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Original article

Cost-effectiveness of using an extensively hydrolysed casein formula supplemented with *Lactobacillus rhamnosus* GG in managing IgE-mediated cow's milk protein allergy in the UK

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Abstract

Objective: To estimate the cost-effectiveness of using an extensively hydrolysed casein formula (eHCF) plus the probiotic *Lactobacillus rhamnosus* GG (eHCF plus LGG; Nutramigen LGG) compared to an eHCF alone as first-line dietary management for Immunoglobulin (IgE) - mediated cow's milk protein allergy (CMPA) in the UK.

Methods: Decision modelling was undertaken to estimate the probability of IgE-mediated cow's milk allergic infants being symptom-free (i.e. not experiencing urticaria, eczema, asthma, or rhinoconjunctivitis) and developing tolerance to cow's milk by 5 years. The model also estimated the cost (at 2016/2017 prices) of health care resource use funded by the UK's National Health Service (NHS) over 5 years after starting a formula, as well as the relative cost-effectiveness of the two dietary formulae.

Results: At 5 years after the start of a formula the probability of being symptom-free was estimated to be 0.97 and 0.76 among infants who were originally fed eHCF plus LGG and an eHCF alone, respectively. This encompassed the probability of children being asthma-free at 5 years after the start of treatment, which was 0.99 and 0.91 in the eHCF plus LGG and eHCF alone groups, respectively. Additionally, the probability of tolerance acquisition to cow's milk was estimated to be 0.94 and 0.66 among infants who were originally fed eHCF plus LGG and an eHCF alone, respectively. The estimated total healthcare cost over 5 years of initially feeding infants with eHCF plus LGG was less than that of feeding infants with an eHCF alone (£4,229 versus £5,136 per patient).

Conclusion: First-line management of newly-diagnosed infants with IgE-mediated CMPA with eHCF plus LGG instead of eHCF alone improves outcome, releases healthcare resources for alternative use, reduces the NHS cost of patient management and thereby affords a cost-effective dietetic strategy to the NHS.

Keywords: Asthma; cost-effectiveness, cow's milk protein allergy, extensively hydrolysed formula, *Lactobacillus rhamnosus* GG, Nutramigen, UK.

Short title: Cost-effectiveness of an extensively hydrolysed casein formula containing LGG in managing IgE-mediated cow's milk protein allergy in the UK

Introduction

Cow's milk protein allergy (CMPA) is one of the most common food allergies in early childhood, with an estimated annual prevalence of 2% to 3%¹. Guidelines for managing infants with CMPA recommend the use of substitutive hypoallergenic formulae^{2,3}. Two studies comparing different formulae found that feeding cow's milk allergic children with an extensively hydrolysed casein formula (eHCF) supplemented with the probiotic *Lactobacillus rhamnosus* GG (LGG) (Nutramigen LGG; eHCF plus LGG) resulted in higher tolerance acquisition to cow's milk protein compared with those fed an eHCF without LGG and other formulae^{4,5}. Additionally, feeding eHCF plus LGG first-line to both Immunoglobulin E (IgE)-mediated and non-IgE mediated cow's milk allergic infants, compared to feeding with an eHCF alone or an amino acid formula was found to be cost-effective in Italy⁶, Spain⁷, Poland⁸ and the US^{9,10}.

Food-related reactions are associated with a broad range of signs and symptoms that may involve several body systems, including the skin, gastrointestinal and respiratory tracts¹¹. Results from a recent randomised controlled trial (RCT) found that the relative risk for the occurrence of at least one allergic manifestation (urticaria, eczema, asthma, and rhinoconjunctivitis) was reduced by 49% over 3 years among IgE-mediated cow's milk allergic children who were fed eHCF plus LGG compared with those fed eHCF alone¹². The comparative health economic impact of these two formulae in reducing allergic manifestations in cow's milk allergic infants is unknown. Consequently, the objective of the current study was to use data from the aforementioned RCT¹² to estimate the medium to long-term cost-effectiveness of feeding IgE-mediated cow's milk allergic infants with eHCF plus LGG, compared with an eHCF alone, from the perspective of the UK's National Health Service (NHS).

Methods

Economic model

A Markov model was constructed to simulate the management of infants with IgE-mediated CMPA who are managed first-line with eHCF plus LGG or an eHCF alone over a period of 5 years (Figure 1). The model structure and health states were based on the aforementioned RCT¹². The Markov Model comprised the following 5 health states: initial presentation of the symptoms of CMPA/urticaria; eczema; asthma; rhinoconjunctivitis and symptom-free (no allergic manifestations). Within the model patients can also acquire tolerance to cow's milk at any time.

Patients enter the model at the time of initial presentation of the symptoms of CMPA. Patients either remain in this health state or move to one of the other health states. Patients transition in the model every year. The model was populated with (1) estimates of clinical outcomes reported in the aforementioned RCT¹² and (2) estimates of health care resource use derived from the clinical authors and interviews with two other general practitioners (GPs) in the UK with experience of managing CMPA.

