APPENDIX 2-1.

Question 1, Profile 1. Should Skin Prick Tests Be Used for the Diagnosis of IgE-Mediated CMA in Patients Suspected of CMA?

Cut-Off ≥3 mm/All Populations

Outcome	No. of Studies	Study Design	Limitations					Final Quality	Effect Per 1000*	Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication Bias			
True positives (patients with CMA)	23 studies (2302 patients)	Consecutive or nonconsecutive series	Serious†	None	Serious‡	None	Undetected	⊕⊕00 low	Prev 80%: 536 Prev 40%: 268 Prev 10%: 67	Critical
True negatives (patients without CMA)	23 studies (2302 patients)	Consecutive or nonconsecutive series	Serious†	None	Serious‡	None	Undetected	⊕⊕00 low	Prev 80%: 108 Prev 40%: 324 Prev 10%: 486	Critical
False positives (patients incorrectly classified as having CMA)	23 studies (2302 patients)	Consecutive or nonconsecutive series	Serious†	Serious§	Serious‡	None	Undetected	⊕000 very low	Prev 80%: 92 Prev 40%: 276 Prev 10%: 414	Critical
False negatives (patients incorrectly classified as not having CMA)	23 studies (2302 patients)	Consecutive or nonconsecutive series	Serious†	None	Serious‡	None	Undetected	⊕⊕00 low	Prev 80%: 264 Prev 40%: 132 Prev 10%: 33	Critical
Inconclusive*	1 study (310 patients)	Nonconsecutive series	—	—	—	—	—	—	—	Important
Complications	Not reported	—	—	—	—	—	—	—	—	Not important
Cost	Not reported	—	—	—	—	—	—	—	—	Not important

*Based on combined sensitivity of 67% (95% CI: 64–70) and specificity of 74% (95% CI: 72–77).

†Most studies enrolled highly selected patients with atopic eczema or gastrointestinal symptoms, no study reported if an index test or a reference standard were interpreted without knowledge of the results of the other test, but it is very likely that those interpreting results of one test knew the results of the other; all except for one study that reported withdrawals did not explain why patients were withdrawn.

‡Estimates of sensitivity ranged from 10 to 100%, and specificity from 14 to 100%; we could not explain it by quality of the studies, tests used or included population.

§There is uncertainty about the consequences for these patients; in some a diagnosis of other potentially serious condition may be delayed.

*One study in children <12 months of age reported 8% inconclusive challenge tests but did not report number of inconclusive skin prick tests.

APPENDIX 2-1.

Question 1, Profile 2. Should Skin Prick Tests Be Used for the Diagnosis of IgE-Mediated CMA in Children Younger Than 12 Months Suspected of CMA?
Cut-Off ≥3 mm/Children Younger Than 12 Months Suspected of IgE-Mediated CMA

			Factors that may Decrease Quality of Evidence							
Outcome	No. of Studies	Study Design	Limitations				Publication Bias	Final Quality	Effect per 1000*	Importance
True positives (patients with CMA)	5 studies (587 patients)	Consecutive or nonconsecutive series	Serious†	None	Serious‡	None	Undetected	⊕⊕OO low	Prev 80%: 440 Prev 40%: 220 Prev 10%: 55	Critical
True negatives (patients without CMA)	5 studies (587 patients)	Consecutive or nonconsecutive series	Serious†	None	Serious‡	None	Undetected	⊕⊕OO low	Prev 80%: 150 Prev 40%: 450 Prev 10%: 675	Critical
False positives (patients incorrectly classified as having CMA)	5 studies (587 patients)	Consecutive or nonconsecutive series	Serious†	Serious§	Serious‡	None	Undetected	⊕OOO very low	Prev 80%: 50 Prev 40%: 150 Prev 10%: 225	Critical
False negatives (patients incorrectly classified as not having CMA)	5 studies (587 patients)	Consecutive or nonconsecutive series	Serious†	None	Serious‡	None	Undetected	⊕⊕OO low	Prev 80%: 360 Prev 40%: 180 Prev 10%: 45	Critical
Inconclusive‖	1 study (310 patients)	Nonconsecutive series	–	–	–	–	–	–	–	Important
Complications	Not reported	–	–	–	–	–	–	–	–	Not important
Cost	Not reported	–	–	–	–	–	–	–	–	Not important

*Based on combined sensitivity of 55% (95% CI: 49–61) and specificity of 75% (95% CI: 69–80).
†Most studies enrolled highly selected patients with atopic eczema or gastrointestinal symptoms, no study reported if an index test or a reference standard were interpreted without knowledge of the results of the other test, but it is very likely that those interpreting results of one test knew the results of the other; all except for one study that reported withdrawals did not explain why patients were withdrawn.
‡Estimates of sensitivity ranged from 10 to 100%, and specificity from 14 to 100%; we could not explain it by quality of the studies, tests used or included population.
§There is uncertainty about the consequences for these patients; in some a diagnosis of other potentially serious condition may be delayed.
‖One study reported 8% inconclusive challenge tests but did not report number of inconclusive skin prick tests.

APPENDIX 2-1.

Question 1, Profile 3. Should Skin Prick Tests Be Used for the Diagnosis of IgE-Mediated CMA in Children Older Than 12 Months Suspected of CMA?
Cut-Off ≥3 mm/Children Older Than 12 Months Suspected of IgE-Mediated CMA

			Factors that may Decrease Quality of Evidence							
Outcome	No. of Studies	Study Design	Limitations				Publication Bias	Final Quality	Effect per 1000*	Importance
True positives (patients with CMA)	11 studies (1088 patients)	Consecutive or nonconsecutive series	Serious†	None	Serious‡	None	Undetected	⊕⊕OO low	Prev 80%: 648 Prev 40%: 324 Prev 10%:81	Critical
True negatives (patients without CMA)	11 studies (1088 patients)	Consecutive or nonconsecutive series	Serious†	None	Serious‡	None	Undetected	⊕⊕OO low	Prev 80%: 144 Prev 40%: 432 Prev 10%: 648	Critical
False positives (patients incorrectly classified as having CMA)	11 studies (1088 patients)	Consecutive or nonconsecutive series	Serious†	Serious§	Serious‡	None	Undetected	⊕OOO very low	Prev 80%: 56 Prev 40%: 168 Prev 10%: 252	Critical
False negatives (patients incorrectly classified as not having CMA)	11 studies (1088 patients)	Consecutive or nonconsecutive series	Serious†	None	Serious‡	None	Undetected	⊕⊕OO low	Prev 80%: 152 Prev 40%: 76 Prev 10%: 19	Critical
Inconclusive¶	Not reported	–	–	–	–	–	–	–	–	Important
Complications	Not reported	–	–	–	–	–	–	–	–	Not important
Cost	Not reported	–	–	–	–	–	–	–	–	Not important

