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Working Title: The longitudinal impact of Probiotic and Peanut Oral Immunotherapy (PPOIT) on health related quality of life (HRQL).

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Statements of conflicts of interest

MLKT is a member of Medical Advisory Board Oceania for Nestle Nutrition Institute, is an employee of and holds share options/interest in Prota Therapeutics. No conflict of interest for the other authors listed above.
All authors provided data for the study and/or were involved in writing and editing the manuscript.
ADG, SM, ALP, KCH declare no conflict of interest

Statements of contribution

MLKT conceived and designed the study, and contributed to the conduct of the study, the analysis and interpretation of data, drafting the article, revising the article critically for important intellectual content and approved the final version. ALP contributed to the design and conduct of the study, the analysis and interpretation of data, drafting the article, revising the article critically for important intellectual content and approved the final version.
ADG, SM and KCH contributed to the analysis and interpretation of data, drafting the article, revising the article critically for important intellectual content and approved the final version.

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Abstract (250 words)

Background

We previously reported that Probiotic and Peanut Oral Immunotherapy **(**PPOIT) was effective at inducing sustained unresponsiveness compared with placebo in a double-blind, placebo-controlled randomized trial. This study evaluated the impact of PPOIT on health related quality of life (HRQL).

Method

Fifty-one participants (PPOIT 24; Placebo 27) from the PPOIT trial completed Food Allergy Quality of Life Questionnaire (FAQLQ-PF) and Food Allergy Independent Measure (FAIM) at pre-treatment, end-of-treatment and 3-months after end-of-treatment. 42 participants (20 PPOIT; 22 Placebo) completed measures at 12 months post-treatment. Changes over time in PPOIT and Placebo groups were examined by repeated measures analysis of variance and paired t-tests.

Results

PPOIT was associated with significant improvement in FAQLQ-PF (F=3.63, p=0.02), with Mean Difference 0.8 at 3 months post-treatment (p=0.05) and 1.3 at 12 months post-treatment (p=0.005), exceeding the 0.5 minimal clinically important difference for FAQLQ-PF. For FAIM, mean difference was 0.5 (p=0.03) at 3 months and 0.4 (p=0.04) at 12 months. In placebo group, post-treatment FAQLQ and FAIM remained unchanged from pre-treatment**.** Improvement in FAQLQ-PF and FAIM scores related specifically to acquisition of sustained unresponsiveness rather than to receiving PPOIT treatment or participation in the trial.

Conclusions

PPOIT has a sustained beneficial effect on psychosocial impact of food allergy at 3 months and 12 months after end-of-treatment. Treatment was not associated with reduced HRQL relative to baseline in either PPOIT or placebo groups, indicating that PPOIT was well tolerated and psychological wellbeing was not negatively impacted. Improved HRQL was specifically associated with acquisition of sustained unresponsiveness.

Manuscript

Introduction

Food allergy (FA) is major public health concern (1-3). In Australia, anaphylaxis hospital admissions increased 3.5 fold between 1994 and 2005, and a further 3-fold between 2005 and 2012, with peanut anaphylaxis showing the greatest increase (4-5). Similar increases have been reported for the UK (6) and US (7). Avoidance of the trigger food(s) is central to management but accidental ingestion is common, causing frequent and sometimes life-threatening reactions (8-9). There are no reliable means to predict reaction severity, so patients and parents

live in fear of a life-threatening allergic reaction, where the threat is ever present but the timing is unpredictable. This uncertainty can give rise to extreme anxiety and avoidance on the one hand or frustration and risky behaviours on the other (10-11).

Health Related Quality of Life (HRQL) is a multi-dimensional construct, which evaluates physical, psychological, and social components that may be impacted by a disease or medical condition, from the patient perspective. In recent years, an increasing number of HRQL studies on patients with food allergies and anaphylaxis, as well as how they deal with emergency medication and food, have been published. Results have shown a strong adverse impact on HRQL for the child, teen, adult and parent (12-18), and effects are greater with increasing age (14-15). Generic measures also show worse HRQL in food allergy compared to other paediatric chronic diseases, such as Diabetes Type 1 (13). Findings provide an insight into the everyday impact of food allergy on HRQL, and hence, which specific factors to address in a particular context, intervention, policy or in practice. It is likely that a curative treatment that induces tolerance (or sustained unresponsiveness) would improve the lives of people with food allergy and avoid deaths, particularly for peanut allergy. Nevertheless, long-term patient reported outcomes from clinical trials evaluating potential food allergy treatments are lacking. Oral immunotherapy (OIT) is suggested as a potential treatment for food allergy with trials showing effective desensitisation in the majority of treated participants and sustained unresponsiveness in a smaller proportion (≤35%) (19). To date, the effect of OIT on HRQL is unclear, for patients in both the intervention and control groups, particularly with regard to longitudinal impact. Research suggests that OIT has a positive impact on HRQL of caregivers and children, when measured at treatment end (20-22). However, the impact of OIT on HRQL during the treatment process, and long-term effects after completing OIT treatment have not been examined. Moreover, there are no studies comparing HRQL in OIT-treated and placebo-treated participants within a randomised trial. It is vital to track HRQL over time, both during and beyond the end of a clinical trial, to determine if the treatment has a sustained impact on HRQL (9,23-24) and to also understand whether OIT might be associated with a negative impact on HRQL during the treatment period compared with a placebo intervention.