Model inputs – clinical outcomes

The RCT¹² was performed between October 2008 and December 2014. Otherwise healthy infants (n=220; median age at recruitment of 5.0 months; 66-68% male; mean body weight 7.4-7.5kg) were referred to a tertiary paediatric allergy centre for a diagnostic double-blind, placebo-controlled food challenge (DBPCFC) for suspected CMPA. Infants with a positive result were randomised to one of the study's formula. During the study, patients were managed by their family practitioner and a dietitian. Additionally, they attended the tertiary paediatric allergy centre at 1, 2 and 3 years after randomisation to undergo a skin prick test and a DBPCFC to assess whether they were still allergic to cow's milk. At these visits, the children were physically examined by a paediatrician, body growth was assessed, and a structured interview was undertaken to assess any health problems, including the development of any allergic manifestations.

Allergic urticaria was diagnosed if at least 2 episodes of itching eruptions or swelling with typical appearance were observed by the parents or a physician and were caused by the same allergen. Atopic eczema was diagnosed based on pruritus, typical morphology and distribution, a chronic or chronically relapsing course, and personal or family atopic history. Allergic rhinoconjunctivitis was diagnosed based on the symptoms of rhinitis, such as nasal congestion, sneezing, itching, rhinorrhoea, current use of medication for these symptoms, and/or conjunctivitis, after exclusion of infection. A diagnosis of asthma was based on the presence of recurrent wheeze (more than once a month), difficulty in breathing, chest tightness, or both; cough (worse at night); clinical improvement during treatment with short-acting bronchodilators and inhaled steroids; and worsening when treatment was stopped. Alternative causes of recurrent wheezing were considered and excluded¹².

Infants were excluded from the study if they had cow's milk protein-induced anaphylaxis, food protein-induced enterocolitis syndrome, other food allergies, other allergic diseases, non-CMPA-related atopic eczema, eosinophilic disorders of the gastrointestinal tract, chronic systemic diseases, congenital cardiac defects, active tuberculosis, autoimmune diseases, immunodeficiency, chronic inflammatory bowel diseases, celiac disease, cystic fibrosis,

metabolic diseases, malignancy, chronic pulmonary diseases, malformations of the gastrointestinal and/or respiratory tract, and fed prebiotics or probiotics in the previous four weeks before enrolment ¹².

The study reported that at 3 years, 2.0%, 1.0%, 1.0% and 2.0%, of infants fed eHCF plus LGG were experiencing urticaria, eczema, asthma and rhinoconjunctivitis, respectively, compared with 2.1%, 6.3%, 8.4% and 16.8% of those fed an eHCF alone ¹². Additionally, 81% of infants fed eHCF plus LGG had acquired tolerance to cow's milk (defined as the negativisation of a double-blind food challenge) by 3 years compared to 55% of those fed an eHCF alone ¹². Time-series forecasting was used to extrapolate the percentage of children experiencing allergic symptoms or acquiring tolerance to cow's milk with each formula up to 5 years (Figure 2). These percentages were used to populate the model with the probability of infants experiencing urticaria, eczema, asthma and rhinoconjunctivitis or developing tolerance to cow's milk at 12-monthly intervals up to 5 years (Table 1).

Model inputs – resource use

The model was populated with estimates of health care resource use pertaining to the management of infants with CMPA in the UK. These estimates were derived from the clinical authors and interviewed GPs who managed infants with CMPA according to their local clinical protocol and guidelines from the National Institute for Health and Care Excellence (NICE) ¹³. The estimates of resource use derived from the clinical authors and interviewed GPs that were incorporated into the model are summarised in Table 2.

According to the clinicians, infants would receive a mean of 11 cans of clinical nutrition per month up to 6 months of age, a mean of 9 cans per month between 6 and 12 months of age, a mean of 7 cans per month between 12 and 18 months of age and in some practices, a mean of 6 cans per month between 18 and 24 months of age.

Model outputs

The primary measure of clinical effectiveness was the probability of being free of allergic symptoms (i.e. urticaria, eczema, asthma and rhinoconjunctivitis). The secondary measure of clinical effectiveness was the probability of tolerance acquisition to cow's milk.

Unit costs at 2017/18 prices (Table 3) ^{14,15} were assigned to the estimates of resource use in order to calculate the NHS cost of healthcare resource per patient. Costs were discounted from the second and subsequent year at 3.5% per annum, in accordance with the recommended rate ¹⁶.

The model was used to estimate the cost-effectiveness of using eHCF plus LGG compared with eHCF alone in terms of the incremental cost for each additional infant who was (1) symptom-free and (2) tolerant to cow's milk. This was calculated as the difference between the expected costs of the two dietetic strategies divided by the difference between the probability of effectiveness of the two strategies. If one of the formulae improved outcome for less cost, it was considered to be the dominant (cost-effective) dietetic strategy.