*Based on combined sensitivity of 81% (95% CI: 77–85) and specificity of 72% (95% CI: 68–76).
†Most studies enrolled highly selected patients with atopic eczema or gastrointestinal symptoms, no study reported if an index test or a reference standard were interpreted without knowledge of the results of the other test, but it is very likely that those interpreting results of one test knew the results of the other; all except for one study that reported withdrawals did not explain why patients were withdrawn.
‡Estimates of sensitivity ranged from 10 to 100%, and specificity from 14 to 100%; we could not explain it by quality of the studies, tests used or included population.
§There is uncertainty about the consequences for these patients; in some a diagnosis of other potentially serious condition may be delayed.
¶One study in a different population (children younger than 12 months) reported 8% inconclusive challenge tests but did not report number of inconclusive skin prick tests.

APPENDIX 2-2.

Question 2. Profile 1. Should In Vitro Cow's Milk-Specific IgE Determination Be Used for the Diagnosis of IgE-Mediated CMA? Threshold: ≥0.35 IU/L/All Populations

True negatives(patients 14 studies (1646 nonconsecutive Limitations Indirectness Inconsistency Imprecision Publication very low Prev 80%: 648 Importance

			Factors that may Decrease Quality of Evidence							
Outcome	No. of Studies	Study Design	Limitations	Indirectness	Inconsistency	Imprecision	Publication Bias	Final Quality	Effect per 1000*	Importance
True positives (patients with CMA)	14 studies (1646 patients)	Consecutive or nonconsecutive series of patients	Serious†	None	Serious‡	None	Undetected	⊕⊖00 low	Prev 80%: 576 Prev 40%: 288 Prev 10%: 72	Critical
True negatives (patients without CMA)	14 studies (1646 patients)	Consecutive or nonconsecutive series of patients	Serious†	None	Serious‡	None	Undetected	⊕⊖00 low	Prev 80%: 114 Prev 40%: 342 Prev 10%: 513	Critical
False positives (patients incorrectly classified as having CMA)	14 studies (1646 patients)	Consecutive or nonconsecutive series of patients	Serious†	Serious§	Serious‡	None	Undetected	⊕000 very low	Prev 80%: 86 Prev 40%: 258 Prev 10%: 387	Important
False negatives (patients incorrectly classified as not having CMA)	14 studies (1646 patients)	Consecutive or nonconsecutive series of patients	Serious†	None	Serious‡	None	Undetected	⊕⊖00 low	Prev 80%: 224 Prev 40%: 112 Prev 10%: 28	Critical
Inconclusive¶	1 study (310 patients)	Nonconsecutive series	–	–	–	–	–	–	–	Important
Complications	Not reported	–	–	–	–	–	–	–	–	Important
Cost	Not reported	–	–	–	–	–	–	–	–	Important

*Based on combined sensitivity of 0.72 (95% CI: 0.690.75) and the specificity of 0.57 (95% CI: 0.54–0.60).

†Half of the studies enrolled highly selected patients with atopic eczema or gastrointestinal symptoms, no study reported if an index test or a reference standard were interpreted without knowledge of the results of the other test, but it is very likely that those interpreting results of one test knew the results of the other; all except for one study that reported withdrawals did not explain why patients were withdrawn.

‡Estimates of sensitivity ranged from 12 to 100%, and specificity from 30 to 100%; we could not explain it by quality of the studies, tests used or included population.

§There is uncertainty about the consequences for these patients; in some a diagnosis of other potentially serious condition may be delayed.

¶One study in children <12 months of age reported 8% inconclusive challenge tests but did not report number of inconclusive IgE tests.

APPENDIX 2-2.

Question 2. Profile 2. Should In Vitro Cow's Milk-Specific IgE Determination Be Used for the Diagnosis of IgE-Mediated CMA in Children <12 Months of Age?
Threshold: ≥0.35 IU/L/Children Younger Than 12 Months Suspected of IgE-Mediated CMA

			Factors that may Decrease Quality of Evidence							
Outcome	No. of Studies	Study Design	Limitations				Publication Bias	Final Quality	Effect per 1000*	Importance
True positives (patients with CMA)	2 studies (403 patients)	Consecutive or nonconsecutive series of patients	Serious†	None	Serious‡	None	Undetected	⊕⊕OO low	Prev 80%: 616 Prev 40%: 308 Prev 10%: 77	Critical
True negatives (patients without CMA)	2 studies (403 patients)	Consecutive or nonconsecutive series of patients	Serious†	None	Serious‡	None	Undetected	⊕⊕OO low	Prev 80%: 104 Prev 40%: 312 Prev 10%: 468	Critical
False positives (patients incorrectly classified as having CMA)	2 studies (403 patients)	Consecutive or nonconsecutive series of patients	Serious†	Serious§	Serious‡	None	Undetected	⊕OOO very low	Prev 80%: 96 Prev 40%: 288 Prev 10%: 432	Important
False negatives (patients incorrectly classified as not having CMA)	2 studies (403 patients)	Consecutive or nonconsecutive series of patients	Serious†	None	Serious‡	None	Undetected	⊕⊕OO low	Prev 80%: 184 Prev 40%: 92 Prev 10%: 23	Critical
Inconclusive¶	1 study (310 patients)	Nonconsecutive series	–	–	–	–	–	–	–	Important
Complications	Not reported	–	–	–	–	–	–	–	–	Important
Cost	Not reported	–	–	–	–	–	–	–	–	Important

*Based on combined sensitivity of 0.77 (95% CI: 0.71–0.83) and the specificity of 0.52 (95% CI: 0.45–0.59).
†Half of the studies enrolled highly selected patients with atopic eczema or gastrointestinal symptoms, no study reported if an index test or a reference standard were interpreted without knowledge of the results of the other test, but it is very likely that those interpreting results of one test knew the results of the other; all except for one study that reported withdrawals did not explain why patients were withdrawn.
‡Estimates of sensitivity ranged from 12 to 100%, and specificity from 30 to 100%; we could not explain it by quality of the studies, tests used or included population.
§There is uncertainty about the consequences for these patients; in some a diagnosis of other potentially serious condition may be delayed.
¶One study in children <12 months of age reported 8% inconclusive challenge tests but did not report number of inconclusive IgE tests.