Recently, we conducted a double-blind, placebo-controlled randomized trial evaluating a novel treatment approach comprising combined administration of a probiotic and peanut oral immunotherapy (PPOIT) in children with peanut allergy (25). PPOIT treatment resulted in high rates of sustained unresponsiveness compared with placebo (82% vs 3.6%) equating to a number needed to treat of 1.27. The present study sought to evaluate the impact of PPOIT on child HRQL and on expectation of outcome following allergen exposure during and after treatment using both longitudinal within-group analysis and between group comparisons with placebo.

Methods

The PPOIT study was a double-blind, placebo-controlled randomized trial that evaluated the effectiveness of PPOIT for the induction of sustained unresponsiveness in peanut allergy (25). Briefly, 62 children with peanut

allergy were randomised to receive PPOIT or placebo for 18 months. A double-blind placebo-controlled food challenge (DBPCFC) was performed at 18 months (end-of-treatment, T1) to assess for desensitisation; if this challenge was passed a second DBPCFC was performed 2-6 weeks later to assess for sustained unresponsiveness (T2). Participants who failed the first or second DBPCFC were advised that they remained allergic to peanut and should avoid all peanut in the diet. Participants who passed both the first and second DBPCFC were informed that they had attained sustained unresponsiveness and were instructed to introduce peanut into the diet and continue intake on a regular basis without specific advice on amount or frequency. The parent study concluded at 3 months after end-of-treatment. In a follow-up study, participants were assessed at 6 months post end-of-treatment by telephone questionnaire and at 12 months post end-of-treatment by clinic visit. A validated parent proxy HRQL measure (16-17) and the Food Allergy Independent Measure (26) were administered at: pre-treatment (T0), end-of-treatment (when status of peanut allergy vs tolerance was not yet known, T1); 3-months after end-of-treatment (when status of peanut allergy vs tolerance was known, T3); and 12 months after end-of-treatment (T4) (Figure 1).

Participants

Inclusion criteria were age 1-10 years (at enrolment); and diagnosis of peanut allergy, defined as either (i) an immediate allergic reaction to peanut during the past two years and a positive peanut skin prick test (SPT) or specific Immunoglobulin E (sIgE) or (ii) any previous immediate allergic reaction to peanut and a peanut SPT ≥8 mm or sIgE ≥15 kU/L (representing 95% positive predictive values for clinical allergy) (27). Fifty-one participants (PPOIT 24; Placebo 27) completed HRQL measures at pre-treatment (T0), end-of-treatment (T1), and 3-months after end-of-treatment (T3); and 42 participants (PPOIT 20; Placebo 22) completed measures at 12 months after end-of-treatment (T4).

[insert figure 1 here]

Measures

The Food Allergy Quality of Life Questionnaire – Parent Form (FAQLQ-PF) is a disease-specific HRQL questionnaire with excellent validity, and reliability (16-17). The psychometric tool was developed to assess quality of life in children with food allergies (aged 0-12 years) and allows parents to report children's HRQL from the child's perspective. FAQLQ-PF is presented in a single form for all age groups (0–3; 4–6; 7–12 years) and is therefore 'user-friendly'. The FAQLQ-PF contains 30 items, and the response scale ranges from 0 (minimal impairment in HRQL) to 6 (maximal impairment in HRQL). The measure has 3 subscales assessing three factors found to be essential for assessing the global impact of food allergy on HRQL: general emotional impact (EI); food anxiety (FA); social and dietary limitations (SDL). The total score is calculated as the mean of items. The questionnaire also includes: parent's level of worry about children's physical and emotional health, the extent to which food allergy limits the type of activities in which children and families can take part, the number of foods avoided and type and number of symptoms experienced. The European Academy of Allergy and Clinical

Immunology identified the FAQLQ-PF as the preferred tool for assessment of this age group (28). The minimal clinically important difference (MCID) for FAQLQ-PF is 0.5 (17).