Sensitivity analyses

To assess uncertainty within the model, probabilistic sensitivity analysis was undertaken (10,000 iterations of the model) by simultaneously varying the probabilities, clinical outcomes, resource use values, and unit costs. A beta distribution was used to represent uncertainty in probability values by assuming a 10% standard deviation around the mean values. Resource use estimates and unit costs were varied randomly according to a gamma distribution by also assuming a 10% standard deviation around the mean values. The outputs from these analyses were used to estimate the probability of eHCF plus LGG being cost-effective at different willingness to pay thresholds over 5 years.

In addition, deterministic sensitivity analyses were performed to identify how the incremental cost-effectiveness of eHCF plus LGG compared with eHCF alone would change by varying different parameters in the model.

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Results

Probability of allergic manifestation and tolerance acquisition to cow's milk

The probability of allergic manifestation was lower among infants who were initially fed with eHCF plus LGG. Similarly, the probability of developing tolerance to cow's milk was higher among infants who were initially fed with this formula (Table 4).

Health care resource use and corresponding costs

An infant who is initially managed with eHCF plus LGG was estimated to consume fewer healthcare resources than infants managed with eHCF alone (Table 5). Hence, initially feeding infants with eHCF plus LGG instead of the other formulae is expected to free-up healthcare resources for alternative use by other patients. Consequently, the total healthcare cost of initially feeding infants with eHCF plus LGG was estimated to be less than that of feeding infants with eHCF alone (Table 6).

The cost of managing CMPA/urticaria accounted for up to 92% and 88% of the total cost of managing patients in the eHCF plus LGG and eHCF alone groups, respectively. Managing asthma accounted for a further 3% and 6% of the total cost of managing patients in the eHCF plus LGG and eHCF alone groups, respectively. Managing eczema and rhinoconjunctivitis accounted for the remainder. This cost distribution was to be expected since all the infants in the study had CMPA and the acquisition costs of the prescribed formulae for managing the allergy were the primary cost driver of patient management (Table 6). GP visits were the secondary cost driver (Table 6), the majority of which were for CMPA/urticaria (Table 2). Only a small proportion of infants in the study developed eczema, asthma and rhinoconjunctivitis. Therefore, the additional amount of resource use due to these allergic manifestations was small relative to the amount of resources required to manage the CMPA.

Cost-effectiveness analyses

Feeding infants with eHCF plus LGG instead of eHCF alone resulted in a greater probability of being both symptom-free and of developing tolerance to cow's milk for a lower cost (Table 7). Hence, starting feeding with eHCF plus LGG was found to be the dominant strategy from the perspective of the UK's NHS. (Table 7). Additionally, the probability of children being asthma-free at 3 years after the start of treatment was 0.99 and 0.92 in the eHCF plus LGG and eHCF alone groups, respectively and at 5 years it was 0.99 and 0.91 in the eHCF plus LGG and eHCF alone groups, respectively. Hence initially feeding IgE-mediated cow's milk allergic infants with eHCF plus LGG was also viewed as a dominant dietetic strategy when the measure of cost-effectiveness is the incremental cost for each additional infant who was asthma-free.

Sensitivity analyses

Probabilistic sensitivity analyses enabled the distribution in the incremental costs and incremental probabilities of the alternative formulae at 5 years following the start of treatment to be generated (Figure 3). Outputs from these analyses showed that from the NHS' perspective, at an incremental cost-effectiveness threshold of £11.21 (i.e. the cost of a 400g can of eHCF plus LGG) for each additional infant becoming:

- free of allergic symptoms, up to 79% of a cohort would be cost-effectively treated with eHCF plus LGG compared to an eHCF alone.
- tolerant to cow's milk, up to 80% of a cohort would be cost-effectively treated with eHCF plus LGG compared to an eHCF alone.

Probabilistic sensitivity analyses also showed that at an incremental cost-effectiveness threshold of £11.21 for each additional infant becoming asthma-free, up to 78% of a cohort would be cost-effectively treated with eHCF plus LGG compared to an eHCF alone.

Sensitivity analyses (Table 8) indicated that extrapolating the outcomes from the RCT¹² from 3 to 5 years has negligible impact on the relative cost-effectiveness of eHCF plus LGG. Additionally, changes in the estimates of resource use also have negligible impact on the relative cost-effectiveness of eHCF plus LGG. The base case analysis assumes that the cost of the two formulae is same. The sensitivity analyses (Table 8) showed that if the cost of eHCF alone is reduced to £9.20 per 400g can, then initial treatment with eHCF plus LGG still affords a cost-effective dietetic strategy as the total healthcare cost at 5 years after the start of treatment with this formula was estimated to be a discounted £500 less than that of feeding infants with eHCF alone.