APPENDIX 2-2.

Question 2. Profile 3. Should In Vitro Cow's Milk-Specific IgE Determination be Used for the Diagnosis of IgE-Mediated CMA in Children >12 Months of Age?
Threshold: ≥0.35 IU/L/Children Older Than 12 Months Suspected of IgE-Mediated CMA

True negatives aaaaaa6 studies (500 nonconsecutive Limitations Indirectness Inconsistency Imprecision Publication very low aaaa Prev 80%: 416 Importance

			Factors that may Decrease Quality of Evidence							
Outcome	No. of Studies	Study Design	Limitations	Indirectness	Inconsistency	Imprecision	Publication Bias	Final Quality	Effect per 1000*	Importance
True positives (patients with CMA)	6 studies (500 patients)	Consecutive or nonconsecutive series of patients	Serious[†]	None	Serious[‡]	None	Undetected	⊕⊕00 low	Prev 80%: 416 Prev 40%: 208 Prev 10%: 52	Critical
True negatives (patients without CMA)	6 studies (500 patients)	Consecutive or nonconsecutive series of patients	Serious[†]	None	Serious[‡]	None	Undetected	⊕⊕00 low	Prev 80%: 142 Prev 40%: 426 Prev 10%: 639	Critical
False positives (patients incorrectly classified as having CMA)	6 studies (500 patients)	Consecutive or nonconsecutive series of patients	Serious[†]	Serious[§]	Serious[‡]	None	Undetected	⊕000 very low	Prev 80%: 58 Prev 40%: 174 Prev 10%: 261	Important
False negatives (patients incorrectly classified as not having CMA)	6 studies (500 patients)	Consecutive or nonconsecutive series of patients	Serious[†]	None	Serious[‡]	None	Undetected	⊕⊕00 low	Prev 80%: 384 Prev 40%: 192 Prev 10%: 48	Critical
Inconclusive[¶]	1 study (310 patients)	Nonconsecutive series	–	–	–	–	–	–	–	Important
Complications	Not reported	–	–	–	–	–	–	–	–	Important
Cost	Not reported	–	–	–	–	–	–	–	–	Important

*Based on combined sensitivity of 0.52 (95% CI: 0.45–0.58) and the specificity of 0.71 (95% CI: 0.64–0.77).
[†]Half of the studies enrolled highly selected patients with atopic eczema or gastrointestinal symptoms, no study reported if an index test or a reference standard were interpreted without knowledge of the results of the other test, but it is very likely that those interpreting results of one test knew the results of the other; all except for one study that reported withdrawals did not explain why patients were withdrawn.
[‡]Estimates of sensitivity ranged from 12 to 100%, and specificity from 30 to 100%; we could not explain it by quality of the studies, tests used or included population.
[§]There is uncertainty about the consequences for these patients; in some a diagnosis of other potentially serious condition may be delayed.
[¶]One study in children <12 months of age reported 8% inconclusive challenge tests but did not report number of inconclusive IgE tests.

APPENDIX 2-2.

Question 2. Profile 4. Should In Vitro Cow's Milk-Specific IgE Determination Be Used for the Diagnosis of IgE-Mediated CMA?
Threshold: ≥0.7 IU/L/Patients Suspected of IgE-Mediated CMA

True negatives aaaaaaa4 studies (481 nonconsecutive Limitations Indirectness Inconsistency Imprecision Publication very low aaaaPrev 80%: 464 Importance

			Factors that may Decrease Quality of Evidence							
Outcome	No. of Studies	Study Design	Limitations	Indirectness	Inconsistency	Imprecision	Publication Bias	Final Quality	Effect per 1000*	Importance
True positives (patients with CMA)	4 studies (481 patients)	Consecutive or nonconsecutive series of patients	Serious†	None	None	Serious‡	Undetected	⊕⊕OO low	Prev 80%: 464 Prev 40%: 232 Prev 10%: 58	Critical
True negatives (patients without CMA)	2 studies (81 patients)	Consecutive or nonconsecutive series of patients	Serious†	None	Serious§	Serious‡	Undetected	⊕OOO very low	Prev 80%: 152 Prev 40%: 456 Prev 10%: 684	Critical
False positives (patients incorrectly classified as having CMA)	2 studies (81 patients)	Consecutive or nonconsecutive series of patients	Serious†	Serious¶	Serious§	Serious‡	Undetected	⊕OOO very low	Prev 80%: 48 Prev 40%: 144 Prev 10%: 216	Important
False negatives (patients incorrectly classified as not having CMA)	2 studies (81 patients)	Consecutive or nonconsecutive series of patients	Serious†	None	None	Serious‡	Undetected	⊕⊕OO low	Prev 80%: 336 Prev 40%: 168 Prev 10%: 42	Critical
Inconclusive**	1 study (310 patients)	Nonconsecutive series	–	–	–	–	–	–	–	Important
Complications	Not reported	–	–	–	–	–	–	–	–	Important
Cost	Not reported	–	–	–	–	–	–	–	–	Important

*Based on combined sensitivity of 0.58 (95% CI: 0.52–0.65) and the specificity of 0.76 (95% CI: 0.70–0.81).
†One study enrolled highly selected patients with atopic eczema, in another study not all patients received verification using a reference standard and a different reference standard was used based on the results of the index test.
‡Only 80 patients.
§There was serious inconsistency in the estimation of specificity.
¶There is uncertainty about the consequences for these patients; in some a diagnosis of other potentially serious condition may be delayed.
**One study in children <12 months of age reported 8% inconclusive challenge tests but did not report number of inconclusive IgE tests.

APPENDIX 2-2.

