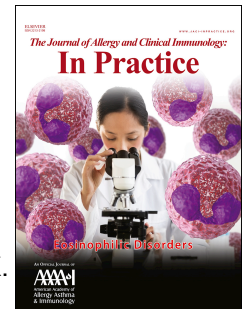


Journal Pre-proof

Long-term benefit of Probiotic Peanut Oral Immunotherapy (PPOIT) on quality of life in a randomised trial

Audrey Dunn Galvin, PhD, Melanie Lloyd, PhD, Kuang-Chih Hsiao, MBChB, Mimi LK. Tang, MBBS, PhD, on behalf of the PPOIT-001 study team



PII: S2213-2198(21)00888-6

DOI: <https://doi.org/10.1016/j.jaip.2021.07.047>

Reference: JAIP 3776

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 9 March 2021

Revised Date: 20 July 2021

Accepted Date: 21 July 2021

Please cite this article as: Galvin AD, Lloyd M, Hsiao KC, Tang ML, on behalf of the PPOIT-001 study team, Long-term benefit of Probiotic Peanut Oral Immunotherapy (PPOIT) on quality of life in a randomised trial, *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: <https://doi.org/10.1016/j.jaip.2021.07.047>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

Title page

Title: Long-term benefit of Probiotic Peanut Oral Immunotherapy (PPOIT) on quality of life in a randomised trial

Authors:

Audrey Dunn Galvin (PhD) – School of Applied Psychology, University College Cork, Ireland. Email: a.dunngalvin@ucc.ie

Melanie Lloyd (PhD) - Allergy Immunology, Murdoch Children's Research Institute, Melbourne, Australia. Email: melanie.lloyd@mcri.edu.au

Kuang-Chih Hsiao (MBChB) - Department of Immunology, Starship Children's Hospital, Auckland, New Zealand; Department of Paediatrics, University of Auckland, Auckland, New Zealand; Allergy Immunology, Murdoch Children's Research Institute, Melbourne, Australia. Email: kc.hsiao@auckland.ac.nz

Mimi LK Tang (MBBS, PhD) - Allergy Immunology, Murdoch Children's Research Institute; Department of Paediatrics, University of Melbourne; and Department of Allergy and Immunology, The Royal Children's Hospital; Melbourne, VIC, Australia. Email: mimi.tang@rch.org.au

on behalf of the PPOIT-001 study team

Corresponding author: Mimi LK Tang; Address: Murdoch Children's Research Institute, 50 Flemington Road, Parkville 3065, Australia; Telephone: +61-3-9345 5911; Email: mimi.tang@rch.org.au

Journal Pre-proof

22 COI statement:

23 **Audrey Dunn Galvin:** Consultant (Research grant; Advisory panel): DBV Technologies;
24 Consultant (Research grant; Advisory panel): Aimmune Therapeutics.

25 **Melanie Lloyd:** No COI to declare.

26 **Kuang-Chih Hsiao:** No COI to declare.

27 **Mimi LK Tang:** Employee and Share interest/options: Prota Therapeutics; Speaker fees:
28 Abbott nutrition and Nestle Health Science; Consultant fees: Bayer Pharmaceuticals and
29 Pfizer; Patents: Inventor on patents covering PPOIT.

30 **Declaration of funding sources for the research reported in the manuscript:** The parent trial was
31 supported by the Food Allergy and Anaphylaxis Network (FAAN), the Murdoch Children's
32 Research Institute, Perpetual Philanthropy (grant ID 493), the CASS Foundation, the Financial
33 Markets Foundation for Children and the National Health and Medical Research Council Australia
34 (NHMRC project grant no. 1029690). The 4 year follow-up was supported by the Murdoch
35 Children's Research Institute and the Australian Food Allergy Foundation. Nestle Health Science
36 provided the probiotic and placebo treatments. The Murdoch Children's Research Institute is
37 supported by the Victorian Government's Operational Infrastructure Support Program. This trial
38 was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12608000594325,
39 25/11/2008).

40 **Text word count:** 986.