Discussion

This study is the first to show that initial management with eHCF plus LGG affords a cost-effective dietetic strategy over a period of 5 years (irrespective of whether the measure of effectiveness is tolerance acquisition to cow's milk or being free of the symptoms of urticaria, eczema, rhinoconjunctivitis and asthma). The analysis is constrained by the fact that only infants with IgE-mediated CMPA were evaluated and the only comparator formula was eHCF alone. Notwithstanding this, the underlying IgE-mediation of the allergy suggests that this population is at a higher risk of developing other allergies such as eczema, rhinoconjunctivitis and asthma than those with non-IgE-mediated CMPA¹².

Other limitations reflect the fact that the clinical basis of the economic analysis was the RCT conducted in Italy¹². The advantage of using this clinical data was that the treatment effect reflects the findings from a RCT. However, the findings from a protocol-driven RCT may not necessarily be reproducible in the UK or reflect clinical practice in the UK. Additionally, the analysis was informed with assumptions about management patterns from four centres in the UK. Hence, the estimated levels of healthcare resource use incorporated into the model may not be representative of the whole UK. However, changes to these estimates had negligible effect on the results.

The model used resource estimates for the 'average infant' and does not consider the impact of other factors that may affect the results, such as co-morbidities, underlying disease severity and pathology of the underlying disease. The model also excluded the possibility of infants experiencing multiple allergic manifestations either at initial presentation or during the subsequent 5 years, however this is unlikely to affect the relative cost-effectiveness of the two formulae. The results of the 3-year RCT were extrapolated to 5 years, but this had negligible impact on the results (as shown in Table 7). Additionally, the study excluded the cost and consequences of managing children beyond this period. The analysis also excluded the indirect costs incurred by society as a result of employed parents taking time off work and non-treatment-related costs incurred by parents. Changes in quality of life and improvements in general well-being of sufferers and their parents as well as parents' preferences as also excluded. Consequently, this study may have underestimated the relative cost-effectiveness of eHCF plus LGG.

The results from this economic analysis were based on extrapolating the clinical results from the aforementioned RCT¹² from 3 to 5 years, since many planning Authorities allocate resources over a three-to-five-year fiscal period. However, the economic analysis also showed that initial management with eHCF plus LGG affords a cost-effective dietetic strategy over a period of 3 years across all measures of effectiveness. Additionally, we have previously reported that initial management of both IgE-mediated and non-IgE-mediated CMPA with eHCF plus LGG affords a cost-effective dietetic strategy when compared to both an eHCF alone and amino acid formulae over a period of 18 months in different countries⁶⁻¹⁰. Consequently, our studies would suggest that the probability of eHCF plus LGG being a cost-effective formula for the initial management of CMPA is sustained from 18 months over a period of 5 years. Moreover, the relative cost-effectiveness of the formula increases as the time-horizon lengthens. This is relevant since the most recent evidence suggests that the natural history of CMPA has changed over time, with the proportion of children with disease persistence increasing through to 5 years and possibly older^{17,18}.

The distribution and pattern of allergies change as a child matures. Infants are more likely to present with food allergy, atopic eczema, gastrointestinal symptoms and wheezing, whilst older children typically present with asthma and allergic rhinoconjunctivitis¹⁹. Furthermore, children in the US with a food allergy are up to four times more likely to have other allergic manifestations, such as asthma (4.0 times), atopic eczema (2.4 times) and respiratory allergies (3.6 times), compared with children without a food allergy²⁰. Hence, reducing the risk of asthma manifestation in infants with CMPA can have substantial clinical and economic sequelae over the medium to long-term. Children's health in the UK has been reported to lag behind other Western European nations and unplanned hospital admissions have steadily increased^{21,22}. Hospital admissions have been increasing partly due to the challenges faced by the NHS in adapting to a growing chronic disease burden in children²² and policies that seem to have delayed children's access to primary care²³. In a cohort study among 319,780 children born between January 2000 and March 2013, 8.9% of the cohort had a diagnosis of asthma²⁴. These children had a mean of 2.2 asthma-related visits per year with their general practitioner between the ages of 5-9 years and 84 unplanned asthma-related hospital admissions per 1,000 children²⁴. Additionally, in 2016/17, there were 24,467 hospital admissions for asthma among children aged 9 years or less. This number increases to 31,427 asthma-related admission when children aged 10 to 14 years are included²⁵. Moreover, asthma has a major impact on absenteeism from school²⁶.

In recent years, hospital admission rates for adults with chronic diseases, such as asthma, are reported to have fallen following incentives in primary care to improve chronic disease management²⁷. This suggests there is scope for a similar policy intervention for children, although the healthcare needs of children differ from those of adults since there is a greater dependency on parents, and education remains an important component of a family's ability to care. Such a policy might include feeding infants with IgE-mediated CMPA with eHCF plus LGG, not only because it is a cost-effective dietetic strategy, but because of its potential to reduce asthma in children. Further work is required to better understand how primary care can serve the needs of children with allergies in order to minimise the risk of paediatric allergies leading to long-term or complex conditions.