Question 2. Profile 5. Should In Vitro Cow's Milk-Specific IgE Determination Be Used for the Diagnosis of IgE-Mediated CMA?
Threshold: ≥2.5 IU/L/Patients Suspected of IgE-Mediated CMA

			Factors that may Decrease Quality of Evidence							
Outcome	No. of Studies	Study Design	Limitations				Publication Bias	Final Quality	Effect per 1000*	Importance
True positives (patients with CMA)	1 study (161 patients)	Consecutive series of patients	Serious†	None	None	Serious‡	Undetected	⊕⊕00 low	Prev 80%: 384 Prev 40%: 192 Prev 10%: 48	Critical
True negatives (patients without CMA)	1 study (161 patients)	Consecutive series of patients	Serious†	None	None	Serious‡	Undetected	⊕⊕00 low	Prev 80%: 190 Prev 40%: 570 Prev 10%: 855	Critical
False positives (patients incorrectly classified as having CMA)	1 study (161 patients)	Consecutive series of patients	Serious†	Serious§	None	Serious‡	Undetected	⊕000 very low	Prev 80%: 10 Prev 40%: 30 Prev 10%: 45	Important
False negatives (patients incorrectly classified as not having CMA)	1 study (161 patients)	Consecutive series of patients	Serious†	None	None	Serious‡	Undetected	⊕⊕00 low	Prev 80%: 416 Prev 40%: 208 Prev 10%: 52	Critical
Inconclusive¶	1 study (310 patients)	Nonconsecutive series	–	–	–	–	–	–	–	Important
Complications	Not reported	–	–	–	–	–	–	–	–	Important
Cost	Not reported	–	–	–	–	–	–	–	–	Important

*Based on combined sensitivity of 0.48 (95% CI: 0.35–0.60) and the specificity of 0.94 (95% CI: 0.88–0.98).
†Not all patients received verification using a reference standard and a reference standard used is likely to overestimate the prevalence of CMA (open food challenge).
‡Only 160 patients.
§There is uncertainty about the consequences for these patients; in some a diagnosis of other potentially serious condition may be delayed.
¶One study in children <12 months of age reported 8% inconclusive challenge tests but did not report number of inconclusive IgE tests.

APPENDIX 2-2.

Question 2. Profile 6. Should In Vitro Cow's Milk-Specific IgE Determination Be Used for the Diagnosis of IgE-Mediated CMA?
Threshold: ≥3.5 IU/L/Patients Suspected of IgE-Mediated CMA

			Factors that may Decrease Quality of Evidence							
Outcome	No. of Studies	Study Design	Limitations				Publication Bias	Final Quality	Effect per 1000*	Importance
True positives (patients with CMA)	1 study (239 patients)	Nonconsecutive series of patients	None†	None	None	None	Undetected	⊕⊕⊕⊕ high	Prev 80%: 200 Prev 40%: 100 Prev 10%: 25	Critical
True negatives (patients without CMA)	1 study (239 patients)	Nonconsecutive series of patients	None†	None	None	None	Undetected	⊕⊕⊕⊕ high	Prev 80%: 196 Prev 40%: 588 Prev 10%: 882	Critical
False positives (patients incorrectly classified as having CMA)	1 study (239 patients)	Nonconsecutive series of patients	None†	Serious‡	None	None	Undetected	⊕⊕⊕O moderate	Prev 80%: 4 Prev 40%: 12 Prev 10%: 18	Important
False negatives (patients incorrectly classified as not having CMA)	1 study (239 patients)	Nonconsecutive series of patients	None†	None	None	None	Undetected	⊕⊕⊕⊕ high	Prev 80%: 600 Prev 40%: 300 Prev 10%: 75	Critical
Inconclusive§	1 study (310 patients)	Nonconsecutive series	–	–	–	–	–	–	–	Important
Complications	Not reported	–	–	–	–	–	–	–	–	Important
Cost	Not reported	–	–	–	–	–	–	–	–	Important

*Based on combined sensitivity of 0.25 (95% CI: 0.17–0.33) and the specificity of 0.98 (95% CI: 0.94–1.00).
†Withdrawals from the study were not explained and the independent interpretation of the tests was not reported.
‡There is uncertainty about the consequences for these patients; in some a diagnosis of other potentially serious condition may be delayed.
§One study in children <12 months of age reported 8% inconclusive challenge tests but did not report number of inconclusive IgE tests.

APPENDIX 2-3.

Question 3. Should In Vitro Specific IgE Determination Be Used for the Diagnosis of CMA In Patients Suspected of CMA and a *Positive Result of a Skin Prick Test*? Question 4. Should In Vitro Specific IgE Determination Be Used for the Diagnosis of CMA In Patients Suspected of CMA and a *Negative Result of a Skin Prick Test*?
Threshold: skin prick test (3 mm, milk-specific IgE) 0.35 IU/L

			Factors that may Decrease Quality of Evidence							
Outcome	No. of Studies	Study Design	Limitations	Indirectness	Inconsistency	Imprecision	Publication Bias	Final Quality	Effect per 1000*	Importance
True positives† (patients with CMA)	2 studies (36 patients)	Consecutive or nonconsecutive series of patients	Serious‡	None	None	Serious§	Undetected	⊕⊕00 low	Prev 80%: 568 Prev 40%: 284 Prev 10%: 71	Critical
True negatives¶ (patients without CMA)	2 studies (36 patients)	Consecutive or nonconsecutive series of patients	Serious‡	None	None	Serious§	Undetected	⊕⊕00 low	Prev 80%: 186 Prev 40%: 558 Prev 10%: 837	Important
False positives (patients incorrectly classified as having CMA)	2 studies (36 patients)	Consecutive or nonconsecutive series of patients	Serious‡	Serious	None	Serious§	Undetected	⊕000 very low	Prev 80%: 14 Prev 40%: 42 Prev 10%: 63	Important
False negatives (patients incorrectly classified as not having CMA)	2 studies (36 patients)	Consecutive or nonconsecutive series of patients	Serious‡	None	None	Serious§	Undetected	⊕⊕00 low	Prev 80%: 232 Prev 40%: 116 Prev 10%: 29	Critical
Inconclusive	3 studies (57 patients)	Consecutive or nonconsecutive series of patients	Serious‡	None	None	Serious**	Undetected	⊕⊕00 low	28%	Important
Complications	Not reported	–	–	–	–	–	–	–	–	Important
Cost	Not reported	–	–	–	–	–	–	–	–	Important

*Based on combined sensitivity of 0.71 (95% CI 0.29–0.96) and specificity of 0.93 (95% CI 0.77–0.99).
†Positive results are defined as both skin prick test and cow's milk-specific IgE tests being positive.
‡One study enrolled only patients with atopic eczema and in all studies the results of the tests were most likely interpreted with the knowledge of other tests.
§Only 36 patients and wide confidence intervals.
¶Negative results are defined as both skin prick test and cow's milk-specific IgE tests being negative.
**Only 16 events.