The Food Allergy Independent Measure (FAIM) is a food allergy-specific measure that has been used in the developmental and longitudinal validation phases of several food allergy-specific questionnaires (26). The FAIM total score is based on four main questions, with a response scale from 0 (no chance) to 6 (very great chance), that assess the parent's perception of the chance of an adverse outcome for the child with food allergy. The questions relate to: (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 effectively treating him/herself or receiving effective treatment, following a food allergic reaction. Additional questions 5 and 6 ask (respectively), how many foods are avoided because of food allergy (categorised as single, two, multiple >2), and how much food allergy limits the type of activities that the child can take part in. Higher expectation of outcome or 'perception of control' in managing chronic allergic conditions such as asthma and allergic rhinitis is a strong predictor of subjective perception of patient well-being (29-30). 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.

Statistical analysis

Preliminary checks were performed to ensure the data met the requirements for the selected tests in terms of linearity and normality (31-32). We only performed analyses on those participants who completed measures at all timepoints (T0-T3 and T0-T4). Due to the different number of participant responses available for the parent study vs follow up study, an attrition analysis was conducted to analyze whether withdrawal from completion of the outcome measures led to a biased sample. A series of t-tests were carried out to examine any potential differences between the profiles of samples in T0-T3 and T0-T4. No significant differences ($p>0.05$) were found between the profiles of the samples in T0-T3 and T0-T4 for child sex, age, number of allergens, previous reactions, or on initial scores on the two outcome variables (FAQLQ and FAIM). In Placebo group, 81% of those who completed measures at T3 also did so at T4 and, in PPOIT group, 83% of those who completed measures at T3 also did so at T4. No significant difference was found in FAQLQ-PF scores at T3 between those who completed the measure at T3 and T4 and those who only completed the measure at T3 ($t=1.08$, $p=0.3$).

Repeated-measures mixed ANOVAs were used to examine changes from T0 to T4 on the outcomes of interest: FAQLQ and FAIM. Main effects of time were examined as a within-subjects factor to answer the primary research question of whether participants' scores were significantly different from T0 to T4. Group status (PPOIT vs Placebo) was entered as a between-subjects factor. An interaction term of Time_Group was entered to determine whether the effects of the intervention were moderated by participant Group. We controlled for the potential confounding effects of age at T0 (≤5years, >5 years) and child sex. If a significant interaction was found between Time and Group, paired group t-test analyses were conducted separately for PPOIT and Placebo groups, and for each time point (T0-T1; T1-T3; T1-T4; T3-T4; T0-T3; T0-T4) to test for which group (PPOIT vs Placebo) and at what time point this improvement occurred.

To determine if any improvement in HRQL was due specifically to beneficial treatment effects (i.e. acquisition of sustained unresponsiveness) or simply to having received PPOIT treatment or more broadly to clinical and/or psychological support as a result of undergoing the trial itself, we carried out paired t-test analyses to examine changes in HRQL measures over time in those who achieved SU and those that did not within the PPOIT group and those who failed to achieve SU in the Placebo group (T0-T3 and T0-T4). As only 1 of 28 placebo-treated participants attained SU, statistical analysis was not performed for this subgroup**.**

Because our patients were randomly allocated to comparison groups, the responses from all groups should be equally affected by potential regression to the mean (RTM) (33). With two groups, placebo and treatment, the mean change in the placebo group provides an estimate of the change caused by RTM (plus any placebo effect). The difference between the mean change in the treatment group and the mean change in the placebo group is then the estimate of the treatment effect after adjusting for RTM.

We calculated the number needed to treat (NNT) based on the MCID of 0.5 (% of patients meeting or exceeding MCID vs patients not meeting or exceeding MCID in PPOIT and Placebo groups) for the FAQLQ-PF at three months post-treatment (T3). NNT=1/ [(*Placebo event rate*)−(*PPOIT event rate*)]. All statistical analyses were performed using SPSS v 22.0 (SPSS Inc., Chicago, IL, USA). Results were taken to be significant if $p<0.05$.

Ethical Considerations

Ethical approval was granted by Royal Children's Hospital Human Research Ethics Committee and School of Applied Psychology's ethics committee, University College Cork. The study was conducted in accordance with the Psychological Society of Ireland's Code of Ethics (2010).

Results

The main characteristics of the sample are shown in Table 1. Participants were aged between 2 and 11 years at current study end (50% male:female); mean age 5.7 years (*SD*=2.6). Twenty-three per cent had a single allergy to peanut, 42% were diagnosed with one other allergy (>90% to nut), and 34% reported three or more food allergies.

[insert Table 1 here]

Food allergy quality of life (FAQLQ)

FAQLQ scores at T0-T4 are shown Table 2a. In line with norms (15), parents of children ≤5 years reported a FAQLQ-PF score of 2.1, and parents of children >5 years reported a FAQLQ-PF score of 2.8 at baseline (T0). Repeated-measures ANOVAs were used to examine changes in HRQL as measured by FAQLQ-PF.