In conclusion, within the study's limitations, first-line management of newly-diagnosed infants with IgE-mediated CMPA with eHCF plus LGG instead of eHCF alone improves outcome, releases healthcare resources for alternative use, reduces the NHS cost of patient management and affords a cost-effective dietetic strategy to the NHS in 80% of cases.

Transparency

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Declaration of financial/other relationships

The authors have no financial relationships or conflicts of interest relevant to this article to disclose. Peer reviewers on this manuscript have no other relevant financial or other relationships to disclose.

Author contributions

JG conceptualized and designed the study, carried out the analyses, drafted the initial manuscript, and reviewed and revised the manuscript.

HS contributed to the analyses, and critically reviewed and contributed to the revised manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Figure and table legends

Table 1: Annual transition probabilities in the Markov model.

Table 2: Estimates of resource use incorporated into the model.

Table 3: Unit resource costs at 2016/17 prices.

Table 4: Expected clinical outcomes at three and five years from the start of treatment.

Table 5: Mean amount of resource use per patient over five years from the start of treatment.

Table 6: Mean cost (at 2016/17 prices) per patient over five years from the start of treatment (percentage of total cost in parentheses).

Table 7: Cost-effectiveness analyses at three and five years from the start of treatment.

Table 8: Sensitivity Analysis

Figure 1: Diagrammatic representation of the Markov model.

Figure 2: Time-series forecasting of the clinical outcomes from the RCT ¹²

Figure 3: Scatterplot of the incremental cost-effectiveness of eHCF plus LGG compared to eHCF alone (10,000 iterations of the model).

Table 1: Annual transition probabilities in the Markov model.

Time (years)	Formula	Probability of moving into each state at the end of a 12 months period				
		CMPA/urticaria	Eczema	Asthma	Rhinoconjunctivitis	Symptom-free
0	eHCF plus LGG	1.00	0.00	0.00	0.00	0.00
1	eHCF plus LGG	0.04	0.14	0.06	0.05	0.71
2	eHCF plus LGG	0.02	0.00	0.02	0.02	0.94
3	eHCF plus LGG	0.02	0.01	0.01	0.01	0.95
4	eHCF plus LGG	0.01	0.02	0.00	0.00	0.97
5	eHCF plus LGG	0.00	0.03	0.00	0.00	0.97
0	eHCF alone	1.00	0.00	0.00	0.00	0.00
1	eHCF alone	0.19	0.18	0.02	0.05	0.56
2	eHCF alone	0.00	0.03	0.08	0.03	0.86
3	eHCF alone	0.02	0.06	0.08	0.06	0.78
4	eHCF alone	0.00	0.07	0.09	0.07	0.77
5	eHCF alone	0.00	0.08	0.09	0.07	0.76

Table 2: Estimates of resource use incorporated into the model.

	Mean amount of resource use per patient in:				
	Year 1	Year 2	Year 3	Year 4	Year 5
Management of CMPA/urticaria					
GP visits (mean per patient)	8.00	3.00	2.00	2.00	2.00
General paediatrician visits (mean per patient)	1.00	1.00	1.00	0.50	0.50
Paediatric allergist visits (mean per patient)	0.84	0.84	0.84	0.42	0.42
Dietitian visits (mean per patient)	2.80	1.64	1.64	1.64	1.64
Accident & emergency attendances (mean per patient)	0.30	0.30	0.00	0.00	0.00
Hospital admissions (mean per patient)	0.08	0.05	0.03	0.02	0.02
Percentage referred to a general paediatrician	50%	0%	0%	0%	0%
Percentage referred to a paediatric allergist	40%	0%	0%	0%	0%
Percentage referred to a dietitian	90%	0%	0%	0%	0%
Percentage prescribed H ₂ antagonists of proton pump inhibitors	28%	0%	0%	0%	0%
Percentage prescribed emollients	85%	0%	0%	0%	0%
Percentage prescribed systemic corticosteroids	3%	3%	3%	3%	3%
Percentage prescribed topical corticosteroids	50%	50%	50%	50%	50%
Percentage prescribed antihistamines	60%	60%	60%	60%	60%
Management of eczema					
GP visits (mean per patient)	4.00	3.00	3.00	3.00	3.00
General paediatrician visits (mean per patient)	0.90	0.90	0.90	0.45	0.45
Paediatric dermatologist visits (mean per patient)	0.03	0.06	0.06	0.03	0.03
Accident & emergency attendances (mean per patient)	0.13	0.13	0.13	0.13	0.13
Hospital admissions (mean per patient)	0.03	0.03	0.03	0.03	0.03
Percentage referred to a general paediatrician	45%	0%	0%	0%	0%
Percentage referred to a dermatologist	3%	0%	0%	0%	0%
Percentage prescribed emollients	100%	100%	100%	100%	100%
Percentage prescribed topical corticosteroids	70%	70%	70%	70%	70%
Percentage prescribed antihistamines	50%	50%	50%	50%	50%
Management of asthma					
GP visits (mean per patient)	7.00	6.00	5.00	5.00	4.00
General paediatrician visits (mean per patient)	2.00	0.90	0.90	0.90	0.90
Accident & emergency attendances (mean per patient)	0.20	0.20	0.20	0.20	0.20
Hospital admissions (mean per patient)	0.40	0.40	0.40	0.40	0.40
Percentage referred to a general paediatrician	65%	0%	0%	0%	0%
Percentage prescribed systemic corticosteroids	40%	40%	40%	40%	40%
Percentage prescribed Ventolin/beta agonists	100%	100%	100%	100%	100%
Percentage prescribed inhaled corticosteroids	55%	55%	55%	55%	55%

