were involved: (1) in identifying and prioritising the research question, (2) in designing the study and (3) in developing the grant proposal.

Four different approaches were used; three of them were addressed to allergic individuals, and one to the general public.

In the first three approaches, the patients/parents of patients were asked to fill in a survey with 10 questions. The survey was structured in co-operation with Research Design Services Northwest. It was given to a total of 30 patients/parents of patients. Graphs of the results are included below (*Figure 3*); in brief, the results established

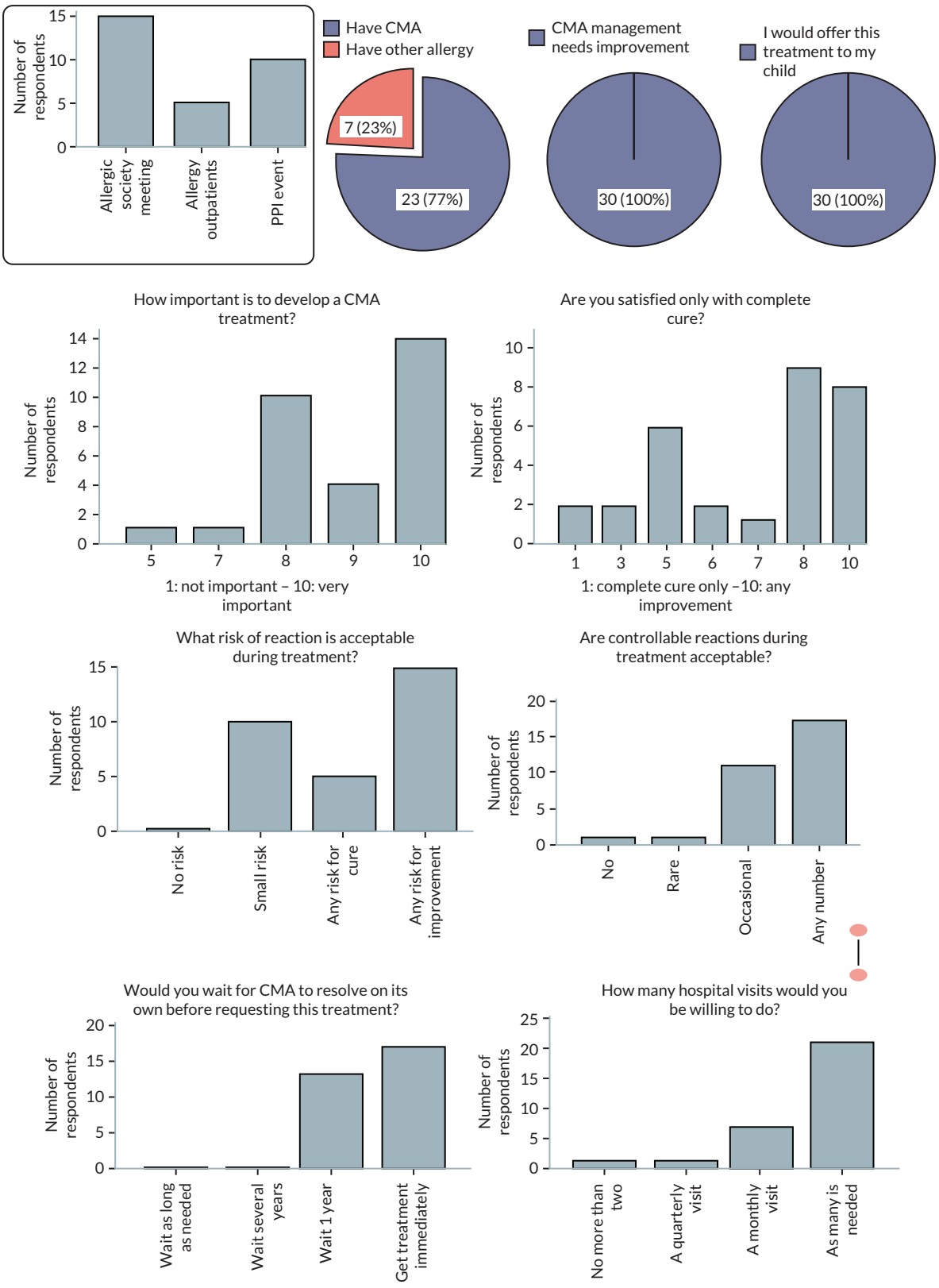

FIGURE 3 Findings from the PPI questionnaire.