41 Clinical Implications Box

42 PPOIT leads to substantial, continued improvement in QoL to 4-years post-treatment. Achieving
43 sustained unresponsiveness following immunotherapy allows patients to eat peanut freely as part
44 of their normal diet, with greatest QoL benefit seen in individuals ingesting large amounts of
45 peanut.

46 **Keywords:** Food allergy; Quality of life; Oral immunotherapy; Randomised controlled trial;
47 Probiotics; Peanut Allergy.

48

Food allergy prevalence has increased globally in recent decades (1-3). Management relies on avoidance of trigger foods but accidental ingestion is common, causing frequent and sometimes life-threatening reactions (4). With no reliable means to predict reaction severity or timing, patients and caregivers live in fear of unpredictable life-threatening allergic reactions. This uncertainty gives rise to extreme anxiety and avoidance on the one hand, or frustration and risky behaviours on the other (5-6). Intense effort has been directed towards identifying an effective food allergy treatment that can improve health-related quality of life (QoL).

Multiple food immunotherapies are currently in development, however, there is limited data regarding their effect on QoL, particularly from high quality randomized controlled trials. (7-8) We previously reported that probiotic peanut oral immunotherapy (PPOIT) significantly improved QoL compared with placebo, with improvement linked to achieving sustained unresponsiveness (SU). This present study aimed to determine if improved QoL is maintained out to 4-years post-treatment, and examine associations between QoL and peanut ingestion.

The PPOIT-001 study was a double-blind, placebo-controlled randomized trial that evaluated the effectiveness of PPOIT for the induction of SU in children with peanut allergy (9). Participants who attained SU post-treatment were instructed to introduce peanut freely into the diet. Other participants were advised to continue avoiding peanut.

Subjects (n=57) completed Food Allergy Quality of Life Questionnaire-Parent Form (FAQLQ-PF) and Food Allergy Independent Measure (FAIM) outcome measurements at pre-treatment (T0), end-of-treatment (T1), and 3-months (T3), 12-months (T4) and 4-years post-treatment (T5). FAQLQ-PF is a disease-specific QoL questionnaire with demonstrated validity and high reliability

(9). At the 4-year follow-up, participants were asked if they were ingesting peanut (yes/no) and the amount they were ingesting (none/small amount: <1 teaspoon peanut butter/<8 peanut/<2g peanut protein, moderate amount: 1-2 teaspoon peanut butter/8-16 peanuts/2g-4g peanut protein, large amount: >2 teaspoon peanut butter/>16 peanuts/>4g peanut protein).

Paired group t-test analyses were conducted separately for PPOIT and Placebo groups at each time point. Repeated-measures mixed ANOVAs were used to examine overall changes from pre-treatment to 4-years post-treatment, controlling for potential confounders (age, sex). A further ANOVA controlled for SU at end-of treatment and 4-years post-treatment. Primary analysis was on participants who completed measures at all time points (pre-treatment, end-of-treatment, 3-months, 12-months and 4-years post-treatment). Sensitivity analyses examined: 1) participants who completed measures at all time points to 3-months post-treatment, and any data thereafter; 2) participants who completed measures at any time point.

In PPOIT group alone, we performed a linear analysis to examine FAQLQ total scores at 4-years post-treatment (dependent variable) controlling for FAQLQ at pre-treatment, according to amount of peanut ingested (none, small, moderate, large).

Ethics approval for the study was granted by the Royal Children's Hospital Human Research Ethics Committee and the School of Applied Psychology's Ethics Committee, University College Cork.

There were no differences in baseline demographics at study entry between treatment groups for all three analysis samples (primary and sensitivity analyses). N=38 (19 Placebo/19 PPOIT) completed QoL assessments at ALL time-points. FAQLQ and FAIM scores improved significantly for PPOIT (but not placebo) from pre-treatment to 4-years post-treatment (both $p=0.001$, Supplementary Table E1 and E2). Figure 1 shows trends of mean FAQLQ-PF total scores over time for PPOIT and Placebo groups. Findings remained unchanged in sensitivity analyses. Multivariable analysis (controlling for sex and age) found a significant interaction for difference between Groups (PPOIT vs Placebo) over Time [F value=4.8, $p=0.006$], with FAQLQ improving over time only for the PPOIT group (effect size [partial eta squared]=0.43). Including an interaction for SU at 4-years post-treatment showed very large effect size [partial eta squared=0.65].