Management of rhinoconjunctivitis					
GP visits (mean per patient)	2.00	2.00	2.00	2.00	2.00
General paediatrician visits (mean per patient)	0.10	0.00	0.00	0.00	0.00
Accident & emergency attendances (mean per patient)	0.03	0.00	0.00	0.00	0.00
Percentage referred to a general paediatrician	5%	0%	0%	0%	0%
Percentage prescribed antihistamines	80%	80%	80%	80%	80%

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Table 3: Unit resource costs at 2016/17 prices.

Resource	Unit Cost
GP clinic visit	£66.90
GP home visit	£80.67
Initial visit general paediatrician	£236.00
Follow-up visit general paediatrician	£189.00
Initial visit paediatric allergist	£244.00
Follow-up visit paediatric allergist	£186.00
Initial visit paediatric dermatologist	£114.00
Follow-up visit paediatric dermatologist	£101.00
Initial visit dietitian	£91.00
Follow-up visit dietitian	£69.00
Accident & emergency attendance	£149.78
Hospital admission	£1,434.00
Weekly prescription for proton pump inhibitors	£103.56
Monthly prescription for emollient	£5.01
Weekly prescription for systemic corticosteroids	£18.08
Monthly prescription for topical corticosteroids	£5.96
Monthly prescription for antihistamines	£5.41
Monthly prescription for inhaled corticosteroids	£10.90
Monthly prescription of salbutamol 100mcg/dose	£1.50
eHCF (per 400g can)	£11.21
eHCF plus LGG (per 400g can)	£11.21

Table 4: Expected clinical outcomes at three and five years from the start of treatment.

	eHCF alone	eHCF plus LGG
Probability of not experiencing any allergic symptoms		
3 years	0.77	0.95
5 years	0.76	0.97
Probability of tolerance acquisition to cow's milk		
3 years	0.55	0.81
5 years	0.66	0.94

Table 5: Mean amount of resource use per patient over five years from the start of treatment.

	eHCF alone	eHCF plus LGG
GP visits	20.22	16.70
Specialist visits	5.12	3.74
Dietitian visits	5.73	4.40
Hospital admissions	0.26	0.16
Accident & emergency attendances	0.59	0.48
Prescriptions for H ₂ antagonists/PPIs	1.40	1.40
Prescriptions for emollients	21.40	14.90
Prescriptions for systemic corticosteroids	0.42	0.17
Prescriptions for topical corticosteroids	4.75	3.30
Prescriptions for antihistamines	4.29	2.82
Prescriptions for salbutamol 100mcg/dose	1.68	0.55
Prescriptions for inhaled corticosteroids	1.84	0.61
Clinical nutrition (400g cans)	182.40	166.96

Table 6: Mean cost (at 2016/17 prices) per patient over five years from the start of treatment (percentage of total cost in parentheses).

	eHCF alone		eHCF plus LGG	
GP visits	£1,102.73	(21%)	£892.08	(21%)
Specialist visits	£966.81	(19%)	£729.71	(17%)
Dietitian visits	£399.53	(8%)	£316.10	(7%)
Hospital admissions	£355.25	(7%)	£223.01	(5%)
Accident & emergency attendances	£86.03	(2%)	£70.79	(2%)
Prescribed drugs	£205.42	(4%)	£143.99	(3%)
Clinical nutrition	£2,020.22	(39%)	£1,853.19	(44%)
TOTAL	£5,135.99	(100%)	£4,228.87	(100%)

Table 7: Cost-effectiveness analyses at three and five years from the start of treatment.