APPENDIX 3-1.

Date: 2010-02-06

Question: Should Extensively Hydrolyzed Milk Formula Versus Amino Acid Formula be Used in Children With Cow's Milk Allergy?
References:

1. Isolauri E, Sutas Y, Makinen-Kiljunen S, Oja SS, Isosomppi R, Turjanmaa K. Efficacy and safety of hydrolyzed cow milk and amino acid-derived formulas in infants with cow milk allergy. *J Pediatr.* 1995;127:550-557.

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3. Niggemann B, von BA, Bollrath C, Berdel D, Schauer U, Rieger C, Haschke-Becher E, Wahn U. Safety and efficacy of a new extensively hydrolyzed formula for infants with cow's milk protein allergy. *Pediatr Allergy Immunol.* 2008;19:348-354.

Quality Assessment								Summary of Findings				
No. of Patients		Effect										
No. of Studies	Design	Limitations	Inconsistency	Quality	Indirectness	Imprecision	Other Considerations	Extensively Hydrolyzed Milk Formula	Amino Acid Formula	Relative (95% CI)	Absolute Severe symptoms of CMA (severe laryngeal edema, severe asthma, anaphylaxis), not reported	Importance
0	–	–	–	–	–	–	–	–	–	–	–	Critical Allergic reaction to formula, not reported
0	–	–	–	–	–	–	–	–	–	–	–	Critical Moderate symptoms of CMA (mild laryngeal edema, mild asthma), not reported
0	–	–	–	–	–	–	–	–	–	–	–	Critical Atopic eczema severity (follow-up 6 to 9 months; measured with: SCORAD; range of scores: 0–103; better indicated by lower values)
3	Randomized trials*	Serious†	No serious inconsistency	No serious indirectness	No serious imprecision‡	None	85	95	–	MD 1.39 higher (1.08 lower to 3.86 higher)*	⊕⊕⊕O Moderate	Critical Enteropathy or enteroproctocolitis, not reported

APPENDIX 3-1. (Continued)

Quality Assessment								Summary of Findings				
No. of Patients		Effect										
No. of Studies	Design	Limitations	Inconsistency	Quality	Indirectness	Imprecision	Other Considerations	Extensively Hydrolyzed Milk Formula	Amino Acid Formula	Relative (95% CI)	Absolute Severe symptoms of CMA (severe laryngeal edema, severe asthma, anaphylaxis), not reported	Importance
0	–	–	–	–	–	–	–	–	–	–	–	Critical Failure to thrive (length) (follow-up 6 months; Better indicated by higher values)
1	Randomized trials	Serious[3]	No serious inconsistency	Serious[1]	Serious[1]	None	31	42	–	–**	⊕OOO Very low	Critical Failure to thrive (weight) (follow-up 6 months; measured with percentage points; better indicated by higher values)
1	Randomized trials	Serious[11]	No serious inconsistency	Serious[‡‡]	Serious[§§]	none	22	23	–	MD 2.3 lower (1.9 to 2.7 lower)	⊕OOO Very low	Critical Protein or nutrient deficiency, not reported
0	–	–	–	–	–	–	–	–	–	–	–	Important Mild symptoms of CMA (erythema, urticaria, angioedema, pruritus, diarrhea, rhinitis, conjunctivitis), not reported[¶¶]
0	–	–	–	–	–	–	–	–	–	–	–	Important Vomiting (follow-up 6 months)
1	Randomized trials	Serious[¶¶]	No serious inconsistency	No serious indirectness	Serious***[‹]	None	1/32 (3.1%)	8/30 (26.7%)	RR 0.12 (0.02 to 0.88)	235 Fewer per 1000 (from 32 fewer to 261 fewer)	⊕⊕OO Low	Important Development of secondary sensitization to proteins present in a formula, not reported
0	–	–	–	–	–	–	–	–	–	–	–	Important Quality of life of a patient, not reported

APPENDIX 3-1. (Continued)

Quality Assessment								Summary of Findings				
No. of Patients		Effect										
No. of Studies	Design	Limitations	Inconsistency	Quality	Indirectness	Imprecision	Other Considerations	Extensively Hydrolyzed Milk Formula	Amino Acid Formula	Relative (95% CI)	Absolute Severe symptoms of CMA (severe laryngeal edema, severe asthma, anaphylaxis), not reported	Importance
0	–	–	–	–	–	–	–	–	–	–	–	Important Quality of life of caregivers, not reported
0	–	–	–	–	–	–	–	–	–	–	–	Important
1	Randomized trials	No serious limitations	No serious inconsistency	Very serious[†††]	No. serious imprecision	None	32	30	–	ICE169 Lower	⊕⊕◯◯ Low	Important

*All studies included predominantly children with atopic eczema. They made up to 100% in one study, 90% in the second, and 76% in the third. It is possible that the effected might have been underestimated because of the inclusion of the SCORAD results in children without atopic eczema.

[†]Studies did not report the method of randomization, concealment of allocation, and blinding. One study was clearly not blinded and only results of per protocol analysis were reported.

[‡]Only 180 patients. It is not defined what SCORAD score represents a minimal important difference. However, the upper limit of the 95% CI was 3.86 points which is unlikely to be close to MID on a 103-point SCORAD scale.

[§]The study did not report method of randomization, concealment of allocation, blinding, and method of analysis.

[‖]There is uncertainty to what extent a length for age z-score reflects a change in growth that would have an important consequence for a patient.

[¶]Only 73 patients.

[**]The median value in children receiving amino acid-based formula was 0 SD (range: −2.11 to 2.6) and the median value in children receiving extensively hydrolyzed whey formula was −0.96 (range: −2.54 to 0.61).

[††]The study did not report method of randomization, concealment of allocation, blinding, and method of analysis.

[‡‡]There is uncertainty to what extent a change in weight reflects a change in growth that would have an important consequence for a patient.

[§§]Only 45 patients.