that: (1) the patients/parents feel that current management of CMA is subpar and (2) that they would be keen to participate in the trial.

In detail:

1. Parents of CMA children were identified at outpatient clinics of the Royal Manchester Children's Hospital and were approached to participate in a 'focus group'. Overall, 10 parents of CMA children participated in this event, which entailed presentation of the trial, focus group discussion and completing the survey.
2. Five parents of patients seen at the trust's outpatient clinics were approached to fill in the survey.
3. Nikolaos Papadopoulos attended a monthly meeting of a society of allergic patients where he presented the study and discussed with the group. Fifteen of the participants of the meeting filled in and returned the questionnaire.

A fourth patient and public involvement (PPI) activity also took place, which did not include filling in the survey and targeted the general public. In this activity, the trial's Clinical Research Fellow made a presentation of the trial at a 'Pint of Science' event. This is a well-established activity where researchers make presentations to the public in pubs in informal atmosphere, during scheduled pre-advertised events. More than 40 people attended this presentation; importantly, in contrast to the other PPI activities, most of them were not allergic individuals/parents. The post-presentation discussion with the lay patrons established that the public appreciates the problem and understands the premise of the trial and its structure.

The overall input from the PPI activities affected the trial as follows:

1. Affirmed the acceptability and importance of the trial's premise for the service users.
2. Affirmed the acceptability of the trial's procedures for the service users.
3. Clarified the main target (CM desensitisation) and affirmed its importance for the service users.
4. Guided protocol design: protocol was designed on the basis of input regarding what patients/parents would consider reasonable and acceptable for the study's structure – specifically, the number of steps, the duration of hospital visits and the overall trial duration.
5. Contributed to the grant application: the lay abstract was read by patients/parents, who commented on it and revised it.

In addition to the PPI above, the chief executive officer (CEO) of the 'Anaphylaxis UK' charity was a trial co-applicant. Anaphylaxis UK is a key UK charity solely focusing on people at risk of severe allergic reactions and has a wide national network and operations. Anaphylaxis UK had also representation in the TMG and provided valuable input to the patient-facing documents. Anaphylaxis UK also promoted the trial on their website and on a couple of their patient newsletters. The charity's current CEO is one of the authors of the report.

Impact and learning

Socioeconomic consequences of food allergies are significant and stretch beyond the individuals with food allergy to family members, households and the entire society. Food allergy costs include direct costs, indirect costs and intangible costs to all stakeholders;[51] the expenses associated with CMA are substantial.[52,53] In infants < 1 year of age, 32–45.5% of the expenses come from hypoallergenic formula,[52,53] with just the direct NHS costs being £2.23–2.49M, just for the first 12 months after diagnosis. Overall, CMA imposes a substantial burden on NHS resources,[52] and importantly, these findings applied to 2006–9 prices, and it is highly likely that ever since then, given the rise seen in food allergy cases in the UK, these have considerably increased. Hence, the economic impact of the trial's results which support further research into a mainstream OIT management for such patients can be substantial.