[insert Table 2 here]

For FAQLQ, we did not find an overall effect for Time [F=0.58, p=0.6]. However, there was a statistically significant interaction between Group_Time [F=3.63, p=0.02], with a large effect size (η^2p=0.23). Hence, change in FAQLQ over time was assessed separately for PPOIT and Placebo groups [Table 2b].

For the PPOIT group, the mean difference in FAQLQ score improved over time and exceeded the 0.5 MCID for all comparisons except T0-T1 and T3-T4 (Table 2b). Significant improvements in FAQLQ scores were found from pre-treatment to 3 months post-treatment (Mean Difference T0-T3 0.8, p=0.05) and 12 months post-treatment (Mean Difference T0-T4 1.3 p=0.005). Interestingly, FAQLQ-PF scores continued to improve from end-of treatment to 12 months post-treatment (Mean Difference T1-T4 1.0, p=0.04; Mean Difference T3-T4 0.4, p=0.02). There was a trend for participants >5 years at study entry to have greater improvement in FAQLQ-PF scores from T0-T3 than those ≤5 years (Mean Difference 1.0 vs 0.5; t=0.731, p=0.5) and from T0-T4 (Mean Difference 1.4 vs 0.8; t=0.353, p=0.8). In the placebo group, no significant differences in FAQLQ scores were observed at end-of-treatment (T1), 3 months post-treatment (T3), or 12 months post-treatment (T4) compared to baseline (T0).

Repeated measures mixed ANOVAs showed significantly improved FAQLQ-PF scores from T0 to T4 for the PPOIT group (Figure 2). The trajectory of mean FAQLQ-PF scores from pre-treatment to 3 months and 12 months post-treatment for the PPOIT group was different from that of the placebo group culminating in an improved score for PPOIT-treated participants as compared to placebo-treated participants at T4 (Figure 2).

[insert Figure 2 and Figure 3 here]

The greatest improvement following PPOIT treatment was seen in the Food Anxiety subscale (T3 Mean Difference 1.1, p=0.003; T4 Mean Difference 1.4, p=0.001), followed by Social & Dietary Restrictions (T3 Mean Difference 0.9, p=0.09; T4 Mean Difference 1.2, p=0.005), and Emotional Impact (T3 Mean Difference 0.6, p=0.1; T4 Mean Difference 1.1, p=0.01).

There was also a reduction in level of parent worry about the child's physical health (Mean Difference 1.0, p=0.01) and emotional health (Mean Difference 0.7, p=0.04) from pre-treatment (T0) to 3 months post-treatment (T3). No differences were found for the Placebo group.

Food Allergy Independent Measure (FAIM)

Total FAIM scores are shown in Table 3a. Repeated-measures ANOVAs were used to examine changes in parent's assessment of the chance of adverse outcomes for a child following accidental ingestion of an allergen, as measured by FAIM.

[insert Table 3 here]

We did not find a significant overall effect for Time (F 0.753, p=0.53). However, there was a statistically significant interaction between Group_Time (F=5.349, p=0.004), with a large effect size η^2p=0.31. Hence, changes in FAIM scores over time were assessed separately for PPOIT and Placebo groups [Table 3b].

There were no significant differences in FAIM scores over time for the placebo group, except for a slight deterioration between pre-treatment to 3 months post-treatment (Mean Difference T0-T3 -0.3, p=0.02) when participants were informed of their peanut allergy status; FAIM scores returned to baseline by 12 months post-treatment. For the PPOIT group, FAIM scores improved from pre-treatment to end-of-treatment (Mean Difference T0-T1 0.8, p=0.002), 3 months post-treatment (Mean Difference T0-T3 0.5, p=0.03) and 12 months post-treatment (Mean Difference T0-T4 0.4, p=0.04. Similarly, repeated measures mixed ANOVAs showed that parent perception of the chance of adverse outcomes following accidental ingestion of an allergen by their child was reduced by treatment in the PPOIT group.

With regard to the individual items of FAIM, the greatest improvement following PPOIT treatment was in FAIM 2, chance of having a severe reaction (T3 Mean Difference 1.0, t=2.6, p=0.03; T4 0.8, t=2.1, p=0.04), followed by FAIM 3, chance of dying from allergen ingestion (T3 Mean Difference 1.0, t=1.6, p=0.1; T4 Mean Difference 1.2, t=2.8, p=0.01) and FAIM 1, chance of accidentally eating an allergen (T3 Mean Difference 0.9, t=2.5, p=0.02; T4 0.7, t= 2.1, p=0.04). There was minimal improvement in FAIM 4, chance of a child managing a reaction if it occurs (Mean Difference 0.3, p=0.3 at both T3 and T4).