A strong positive correlation was found between frequency and amount of peanut ingested ($r_s=0.96$, $p=0.001$). In the PPOIT group, a moderate/large amount of peanut ingestion at 4 years predicted greater improvement in FAQLQ score from T0 to T5 ($B=1.9$, $F=8.1$, $p=0.007$), compared to .avoiding or eating a small amount of peanut (Figure 2). At 4-years post-treatment (T5), 52% were eating at least a moderate amount of peanut. Frequency of ingestion followed the same pattern (Figure 2), with QoL more improved in those who ingested peanut protein at least ≥ 3 times per week ($B= -2.2$, $F=5.8$, $p=0.03$).

106

107

108 The pragmatic utility of any intervention is judged by effectiveness in promoting sustained change
109 over an extended period. In this study, QoL in PPOIT-treated patients improved significantly
110 compared with placebo-treated patients at 12-months and 4-years post-treatment. Greatest QoL
111 improvement was associated with eating large amounts of peanut rather than limited intake or
112 avoidance. These findings suggest that PPOIT provides long-lasting improvement in QoL, and that
113 the ability to incorporate peanut freely into the diet, particularly in larger amounts, is an important
114 factor driving improved QoL. This is consistent with our previous finding that improved QoL was
115 linked specifically to attainment of SU, which allows free peanut intake (9).

116 Several food allergy treatments in development have been shown to induce desensitisation, the
117 temporary increase in reaction threshold that is only maintained with regular daily allergen
118 ingestion/exposure. Desensitisation provides protection against accidental exposure to small
119 amounts of allergen such as might be encountered through cross-contamination, however, there
120 is currently limited evidence that this confers an improvement in QoL (8). This lack of data is
121 particularly pertinent since desensitised patients report more reactions than standard of care
122 (allergen avoidance).

123 The effect of peanut ingestion post-OIT on QoL has not been reported previously. Our finding
124 that the ability to eat peanut freely and in larger amounts is associated with substantial
125 improvement in QoL suggests that therapies that induce more durable SU, and permit ongoing
126 ingestion of larger doses of allergen, can benefit patients greatly.

127 The main limitation of this study was the small sample size which did not allow us to construct
128 complex models, and may also limit the generalisability of our findings. However, the study

129 sample is one of the largest reporting QoL impact of food immunotherapy with comparison to
130 placebo, and this is the first and only study describing the long-term impact of food
131 immunotherapy.

132

133 The parent trial was supported by the Food Allergy and Anaphylaxis Network (FAAN), the
134 Murdoch Children's Research Institute, Perpetual Philanthropy (grant ID 493), the CASS
135 Foundation, the Financial Markets Foundation for Children and the National Health and Medical
136 Research Council Australia (NHMRC project grant no. 1029690). The 4 year follow-up was
137 supported by the Murdoch Children's Research Institute and the Australian Food Allergy
138 Foundation. Nestle Health Science provided the probiotic and placebo treatments. The Murdoch
139 Children's Research Institute is supported by the Victorian Government's Operational
140 Infrastructure Support Program. Funding organisations were not involved in any aspect of the
141 study and did not contribute to study design, interpretation of results or writing of the manuscript.
142 The protocol for this study is available from the authors.

1. Prescott S, Allen KJ. Food allergy: riding the second wave of the allergy epidemic. *Pediatr Allergy Immunol*. 2011;22:155-60.
2. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, et al. ICON: Food allergy. *J Allergy Clin Immunol*. 2012;129:906-20.
3. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongratic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128:e9-17.
4. De Silva IL, Mehr SS, Tey D, Tang MLK. Paediatric anaphylaxis: A 5 year retrospective review. *Allergy*. 2008;63:1071-6.
5. DunnGalvin A, Koman E, Raver E, Frome H, Adams M, Keena A, et al. An Examination of the Food Allergy Quality of Life Questionnaire Performance in a Countrywide American Sample of Children: Cross-Cultural Differences in Age and Impact in the United States and Europe. *J Allergy Clin Immunol Pract*. 2017;5:363-8.e2.
6. Herbert L, DunnGalvin A. Psychotherapeutic Treatment for Psychosocial Concerns Related to Food Allergy: Current Treatment Approaches and Unmet Needs. *J Allergy Clin Immunol Pract*. 2021;9:101-8.
7. Vickery BP, Vereda A, Casale TB, Beyer K, du Toit G, Hourihane JO, et al. AR101 Oral Immunotherapy for Peanut Allergy. *New Engl J Med*. 2018;379:1991-2001.
8. Chu DK, Wood RA, French S, Fiocchi A, Jordana M, Waserman S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. *Lancet*. 2019;393:2222-32.