Research recommendations

1. DREAM showed that pHF formula can be well tolerated by the majority of allergic CM infants of our cohort, with *free-feeding*. OIT is the most promising method to potentially cure food allergies in the future; however, its uptake is limited by the need for strict and cumbersome dose-based schedules. Being able to use free-feeding in an OIT regimen will strongly support the uptake and impact of OIT and could help make it mainstream. It remains to be proven whether pHF free-feeding OIT is effective in inducing tolerance, the main outcome of DREAM study. We recommend that future trials focus on investigating the capacity of *free-feeding* CMA infants/toddler with broken-down milk formulas (such as pHF) to elicit desensitisation or even outright tolerance to CM.
2. The recruitment challenges faced by DREAM, both of sites and participants, were substantial. Given

the likelihood that many presumed allergic patients suffer by non-immediate milk allergy (instead of immediate milk allergy), we recommend that a number of major sites should be confirmed to participate in any trial intending to recruit substantial number of milk-allergic infants.

3. A DBPCFC should be used as the main outcome to ensure that the evidence is strong. Given that this is a rigorous, resource-heavy process, any site intending to take part in research should be assessed early on in regard to their capacity to deliver this process in a busy ward.
4. There can be considerable overlap between different centres in what constitutes routine practice in diagnosing and managing food allergy, and as such, we recommend that all partners are engaged early on in preparation of the budget/SoECAT to ensure that it is acceptable by all in regard to what constitutes research versus treatment costs.
5. DREAM from its early design had arrangements to support breastfeeding as the optimal feeding for infants. It was part of DREAM that exclusively breastfeeding infants would not be actively approached to recruit, and that breastfeeding would not need to be stopped to take part in the trial, but that – in fact – it would be supported and promoted by the DREAM clinicians. Regardless, throughout the trial, it was necessary for further discussions to take place to try and go even further to ensure that breastfeeding was not penalised in DREAM participants, but also – on the other hand – to ensure that breastfeeding mothers were not missing out on participating in the clinical trial. This is a tight balance that can be difficult to get right, but a very important one to get right. We recommend that discussion takes place at the point of trial setup with breastfeeding stakeholders in order to fine-tune the arrangements to a point that is acceptable to all, to ensure that breastfeeding is supported effectively in the context of the trial.
6. It is worth considering revision of the inclusion criteria for future studies regarding what constitutes anaphylaxis history that excludes the patients from participating. In DREAM, having received two doses of adrenaline for a past episode would exclude infants on the basis of safety. However, the use of adrenaline in the community by paramedics may vary, and the threshold for adrenaline use might, on occasion, be low. A safety exclusion criterion that takes account of such variability of adrenaline use in the community could help support recruitment. However, this criterion should be thoroughly discussed and reviewed by all partners in order to ensure that there is a right balance of safety *versus* inclusion.

Conclusions

Partially hydrolysed formula was tolerated by the majority of confirmed CMA infants in the DREAM trial. This demonstrates that pHF holds promise as a potential OIT medium in free-feeding OIT regimens in future research.

Equality, diversity and inclusion

The trial's population was diverse with 9 out of 16 infants being White (56.3%), 5 being of Asian descent (31.3%) and 2 infants (12.6%) reporting either multiple ethnic groups or 'other' ethnic group (*Table 23*).

TABLE 23 Demographics

	Randomised patients		
	Intervention: pHF	Control: eHF	Total
Ethnicity	(*N* = 8)	(*N* = 8)	(*N* = 16)
White	5 (62.5%)	4 (50%)	9 (56.3%)
Mixed/multiple ethnic groups	0	1 (12.5%)	1 (6.3%)
Asian/Asian British	2 (25%)	3 (37.5%)	5 (31.3%)
Black, African, Caribbean or Black British	0	0	0
Other ethnic group	1 (12.5%)	0	1 (6.3%)
Missing	0	0	0

continued

TABLE 23 Demographics (*continued*)