HRQL in participants who did or did not attain sustained unresponsiveness (SU)

The primary outcome measure in the original PPOIT randomised trial was acquisition of SU, assessed by DBPCFC 2-6 weeks after completing treatment. To determine if the changes in HRQL associated with PPOIT treatment related specifically to acquisition of sustained unresponsiveness or to simply having received PPOIT, or more broadly to participation in the clinical trial, we examined change in HRQL over time in participants who achieved sustained unresponsiveness and those who did not, within the PPOIT group. Change in HRQL over time was also examined in placebo-treated participants who failed to achieve SU.

In the Placebo group, 27 of 28 (96.4%) participants failed to achieve SU at end-of-treatment, with only 1 participant achieving SU; therefore, analysis of change in HRQL over time was only performed for those who failed to achieve SU. In the PPOIT-treated group, 23 of 28 (82.1%) participants attained SU, while 5 failed to achieve SU. Placebo-treated participants who failed to achieve SU had no change in FAQLQ-PF scores at 3 months (Mean Difference T0-T3 0.3, SD 1.6; t=0.88, p=0.4) or 12 months (Mean Difference T0-T4 -0.15, SD 1.8; t=-0.38, p=0.7) post-treatment. Similarly, PPOIT-treated participants who failed to achieve SU showed no

improvement in FAQLQ-PF scores at 3 or 12 months post-treatment (Mean Difference T0-T3 -0.58, t=-1.05, p= 0.4; Mean Difference T1-T4 -0.2, t= -0.23, p=0.8).

In contrast, PPOIT-treated participants who achieved SU reported a significant improvement in FAQLQ-PF scores across all subscales at 3 and 12 months post-treatment (Mean Difference T0-T3 1.3, t=2.8, p= 0.01; Mean Difference T0-T4 1.8, t=2.7, p=0.001). Mean differences in subscale scores from pre-treatment ranged between 1.2 to 1.5 ($p < 0.05$) at 3 months post-treatment and between 1.6-1.8 ($p<0.01$) at 12 months post-treatment, with Food Anxiety showing the greatest difference from baseline at both 3 and 12 months post-treatment (1.5 and 1.8, respectively, both p=0.001).

A similar pattern was found for FAIM scores, with no improvement seen in participants who failed to attain SU, irrespective of whether they were in the PPOIT or Placebo group, whereas there was significant improvement in scores over time for PPOIT-treated participants who achieved SU (Mean Difference T0-T3 0.7, t=2.1, p=0.04; Mean Difference T0-T4 0.4, t=1.8, p=0.08).

These results suggest that improvement in HRQL was related to acquisition of SU per se and not to any clinical and/or psychological support associated with receiving PPOIT treatment or with participating in the trial itself.

Number needed to treat (NNT)

The percentage of patients who had reduction in their FAQLQ scores by an amount that was equal to or greater than the MCID of 0.5 at 3 months post-treatment was 77% PPOIT and 34% Placebo, resulting in a NNT of 2.3. On average, 2 patients would have to receive PPOIT (instead of placebo) for one additional patient to have an improved FAQLQ-PF score greater than the MCID [95% CIs, 10 to 2]. The absolute risk reduction was 42.2%.

Discussion

We used the well-validated FAQLQ-PF questionnaire and the Food Allergy Independent Measure (FAIM) to evaluate the potential impact on HRQL in children with peanut allergy during and after treatment intervention in a randomized placebo-controlled trial of PPOIT vs placebo. PPOIT treatment was associated with significant global improvements in HRQL, exceeding the 0.5 minimal clinically important difference (MCID) for FAQLQ-PF at 3 and 12 months after treatment was completed; whereas FAQLQ-PF scores remained unchanged following placebo treatment. Improvement was also seen in FAIM following PPOIT but not placebo treatment. PPOIT treatment did not negatively affect HRQL or key aspects of emotional impact, food anxiety and limitations on social and dietary factors during the treatment phase. Equally important, quality of life in placebo participants was not reduced following treatment and was slightly improved during the treatment phase, with improvement particularly in the anxiety subscale**.** These observations are reassuring as they indicate that, at the very least, involvement in a randomized controlled trial as a placebo participant does not have a negative impact on quality of life. Moreover,

279 although improvement in the placebo group was only transient, this may have some long-term benefit in
280 reframing an individual subject's sense of control over their disease and therefore anxiety.

281 Parent's expectations of adverse outcomes from food exposure (measured by FAIM) were also significantly
282 improved with PPOIT and there was sustained benefit to 12 months after end-of-treatment. Subjective
283 expectation of the outcome after an allergic reaction due to accidental ingestion of an allergen is a reliable
284 predictor and correlate of self-reported HRQL in food allergy (16-17) and in other chronic diseases (29-30). Long-
285 lasting improvement in these expectations is therefore an important additional measure of beneficial outcomes
286 when evaluating a potential food allergy treatment. Although there was improvement in HRQL at 3 months post-
287 treatment for both children ≤5years and >5years in the PPOIT group, differences were greater in those >5 years.
288 Development and age have a strong influence both on the type of event that is encountered by a child with food
289 allergy and on how that event, situation, or reaction is experienced (10). Early intervention may have an added
290 beneficial impact on coping skills and self-efficacy in adolescence and adulthood.