[¶¶]Two randomized food challenges compared amino acid-based formula to extensively hydrolyzed casein formula (Caffarelli 2002, Sampson 1992). Sampson and colleagues enrolled 28 children and there were no reactions with amino acid formula and one with extensively hydrolyzed formula (vomiting, erythema, rhinitis, laryngeal edema, and wheezing). Caffarelli and colleagues enrolled 20 children and 2 children challenged with amino acid formula developed a delayed eczema, 4 children receiving extensively hydrolyzed milk formula had immediate diarrhea, vomiting, urticaria, and delayed eczema.

[***]The study did not report method of randomization and concealment of allocation, was not blinded, and reported the results of per protocol analysis only.

[†††]Only 9 events.

[‡‡‡]There is uncertainty to what extent cost measured in one country and jurisdiction will apply to different settings.

APPENDIX 3-2.

Date: 2009-12-01

Question: Should Extensively Hydrolyzed Milk Formula Versus Extensively Hydrolyzed Rice Formula be Used in Children With Cow's Milk Allergy?

Reference:

1. Agostoni C, Fiocchi A, Riva E, Terracciano L, Sarratud T, et al. Growth of infants with IgE-mediated cow's milk allergy fed different formulas in the complementary feeding period. *Pediatr Allergy Immunol.* 2007;18:599-606.

Quality Assessment								Summary of Findings				
No. of Patients		Effect										
No. of Studies	Design	Limitations	Inconsistency	Quality	Indirectness	Imprecision	Other Considerations	Extensively Hydrolyzed Milk Formula	Extensively Hydrolyzed Rice Formula	Relative (95% CI)	Absolute Severe symptoms of CMA (severe laryngeal edema, severe asthma, anaphylaxis) (follow-up 12 months)	Importance
1	Randomized trials	Serious*	No serious inconsistency	No serious indirectness	Serious†	None	0/35 (0%)	0/36 (0%)	Not estimable‡	–‡	⊕⊕OO Low	Critical Allergic reaction to formula (follow-up mean 12 months)
1	Randomized trials	Serious*	No serious inconsistency	No serious indirectness	Serious†	None	0/35 (0%)	0/36 (0%)	Not estimable‡	–‡	⊕⊕OO Low	Critical Moderate symptoms of CMA (mild laryngeal edema or mild asthma)
1	Randomized trials	Serious*	No. serious inconsistency	No. serious indirectness	Serious†	None	0/35 (0%)	0/35 (0%)	Not estimable‡	–‡	⊕⊕OO Low	Critical Enteropathy or enteroproctocolitis (follow-up 12 months)
1	Randomized trials	Serious*	No serious inconsistency	No serious indirectness	Serious†	None	0/35 (0%)	0/36 (0%)	Not estimable‡	–‡	⊕⊕OO Low	Critical Failure to thrive (measured as: length for age z-score) (follow-up 12 months; better indicated by higher values)
1	Randomized trials	Serious*	No. serious inconsistency	Serious§	Serious†	None	31	30	–	MD 0.33 higher (0.13 lower to 0.79 higher)	⊕OOO Very low	Critical Failure to thrive (measured as: weight for age z-score) (follow-up 12 months; better indicated by higher values)
1	Randomized trials	Serious*	No serious inconsistency	Serious§	Serious†	None	31	30	–	MD 0.04 lower (0.53 lower to 0.45 higher)	⊕OOO Very low	Critical Protein or nutrient deficiency, not reported

APPENDIX 3-2. (Continued).

Quality Assessment								Summary of Findings				
No. of Patients		Effect										
No. of Studies	Design	Limitations	Inconsistency	Quality	Indirectness	Imprecision	Other Considerations	Extensively Hydrolyzed Milk Formula	Soy Formula		Relative (95% CI)	Absolute Severe symptoms of CMA (severe laryngeal edema, severe asthma, anaphylaxis) (follow-up 12 and 24 months)	Importance
0	–	–	–	–	–	–	–	–	–	–		–	Critical Mild symptoms of CMA (any of the following: erythema, urticaria, angioedema, pruritus, diarrhea, rhinitis, conjunctivitis) (follow-up 12 months)
1	Randomized trials	Serious*	No. serious inconsistency	No. serious indirectness	Serious†	None	0/35 (0%)	0/36 (0%)	Not estimable‡	–‡		⊕⊕OO Low	Important Development of secondary sensitization, not reported
0	–	–	–	–	–	–	–	–	–	–		–	Important Quality of life of a patient (follow-up 12 months; as measured by a "good acceptance" [no/some difficulties in getting the meal finished and/or minimal amount generally left out])
1	Randomized trials	Serious*	No serious inconsistency	No serious indirectness	Very serious¶	None	31/35 (88.6%)	30/36 (83.3%)	RR 1.06 (0.86 to 1.32)	50 more per 1000 (from 117 fewer to 267 more)		⊕OOO very low	Important Quality of life of caregivers, not measured
0	–	–	–	–	–	–	–	–	–	–		–	Important Resource utilization (cost), not measured
0	–	–	–	–	–	–	–	–	–	–		–	Important

*Study did not report allocation concealment, was not blinded, and reported the results of per protocol analysis only.
† Only 63 children.
‡No. events.
¶There is uncertainty to what extent a length for age z-score or a weight for age z-score reflect a change in growth that would have an important consequence for a patient.
*Only 63 children. Results do not exclude appreciable benefit or appreciable harm.

APPENDIX 3-3.

Date: 2009-12-01

Question: Should Extensively Hydrolyzed Milk Formula Versus Soy Formula be Used in Children With Cow's Milk allergy?

References:

1. Agostoni C, Fiocchi A, Riva E, Terracciano L, Sarratud T, et al. Growth of infants with IgE-mediated cow's milk allergy fed different formulas in the complementary feeding period. *Pediatr Allergy Immunol.* 2007;18:599-606.
2. Klemola T, Vanto T, Juntunen-Backman K, Kalimo K, Korpela R, Varjonen E. Allergy to soy formula and to extensively hydrolyzed whey formula in infants with cow's milk allergy: a prospective, randomized study with a follow-up to the age of 2 years. *J Pediatr.* 2002;140:219-224.