	Randomised patients		
	Intervention: pHF	**Control: eHF**	**Total**
Birthweight (kg)			
N	7	8	15
Mean (SD)	3.33 (0.37)	3.27 (0.24)	3.30 (0.30)
Median (IQR)	3.40 (0.60)	3.18 (0.34)	3.30 (0.40)
Range (minimum–maximum)	(2.70–3.80)	(3.02–3.70)	(2.70–3.80)
Missing	1	0	1
Gestation time (weeks)			
N	8	7	15
Mean (SD)	39.25 (1.16)	38.86 (1.35)	39.07 (1.22)
Median (IQR)	39.50 (2.00)	39.00 (2.00)	39.00 (2.00)
Range (minimum–maximum)	(38.00–41.00)	(37.00–41.00)	(37.00–41.00)
Missing	0	1	1
Parity			
N	7	8	15
Mean (SD)	1.71 (1.50)	1.25 (0.46)	1.47 (1.06)
Median (IQR)	2.00 (3.00)	1.00 (0.50)	1.00 (1.00)
Range (minimum–maximum)	(0.00–4.00)	(1.00–2.00)	(0.00–4.00)
Missing	1	0	1
Number of siblings living at same house			
N	8	8	16
Mean (SD)	1.00 (1.07)	0.38 (0.52)	0.69 (0.87)
Median (IQR)	1.00 (1.50)	0.00 (1.00)	0.50 (1.00)
Range (minimum–maximum)	(0.00–3.00)	(0.00–1.00)	(0.00–3.00)
Missing	0	0	0

IQR, interquartile range; SD, standard deviation.

There is significant prevalence of CMA in most ethnic groups, but there is some evidence of variation by race, with studies suggesting non-Hispanic Black and non-Hispanic White children are more likely to be sensitised to milk.[54,55] It is also reported that among US-born children, those from immigrant families have a 1.7-fold higher risk of sensitisation than children from non-immigrant households.[56] It could be that genetic, epigenetic and environmental factors play an important role in the development of CMA. The DREAM trial included diverse participants, in order to be able to be representative of most patients who are affected by CMA.

Additional information

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Nikolaos Papadopoulos (https://orcid.org/0000-0002-4448-3468): Conceptualisation, Funding acquisition, Methodology, Investigation, Supervision, Visualisation, Writing – original draft, Writing – review and editing.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

This trial received a favourable opinion on the 9 February 2021 by the London – Central Research Ethics Committee: *Study Title*: 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). *REC Reference:* 20/LO/1254. *Protocol Number:* B00927. *IRAS Project ID:* 279786.

Information governance statement

Manchester University NHS Foundation Trust is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation University of Liverpool is the Data Processor; Manchester University NHS Foundation Trust is the Data Controller and we process personal data in accordance with their instructions. You can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for Manchester University NHS Foundation Trust's Data Protection Officer here: https://mft.nhs.uk.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJGG7715.

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George Raptis declares grants received by his institution by Nutricia, Mead Johnson and Abbott; consultancy fees used for research activities by Nestlé; honoraria used for research activities by Nutricia Ltd, Mead Johnson, Abbott and Nestlé; and declares he is in the Advisory Board of Abbott, Mylan, Nestlé, Aimmune.

Jürgen Schwarze and Simon Williams declare no relevant conflict of interest.

Vibha Sharma declares grants received by her institution from DBV Technologies for unrelated research; honoraria payments for lecture(s) by DBV Technologies; and participation in IDMC committee for unrelated research by Jasper Therapeutics.

Louise Michaelis declares payments made to Newcastle University by the EME programme (NIHR) in relation to this trial; also grants awarded to the Newcastle University by the NIHR and Danone for unrelated research, in the past 36 months.

Nikolaos Papadopoulos declares previous grants for unrelated research in the past 36 months to his institution by Numil Hellas SA, Vianex, Vibrant America; consulting fees from Abbott Nutrition, HAL Allergy Holding B.V, Regeneron Pharmaceuticals, Berlin-Chemie AG; Honoraria from Nestlé Nutrition Institute, Numil Hellas SA, GSK, Menarini International Operations Luxembourg SA, OM Pharma SA and DBV Technologies SA.

The trial product and the comparator product (pHF and eHF) were kindly provided to the TMG by Danone Nutricia Research. Danone Nutricia Research played no other role in the trial, including no role in the distribution of the product to participants/parents, and no role in the design, conduct, analysis and reporting of the trial.