291 The improvement in HRQL measures within the PPOIT-treated group related specifically to successful
292 attainment of SU and not simply to having received the PPOIT intervention or to participation in the trial. FAQLQ-
293 PF (both total and subscale) scores improved significantly for PPOIT-treated participants who attained SU at the
294 end-of-study, with a mean difference exceeding the MCID; whereas no improvement was seen for either PPOIT-
295 treated or Placebo-treated participants who failed to achieve SU. A similar pattern was found for FAIM, with
296 improvement observed only for PPOIT-treated participants who achieved SU. The beneficial effects of PPOIT on
297 HRQL are therefore likely to relate to the outcome of achieving sustained unresponsiveness and not to simply
298 receiving PPOIT treatment or to clinical and/or psychological support from undergoing the trial.
299
300 As only 7% of PPOIT-treated participants were desensitized without achieving sustained unresponsiveness (and
301 were advised that they remained allergic so should continue to avoid all peanut in their diet), our findings are
302 unable to provide information on the potential effect of desensitization on quality of life. Further studies are
303 required to determine whether the different outcomes of sustained unresponsiveness and desensitization have a
304 different impact on quality of life, ideally through comparing quality of life measures within a randomized trial. We
305 have recently commenced a double blind, randomized trial comparing PPOIT vs peanut OIT vs placebo, which
306 will allow us to investigate this. Finally, since this was a single-centre trial conducted in Australia, where there are
307 different practices in peanut avoidance than in other areas of the world, and since country and cultural practices
308 have previously been found to be influential in predicting HRQL, a multi-institutional study across
309 countries/cultures will be helpful in confirming our findings.
310
311 In conclusion, we have previously reported that PPOIT was effective at inducing sustained unresponsiveness as
312 compared with placebo treatment (82% vs 3.6%). We now demonstrate that PPOIT treatment is also associated
313 with significantly improved health related quality of life after completion of treatment and leads to continued

improvement in quality of life during the subsequent 12 months. Benefits are seen for all subscales of quality of life, with reduced emotional impact, food anxiety and social and dietary limitations. Furthermore, PPOIT resulted in reduced parental concern around likelihood of their child experiencing a severe allergic reaction or dying from that reaction. These changes in expectation of outcome are relevant to the overall benefits associated with PPOIT. Conversely, quality of life in placebo participants over time was not impaired, suggesting that no psychological harm occurred through taking part in the trial**.** Improvement was due to the beneficial outcome of attaining SU rather than to having received PPOIT treatment or to the process of undergoing the trial itself. Future studies evaluating potential food allergy treatments should include measures of quality of life to validate the social and emotional benefits of treatment in addition to clinical outcomes.

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Table 1 : Participant characteristics at baseline (T 0)

	Placebo Group N=27	*PPOIT Group* N=24
Age Mean (SD)	5.6 (2.7)	5.8 (2.6)
Age ≤ 5 years n(%)	14 (50)	15 (52)
Age > 5 years n(%)	14 (50)	14 (48)
Male sex n(%)	13 (48)	12 (52)
History of doctor diagnosed eczema (ever) n(%)	17 (63)	15 (63)
Medication for eczema in last 12 months n(%)	14 (50)	13 (52)
History of doctor diagnosed asthma (ever) n(%)	12 (44)	11 (46)
Medication for asthma in last 12 months n(%)	9 (33)	7 (30)
Peanut induced SPT wheal size (mm) Mean (SD)	17.1 (6.1)	17.2 (6.4)
sIgE (kU/L) Mean (SD)	12.2 (6.4)	8.7 (4.0)

Table 2: (a) FAQLQ Total scores at T0-T4 for Placebo and PPOIT groups, shown separately for participants aged ≤5 years and > 5 years; (b) Paired Sample T-tests showing mean differences, and confidence intervals for difference, for FAQLQ Total scores at paired Timepoints for PPOIT and Placebo groups.