		Incremental cost for each additional infant who was:				
		NHS cost per patient	Probability of tolerance to cow's milk	Probability of being symptom-free	tolerant to cow's milk	symptom-free
at 3 years	eHCF plus LGG	£4,091	0.81	0.95		
at 3 years	eHCF alone	£4,588	0.55	0.77		
at 3 years	<i>Difference</i>	<i>-£497</i>	<i>0.26</i>	<i>0.18</i>		
at 3 years	Cost-effectiveness				-£1,922	-£2,754
at 5 years	eHCF plus LGG	£4,229	0.94	0.97		
at 5 years	eHCF alone	£5,136	0.66	0.76		
at 5 years	<i>Difference</i>	<i>-£907</i>	<i>0.28</i>	<i>0.21</i>		
at 5 years	Cost-effectiveness				-£3,240	-£4,320

Table 8: Sensitivity Analysis

Scenario	Incremental cost for each additional infant who was:	
	tolerant to cow's milk	symptom-free
The probability of allergic manifestation and developing tolerance to cow's milk in years 4 and 5 remained unchanged from those at year 3	-£3,417	-£4,897
The probability of allergic manifestation in years 4 and 5 remained unchanged from those at year 3 and the probability of developing tolerance to cow's milk in years 4 and 5 remains as predicted	-£3,196	-£4,956
Reduce the amount of resource use attributable to managing the allergic manifestations of eczema, rhinoconjunctivitis and asthma by 25%	-£2,283	-£3,844
Increase the amount of resource use attributable to managing the allergic manifestations of eczema, rhinoconjunctivitis and asthma by 25%	-£3,330	-£4,440
Decrease the amount of resource use attributable to managing CMPA and the allergic manifestations of eczema, rhinoconjunctivitis and asthma by 25%	-£2,313	-£3,084
Increase the amount of resource use attributable to managing CMPA and the allergic manifestations of eczema, rhinoconjunctivitis and asthma by 25%	-£3,890	-£5,200
Decrease the amount of resource use attributable to managing CMPA and the allergic manifestations of eczema, rhinoconjunctivitis and asthma by 25% but assume all patients were symptom-free and tolerant to cow's milk by year 5	-£14,874	-£11,117
Increase the amount of resource use attributable to managing CMPA and the allergic manifestations of eczema, rhinoconjunctivitis and asthma by 25% but assume all patients were symptom-free and tolerant to cow's milk by year 5	-£23,638	-£19,737
Formula is no longer prescribed once an infant reaches 18 months of age	-£2,941	-£3,922
Change the cost of the comparator eHCF to £9.20 per 400g can	-£1,722	-£2,296

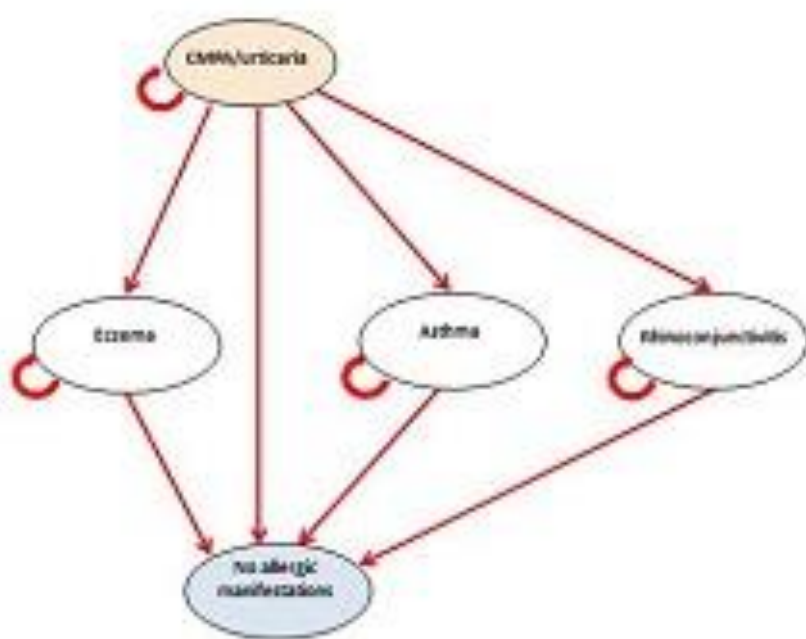


Figure 2: Time-series forecasting of the clinical outcomes from the RCT ¹².