- 163 9. Dunn Galvin A, McMahon S, Ponsonby AL, Hsiao KC, Tang MLK, Burks W, et al. The longitudinal
164 impact of probiotic and peanut oral immunotherapy on health-related quality of life. *Allergy*.
165 2018;73:560-8.

166 **Figure 1.** Time trend for FAQLQ mean total scores (primary analysis) shown by treatment group
167 (PPOIT and Placebo).

168

169 **Figure legend:** T0: pre-treatment; T1: end-of-treatment; post-treatment – T3: 3-months; T4: 12-
170 months; T5: 4-years. FAQLQ-PF total score is calculated as the mean of up to 30 items, with
171 response scale from 0 (minimal impairment in QoL) to 6 (maximal impairment in QoL). A reduced
172 score indicates an improvement in the child's QoL. The minimal clinically important difference
173 (MCID) is 0.45-0.5.

174

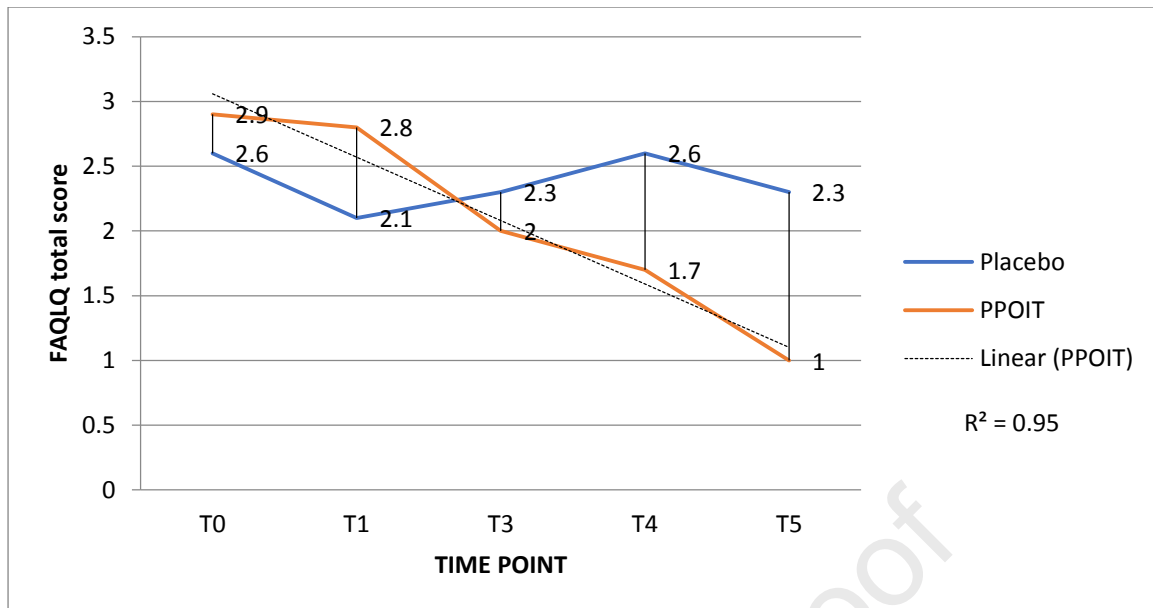
175

176 **Figure 2.** Mean change in FAQLQ score T0 to T5 according to amount of peanut ingested and
177 frequency of peanut ingestion at 4 years post treatment for the PPOIT group.