Department of Health and Social Care disclaimer

This publication presents independent research commissioned by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, MRC, NIHR Coordinating Centre, the Efficacy and Mechanism Evaluation programme or the Department of Health and Social Care.

This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Trial registration

This trial is registered as on ISRCTN37753699.

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This synopsis provided an overview of the research award *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)*. For more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/17/60/44).

About this synopsis

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List of abbreviations

AE	adverse event
BSACI	British Society for Allergy and Clinical Immunology
CEO	chief executive officer
CM	cow's milk
CMA	cow's milk allergy
DBPCFC	double-blind, placebo-controlled food challenge
EASI	Eczema Area and Severity Index
eHF	extensively hydrolysed formula
FPIES	food protein-induced enterocolitis syndrome
IgE	immunoglobulin E
OIT	oral immunotherapy
pHF	partially hydrolysed formula
PIC	Patient Identification Centre

PPI	patient and public involvement
SAE	serious adverse event
SoECAT	Schedule of Events Cost Attribution Tool
SPT	skin prick test
TMG	Trial Management Group
V1	visit 1
V3	visit 3
V4	visit 4

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Appendix 1

Full title	A randomised controlled double-blind trial assessing desensitisation to cow's milk, following pHF or eHF feeding regimens, in children with allergy to cow's milk
Acronym	DREAM
Phase	III
Target condition	Infants aged 6–12 months with moderate to severe IgE-mediated CMA
Sample size	156
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: **V1 inclusion assessments** 1. Infant aged 6–12 months, inclusive, at V1 2. Convincing medical history of *IgE-mediated* allergic reaction following ingestion of CM formula, as determined by trial physician 3. Infant fed with formula, either exclusively or mixed with breastfeeding 4. Written informed consent by parent/legal guardian prior to completing any study-related procedure 5. Titre of CM-specific IgE in serum, equal or higher to 2 kU/l [collected at V1, confirmed prior to visit 2 (V2/3)], at inclusion **or** wheal reaction of equal or over 5 mm to SPT* to CM at inclusion **V2/3 inclusion assessments** 6. Positive result in the challenge to pHF (V2) **or** positive result in the challenge to CM (V3) **V3/4 inclusion assessments** 7. Weight of at least 7.5 kg at randomisation * 5 mm to either whole, fresh milk or commercial milk extract
Exclusion criteria	*Any* of the following will exclude someone from the study. Eligibility will be assessed in a staged manner: **V1 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 CM or CM 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 judgement, are unlikely to comply with the study protocol for any reason (language barrier, communication issues, inability to understand procedures, and so on) 7. History of overnight hospitalisation (only accident and emergency 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 9. Another infant from the same household is currently participating in the study **Visit 2 (V2)/3 exclusion assessments** 10. *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:** pHF **Control:** eHF (normal clinical care)

Full title	A randomised controlled double-blind trial assessing desensitisation to cow's milk, following pHF or eHF feeding regimens, in children with allergy to cow's milk
Randomisation ratio	1 : 1
Primary objective	To determine whether 1 year of feeding with pHF is more efficacious than with eHF as a treatment for 6- to 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 1 year of feeding with pHF is more efficacious than with eHF in inducing CM desensitisation for 6- to 12-month-old *pHF-tolerant* infants with IgE-mediated CMA 3. To determine whether 1 year of feeding with pHF is more efficacious than with eHF in inducing CM desensitisation for 6- to 12-month-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) 6. To characterise participants' reactivity to pHF
Primary outcome	Characterised as CM protein-tolerant in a DBPCFC 12 months after randomisation
Secondary outcomes	1. The dose at which reactivity occurs in the DBPCFC 2. The maximal wheal size of SPT to CM 3. Specific IgE levels to CM, casein, alpha-lactalbumin and beta-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. AEs 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 8 (V8)