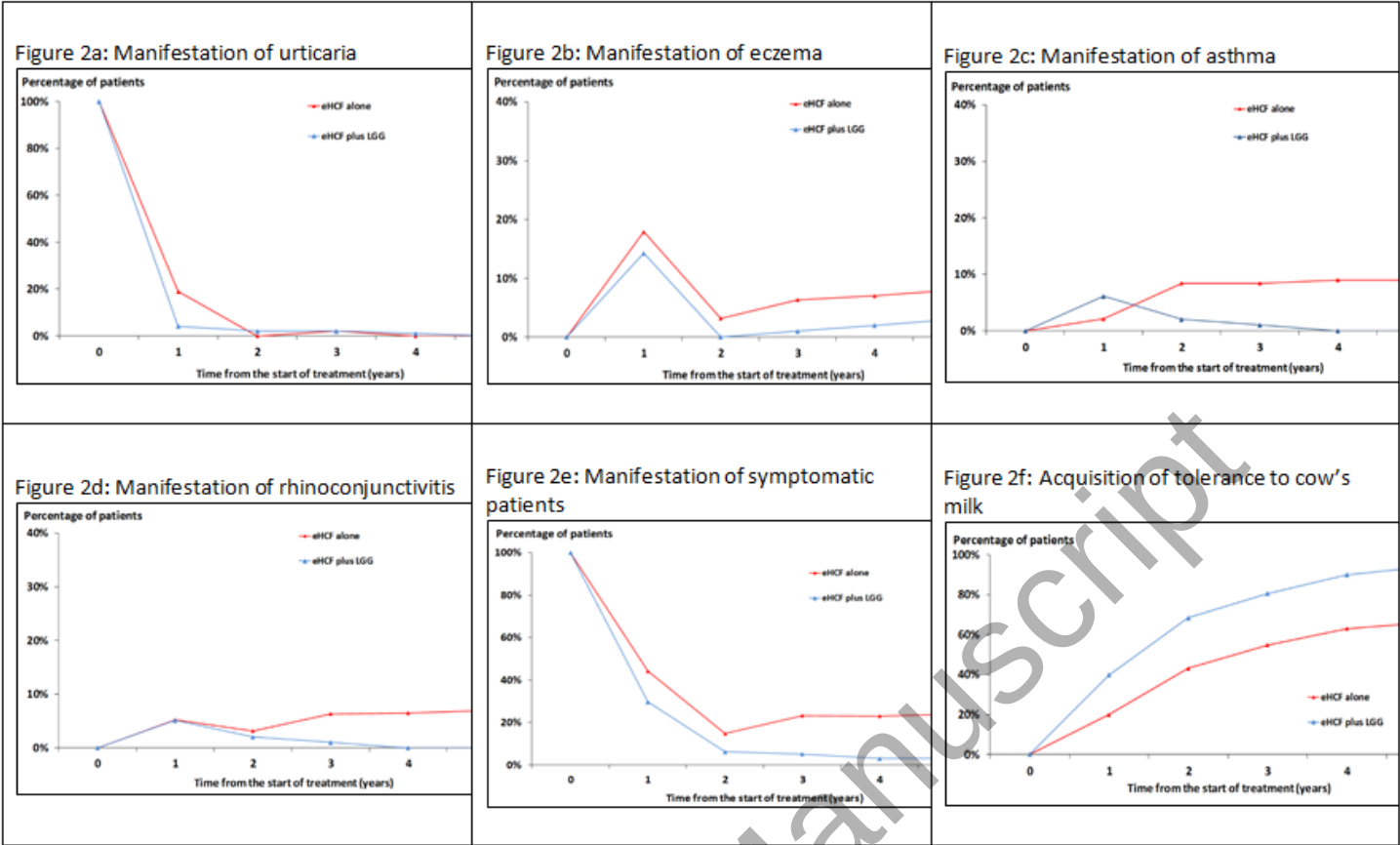


Figure 3: Scatterplot of the incremental cost-effectiveness of eHCF plus LGG compared to eHCF alone (10,000 iterations of the model).

Figure 3a: Measure of effectiveness is probability of being symptom-free.

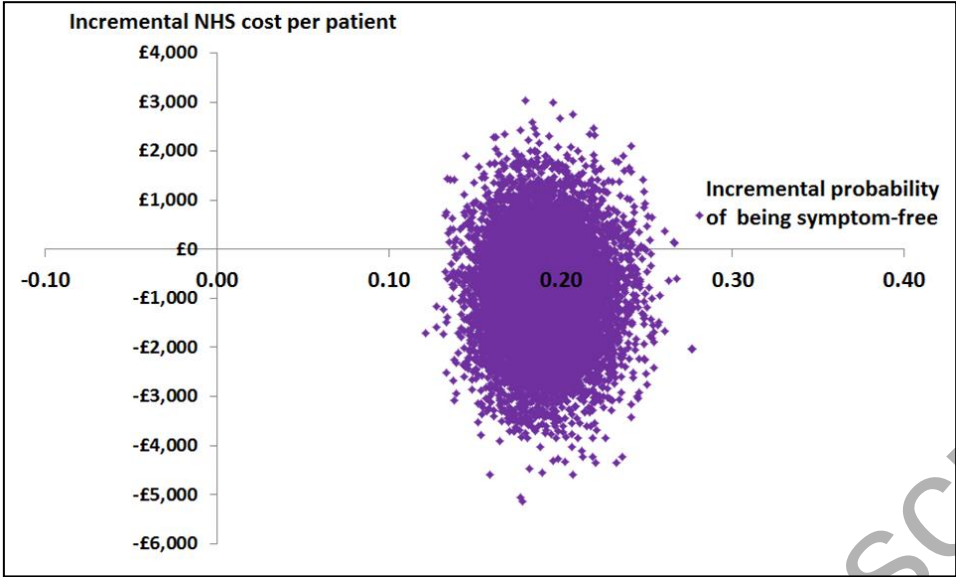


Figure 3b: Measure of effectiveness is probability of acquiring tolerance to cow's milk.