178

179 **Figure legend:** T0: pre-treatment; T5: 4-years post-treatment. FAQLQ-PF total score is calculated
180 as the mean of up to 30 items, with response scale from 0 (minimal impairment in QoL) to 6
181 (maximal impairment in QoL). A reduced score indicates an improvement in the child's QoL. The
182 minimal clinically important difference (MCID) is 0.45-0.5.

183



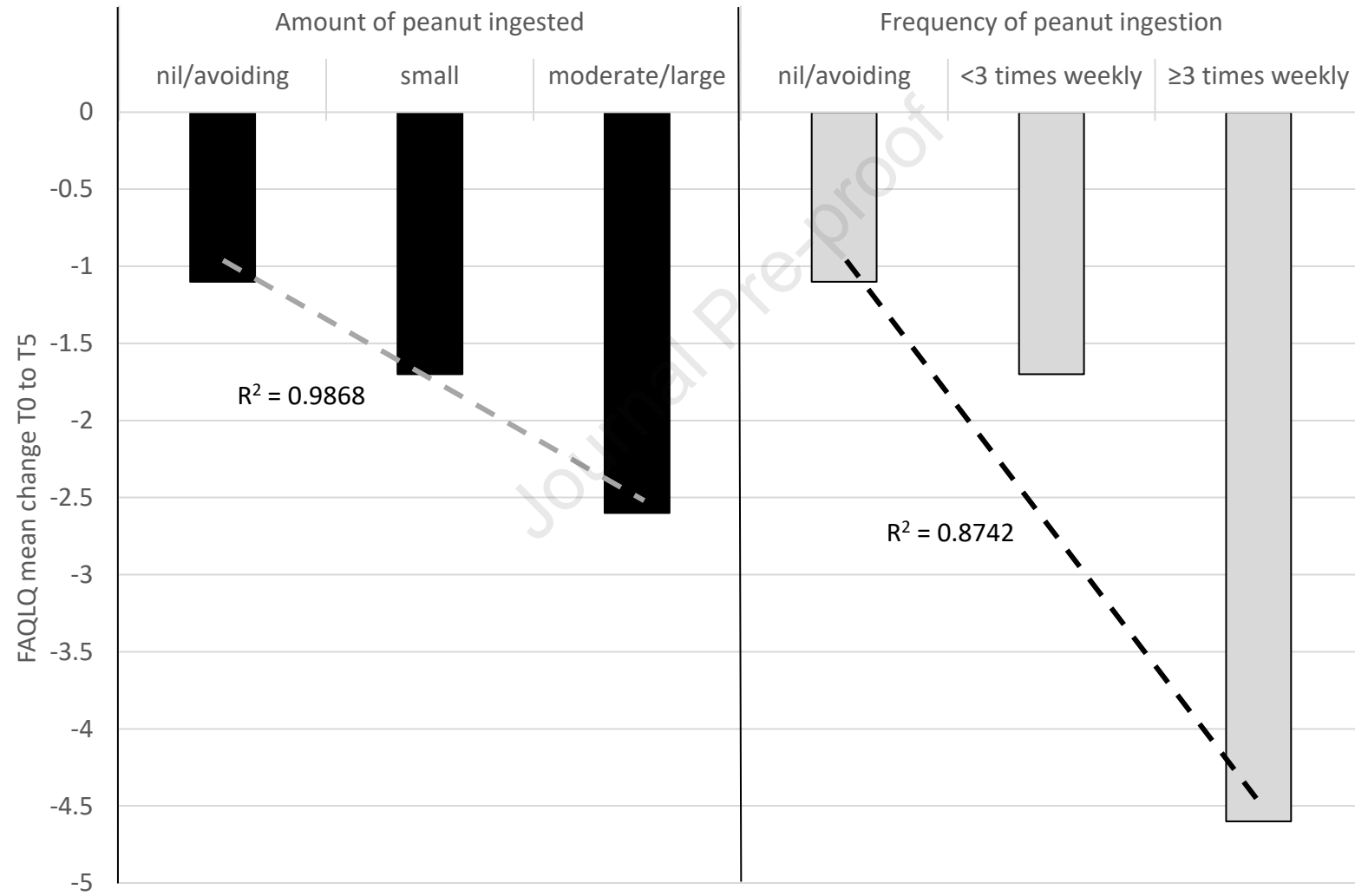


Table E1: Paired sample t-tests showing mean difference in FAQLQ-PF total scores, p-value and confidence intervals for the difference in the primary analysis and sensitivity analyses.