Quality Assessment								Summary of Findings			
No. of Patients		Effect									
No. of Studies	Design	Limitations	Inconsistency	Quality	Indirectness	Imprecision	Other Considerations	Extensively Hydrolyzed Milk Formula	Soy Formula	Relative (95% CI)	Absolute Severe symptoms of CMA (severe laryngeal edema, severe asthma, anaphylaxis) (follow-up 12 and 24 months)	Importance
2	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[b]	None	0/125 (0%)	0/117 (0%)	Not estimable[c]	–[c]	⊕⊕⊕O Moderate	Critical Allergic reaction to formula (follow-up 12 and 24 months)
2	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[d]	None	2/125 (1.6%)	13/117 (11.1%)	RR 0.18 (0.05 to 0.71)	91 fewer per 1000 (from 32 fewer to 106 fewer)	⊕⊕OO Low	Critical Moderate symptoms of CMA (mild laryngeal edema or mild asthma)
2	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[b]	None	0/125 (0%)	0/117 (0%)	Not estimable[e]	–[e]	⊕⊕⊕O Moderate	Critical Enteropathy or enteroproctocolitis (follow-up 12 and 24 months)
2	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[b]	None	0/125 (0%)	0/117 (0%)	Not estimable[f]	–[f]	⊕⊕⊕O Moderate	Critical Failure to thrive (measured as: length for age z-score) (follow-up 12 months; better indicated by higher values)
1	Randomized trials	Serious[a]	No serious inconsistency	Serious[g]	Serious[h]	None	31	32	–	MD 0.27 higher (0.19 lower to 0.73 higher)	⊕OOO Very low	Critical Failure to thrive (measured as: weight for age z-score) (follow-up 12 months; better indicated by higher values)
1	Randomized trials	Serious[a]	No serious inconsistency	Serious[g]	Serious[h]	None	31	32	–	MD 0.23 higher (0.01 to 0.45 higher)	⊕OOO Very low	Critical Protein or nutrient deficiency, not reported

APPENDIX 3-3. (Continued).

Quality Assessment								Summary of Findings				
No. of Patients		Effect										
No. of Studies	Design	Limitations	Inconsistency	Quality	Indirectness	Imprecision	Other Considerations	Extensively Hydrolyzed Milk Formula	Soy Formula	Relative (95% CI)	Absolute Severe symptoms of CMA (severe laryngeal edema, severe asthma, anaphylaxis) (follow-up 12 and 24 months)	Importance
0	–	–	–	–	–	–	–	–	–	–	–	Critical Mild symptoms of CMA (any of the following: erythema, urticaria, angioedema, pruritus, diarrhea, rhinitis, conjunctivitis) (follow-up 12 and 24 months)
2	Randomized trials	Serious*	No serious inconsistency	No serious indirectness	Serious†	None	2/125 (1.6%)	13/117 (11.1%)	RR 0.18 (0.05 to 0.71)	91 fewer per 1000 (from 32 fewer to 106 fewer)	⊕⊕OO Low	Important Development of secondary sensitization (follow-up 12 and 24 months; specific IgE)
2	Randomized trials	Serious**	No serious inconsistency††	Serious‡‡	Serious§§	None	1/125 (0.8%)	10/117 (8.5%)	RR 0.14 (0.03 to 0.76)	74 fewer per 1000 (from 21 fewer to 83 fewer)	⊕OOO Very low	Important Quality of life of a patient (follow-up 12 months; as measured by a "good acceptance" [no/some difficulties in getting the meal finished and/or minimal amount generally left out])
1	Randomized trials	Serious*	No serious inconsistency	No serious indirectness	Serious¶¶	None	31/35 (88.6%)	37/37 (100%)	RR 0.89 (0.75 to 1.02)	110 fewer per 1000 (from 250 fewer to 20 more)	⊕⊕OO Low	Important
0	–	–	–	–	–	–	–	–	–	–	–	Important Resource utilization (cost), not reported
0	–	–	–	–	–	–	–	–	–	–	–	Important

*Allocation concealment was not reported and studies were not blinded. One study reported the results of per protocol analysis only.
†No. events reported in both studies.
‡Only 15 events.
§There is uncertainty to what extent a length for age z-score reflects a change in growth that would have an important consequence for a patient.
¶Only 62 children.
#There is uncertainty to what extent a weight for age z-score reflects a change in growth that would have an important consequence for a patient.
**Allocation concealment was not reported and studies were not blinded. In one study outcome was measured only in patients who developed symptoms.
††One additional study (Salpietro 2005) included children with cow's milk allergy (23%) or intolerance and reported a relative risk of secondary sensitization to extensively hydrolyzed casein formula compared to soy formula of 1.33 (95% CI: 0.37–4.82).
‡‡It is uncertain how important is sensitization alone.
§§Only 11 events.
¶¶Only 4 events.

APPENDIX 3-4.

Date: 2010-02-06

Question: Should Soy Formula Versus Extensively Hydrolyzed Rice Formula be Used in Children With Cow's Milk Allergy?

References:

1. Agostoni C, Fiocchi A, Riva E, Terracciano L, Sarratud T, et al. Growth of infants with IgE-mediated cow's milk allergy fed different formulas in the complementary feeding period. *Pediatr Allergy Immunol.* 2007;18:599-606.

2. D'Auria E, Sala M, Lodi F, Radaelli G, Riva E, Giovannini M. Nutritional value of a rice-hydrolysate formula in infants with cows' milk protein allergy: a randomized pilot study. *J Intl Med Res.* 2003;31:215-222.