2a	**Placebo**		**PPOIT**	
	Mean(SD)		Mean(SD)	
	≤5 years	>5 years	≤5 years	>5 years
T0				
Total Score	2.4 (1.9)	2.9 (1.4)	2.7 (1.7)	2.9 (1.2)
Emotional Impact	2.4 (1.9)	2.9 (1.3)	2.7 (1.8)	2.9 (1.2)
Food Anxiety	2.6 (2.2)	3.2 (1.6)	2.8 (1.5)	3.1 (1.4)
Social & Dietary Restrictions	2.4 (1.6)	3.0 (1.6)	2.6 (1.9)	2.9 (1.3)
T1				

Total Score	1.9 (0.9)	2.3 (1.5)	2.7 (1.8)	2.7 (1.2)
Emotional Impact	1.6 (1.5)	2.1 (1.4)	2.8 (2.0)	2.7 (1.2)
Food Anxiety	1.9 (2.2)	2.4 (2.1)	2.9 (1.5)	2.8 (1.4)
Social & Dietary Restrictions	2.4 (1.7)	2.5 (1.6)	2.6 (1.9)	2.6 (1.3)
T3				
Total Score	2.1 (1.4)	2.4 (1.5)	2.4 (1.9)	2.0 (1.4)
Emotional Impact	2.0 (1.7)	2.1 (1.4)	2.3 (1.5)	2.0 (0.8)
Food Anxiety	2.2 (1.6)	2.6 (1.8)	2.2 (1.5)	2.0 (1.4)
Social & Dietary Restrictions	2.2 (1.5)	2.6 (1.7)	2.4 (1.5)	1.9 (1.4)
T4				
Total Score	2.4 (1.4)	2.9 (1.6)	1.9 (1.4)	1.5 (1.3)
Emotional Impact	2.2 (1.4)	2.7 (1.6)	1.8 (1.3)	1.6 (1.2)
Food Anxiety	2.3 (1.5)	2.9 (1.8)	2.0 (1.1)	1.5 (1.5)
Social & Dietary Restrictions	2.8 (1.7)	3.1 (1.8)	1.8 (2.0)	1.5 (1.3)

2b	**Placebo**			**PPOIT**		
	Mean Difference(SD)	t (p value)	C.I for difference	Mean Difference(SD)	t (p value)	C.I for difference
T0-T1						
Total Score	0.6 (1.5)	1.8 (0.08)	-0.09-1.2	0.3 (1.1)	1.1 (0.3)	-0.2-0.8
T1-T3						
Total Score	0.2 (0.7)	1.1 (0.3)	-0.4-0.1	0.6 (1.8)	1.4 (0.2)	-0.3-1.4
T1-T4						
Total Score	-0.6 (1.2)	-2.5 (0.02)*	-1.2-1.0	1.0 (2.0)	2.2 (0.04)*	0.04-1.9
T3-T4						
Total Score	- 0.5 (1.2)	-1.7 (0.09)	-1.0-0.8	0.4 (0.7)	2.5 (0.02)*	0.06-0.8
T0-T3						
Total Score	0.4 (1.6)	1.1 (0.3)	-0.3-1.1	0.8 (1.8)	2.1 (0.05)*	0.001-1.7
T0-T4						
Total Score	-0.06 (1.7)	-0.15 (0.8)	-0.8-0.7	1.3 (1.8)	3.1 (0.005)*	0.4-2.1

*denotes significant difference between timepoints; (-) in Mean Difference column denotes dis-improvement.

Table 3: (a) FAIM Total scores at T0-T4 for Placebo and PPOIT groups, shown separately for participants aged ≤5 years and > 5 years; (b) Paired Sample T-tests showing mean differences, and confidence intervals for difference, for FAIM Total scores at paired Timepoints for PPOIT and Placebo groups separately.

3a	**Placebo**		**PPOIT**	
	Mean(SD)		Mean(SD)	
	≤5 years	> 5 years	≤5 years	> 5 years
T0				
Total Score	2.7 (1.0)	2.6 (0.8)	2.9 (0.9)	3.0 (0.7)
T1				
Total Score	2.6 (1.1)	2.7 (0.8)	2.4 (1.1)	2.0 (0.9)
T3				
Total Score	2.8 (1.1)	2.8 (1.1)	2.3 (1.1)	2.4 (1.0)
T4				
Total Score	2.5 (0.8)	3.0 (0.9)	2.4 (0.9)	2.7 (1.1)

3b	**Placebo**			**PPOIT**		
	Mean Difference(SD)	t (p value)	C.I for difference	Mean Difference(SD)	t (p value)	C.I for difference
T0-1						
Total Score	-0.2 (0.7)	1.0 (0.3)	-0.5-0.2	0.8 (1.0)	3.6 (0.002)*	0.4-1.3
T1-T3						
Total Score	-0.15 (0.6)	1.0 (0.3)	-0.14-0.15	-0.2 (0.9)	1.3 (0.2)	-0.7-0.2
T1-T4						
Total Score	0.02 (0.7)	0.1 (0.9)	-0.3-0.3	-0.4 (1.4)	1.4 (0.2)	-1.0-0.2
T3-T4						
Total Score	0.16 (0.7)	1.1 (0.3)	-0.14-0.5	-0.1 (1.1)	-0.6 (0.6)	-0.6-0.4
T0-T3						

Total Score	-0.3 (0.5)	2.5 (0.02)*	-0.6-0.04	0.5 (1.1)	2.3 (0.03)*	0.04-1.0
T0-T4						
Total Score	-0.13 (0.6)	1.0 (0.3)	-0.4-0.1	0.4 (0.8)	2.1 (0.04)*	0.01-0.8

*denotes significant difference between timepoints; (-) in Mean Difference column denotes dis-improvement.