	Placebo			PPOIT		
	Mean difference (SD)	p-value	95% CI for difference	Mean difference (SD)	p-value	95% CI for difference
FAQLQ scores for participants who completed measures at all 5 time points (Primary Analysis)						
T0-T3	0.3 (1.5)	0.3	-0.3, 0.9	0.9 (1.7)	0.04	0.01, 1.5
T0-T4	0.0 (1.8)	0.9	-0.9, 0.7	1.2 (1.8)	0.006	0.4, 2.0
T0-T5	0.3 (1.9)	0.5	-0.6, 1.2	1.9 (1.7)	<0.001	1.1, 2.6
FAQLQ scores for participants who completed measures at least to Time 3, but any data thereafter (Sensitivity Analysis 1)						
T0-T3	0.4 (1.6)	0.3	-0.3, 1.1	0.8 (1.8)	0.05	0.001, 1.7
T0-T4	-0.06 (1.7)	0.8	-0.8, 0.7	1.3 (1.8)	0.005	0.4, 2.1
T0-T5	0.35 (1.9)	0.4	-0.6, 1.3	2.2 (1.8)	<0.001	1.3, 3.1
FAQLQ scores for participants who completed measures at any timepoint (Sensitivity Analysis 2)						
T0-T3	0.4 (1.5)	0.3	-0.3, 0.9	0.8 (1.7)	0.04	0.01, 1.5
T0-T4	-0.06 (1.8)	0.9	-0.9, 0.8	1.3 (1.8)	0.006	0.4, 2.0
T0-T5	0.3 (1.9)	0.6	-0.6, 1.2	2.9 (1.7)	<0.001	1.1, 2.6

T0: pre-treatment; T1: end-of-treatment; post-treatment – T3: 3-months; T4: 12-months; T5: 4-years. FAQLQ-PF total score is calculated as the mean of up to 30 items, with response scale from 0 (minimal impairment in QoL) to 6 (maximal impairment in QoL). A reduced score indicates an improvement in the child's QoL. The minimal clinically important difference is 0.45-0.5.

Table E2: Paired sample t-tests showing mean scores at T0, difference scores T5-T0, p-value and confidence intervals for FAIM items 1-4 in the primary analysis set.

Treatment	Outcome	Mean (SD) T0	Mean difference T5-T0	95% CI for difference	p-value
Placebo	FAIM 1	2.6 (1.1)	0.5	1.2, 1.7	0.106
	FAIM 2	3.8 (1.7)	-0.05	0.6, -0.2	0.868
	FAIM 3	1.9 (1.3)	-0.06	0.5, -0.2	0.842
	FAIM 4	3.0 (1.2)	0.2	0.9, -0.6	0.616
PPOIT	FAIM 1	3.6 (1.7)	-1.8	-.6, -3.0	0.007
	FAIM 2	4.5 (1.7)	-2.4	-1.1, -4.1	0.001
	FAIM 3	3.3 (1.8)	-1.9	-.9, -4.0	0.001
	FAIM 4	2.0 (1.3)	-1.2	-.3, -2.9	0.010

T0: pre-treatment; T1: end-of-treatment; post-treatment – T3: 3-months; T4: 12-months; T5: 4-years. The Food Allergy Independent Measure (FAIM) assesses the parent's perception of the chance of an adverse outcome for the child with food allergy, with a response scale from 0 (no chance) to 6 (very great chance). The 4 items are: (1) the chance of accidental exposure, (2) the chance of a severe reaction on food exposure, (3) the chance of dying on food exposure, and (4) the chance of a child receiving effective treatment following a food allergic reaction. A reduced FAIM score indicates an improvement in the parent's perception of the chance of an adverse outcome for their child with food allergy.