Quality Assessment								Summary of Findings				
No. of Patients		Effect										
No. of Studies	Design	Limitations	Inconsistency	Quality	Indirectness	Imprecision	Other Considerations	Extensively Hydrolyzed Milk Formula	Soy Formula	Relative (95% CI)	Absolute Severe symptoms of CMA (severe laryngeal edema, severe asthma, anaphylaxis) (follow-up 12 and 24 months)	Importance
2	Randomized trials	Serious*	No serious inconsistency	No serious indirectness	Serious†,‡	None	0/44 (0%)	0/43 (0%)	Not estimable†	–†	⊕⊕OO+++++Low	Critical Moderate symptoms of CMA (mild laryngeal edema or mild asthma) (follow-up 6 and 12 months)
2	Randomized trials	Serious*	No serious inconsistency	No serious indirectness	Serious†,‡	None	0/44 (0%)	0/43 (0%)	Not estimable†	–†	⊕⊕OO+++++Low	Critical Allergic reaction to formula (follow-up 6 and 12 months)
2	Randomized trials	Serious*	No serious inconsistency	No serious indirectness	Very serious§	None	5/44 (11.4%)	0/43 (0%)	RR 10.71 (0.61 to 186.92)	100 more per 1000 (from 20 fewer to 220 more)	⊕OOO+++++Very low	Critical Enteropathy or enteroproctocolitis (follow-up 6 and 12 months)
2	Randomized trials	Serious*	No serious inconsistency	No serious indirectness	Serious†,‡	None	0/44 (0%)	0/43 (0%)	Not estimable†	–†	⊕⊕OO+++++Low	Critical Failure to thrive (measured as: length for age z-score) (follow-up 6 and 12 months; better indicated by higher values)
2	Randomized trials	Serious*	No serious inconsistency	Serious*	Serious‡	None	44	43	–	MD 0.27 higher (0.14 lower to 0.67 higher)	⊕OOO+++++Very low	Critical Failure to thrive (measured as: weight for age z-score) (follow-up 6 to 12 months; better indicated by higher values)
2	Randomized trials	Serious	No serious inconsistency	Serious*	Serious‡	None	44	43	–	MD 0.18 lower (0.62 lower to 0.26 higher)	⊕OOO+++++Very low	Critical Protein or nutrient deficiency (measured as: total protein concentration) (follow-up 6 months; better indicated by higher values)

APPENDIX 3-4. (Continued).

Quality Assessment									Summary of Findings			
No. of Patients		Effect										
No. of Studies	Design	Limitations	Inconsistency	Quality	Indirectness	Imprecision	Other Considerations	Extensively Hydrolyzed Milk Formula	Soy Formula	Relative (95% CI)	Absolute Severe symptoms of CMA (severe laryngeal edema, severe asthma, anaphylaxis) (follow-up 12 and 24 months)	Importance
1	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[¶]	None	8	8	–	–**	⊕⊕⊕O+++++Moderate	Critical Mild symptoms of CMA (any of the following: erythema, urticaria, angioedema, pruritus, diarrhea, rhinitis, conjunctivitis) (follow-up 6 and 12 months)
2	Randomized trials	Serious*	No serious inconsistency	No serious indirectness	Serious[†,‡]	None	0/44 (0%)	0/43 (0%)	Not estimable[†]	–[‡]	⊕⊕OO+++++Low	Critical Development of secondary sensitization (follow-up 12 months; specific IgE)
1	Randomized trials	Serious[††]	No serious inconsistency	Serious[‡‡]	Very serious[§§]	None	3/37 (8.1%)	0/36 (0%)	RR 6.82 (0.36 to 127.44)	80 more per 1000 (from 20 fewer to 180 more)	⊕OOO+++++Very low	Important Quality of life of a patient, not measured
0	–	–	–	–	–	–	–	–	–	–	–	Important Quality of life of caregivers, not measured
0	–	–	–	–	–	–	–	–	–	–	–	Important Resource utilization (cost), not measured
0	–	–	–	–	–	–	–	–	–	–	–	Important

*Studies did not report allocation concealment, one was not blinded, and one reported the results of per protocol analysis only.
†No. events.
‡Only 87 children.
§Only 5 events. Results do not exclude appreciable benefit or appreciable harm.
¶There is uncertainty to what extent a length for age z-score or a weight for age z-score reflect a change in growth that would have an important consequence for a patient.
‖Only 16 patients.
**There was no difference between the groups: total protein concentration was 65 (Â ± 2) g/l in each group.
††Study did not report allocation concealment, was not blinded, and measured IgE only in children who developed symptoms.
‡‡It is uncertain how important is sensitization alone.
§§Only 3 events. Results do not exclude appreciable benefit or appreciable harm.

APPENDIX 4.

Author(s): JB&EC

Date: 2009-11-26

Question: Should Oral Immunotherapy be Used in Children With Cow's Milk Allergy?
Settings: tertiary care university hospitals
References:

1. Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, Ventura A. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J Allergy Clin Immunol.* 2008;121:343-347.

2. Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol.* 2008;122:1154-1160.

Quality Assessment								Summary of Findings				
No. of Patients		Effect										
No. of Studies	Design	Limitations	Inconsistency	Quality	Indirectness	Imprecision	Other Considerations	Oral Immunotherapy	Control	Relative (95% CI)	Absolute Full tolerance (able to ingest >150 mL of cow's milk) (follow-up 6 and 12 months)	Importance
2	Randomized trials	No serious limitations*	No serious inconsistency	No serious indirectness†	Serious‡	Reporting bias§	17/42 (40.5%)	0/37 (0%)	RR 17.26 (2.42 to 123.23)	400 more per 1000 (from 240 more to 550 more)‖	⊕⊕⊕O Moderate	Critical Partial tolerance (able to ingest 5 to 150 mL of cow's milk) (follow-up 6 and 12 months)
2	Randomized trials	No serious limitations*	No serious inconsistency	No serious indirectness¶	Serious**	Reporting bias§	22/42 (52.4%)	0/42 (0%)	RR 20.72 (2.92 to 147)	530 more per 1000 (from 370 more to 680 more)	⊕⊕⊕O Moderate	Critical Eczema exacerbation (follow-up 6 months)
1	Randomized trials	Serious††	No serious inconsistency	No serious indirectness	Very serious‡‡	None	1/13 (7.7%)	1/7 (14.3%)	RR 0.54 (0.06 to 4.82)	66 fewer per 1000 (from 134 fewer to 546 more)	⊕OOO Very low	Critical Anaphylaxis (follow-up 6 and 12 months; rate of adrenaline injections or nebulizations)
2	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious§§	None	40/42	0/37	Rate ratio 15.90 (1.14 to 221.7)	–	⊕⊕⊕O Moderate	Critical Need for systemic glucocorticosteroids (follow-up 12 months)
1	Randomized trials	Serious**	No serious inconsistency	No serious indirectness	Serious**	None	51/30	1/30	Rate ratio 50.9 (7.0 to 368.6)	–	⊕⊕OO Low	Critical Quality of life of children, not measured
0	–	–	–	–	–	–	–	–	–	–	–	Critical Quality of life of the caregivers, not measured