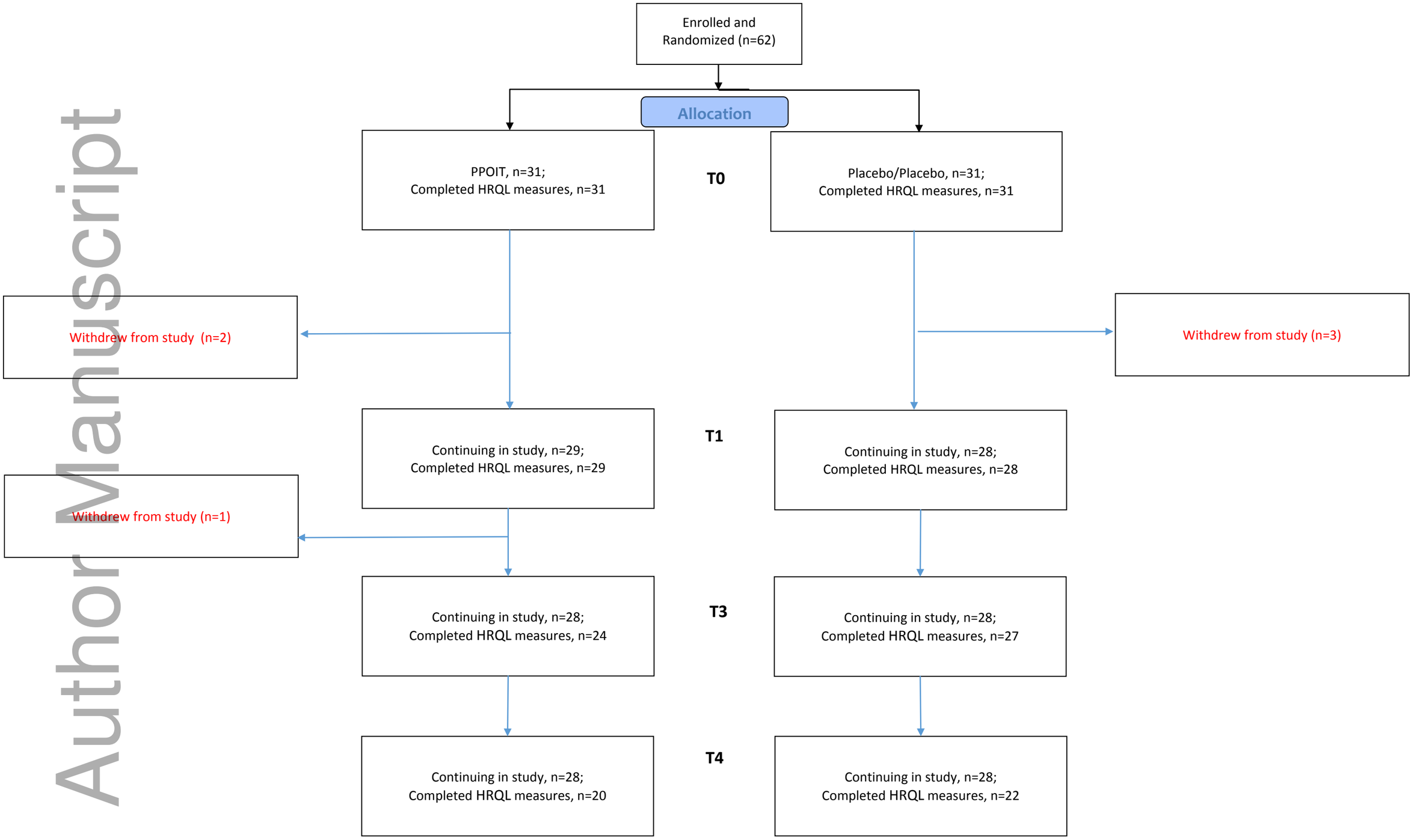

Figure 1: CONSORT diagram of participant flow in the PPOIT randomized controlled trial. T0: pre-treatment; T1: end-of-treatment; T3: 3 months post-treatment; T4: 12 months post-treatment. T2 was at 2-6 weeks post-treatment to assess for sustained unresponsiveness and not shown in this consort diagram as HRQL measures were not assessed.

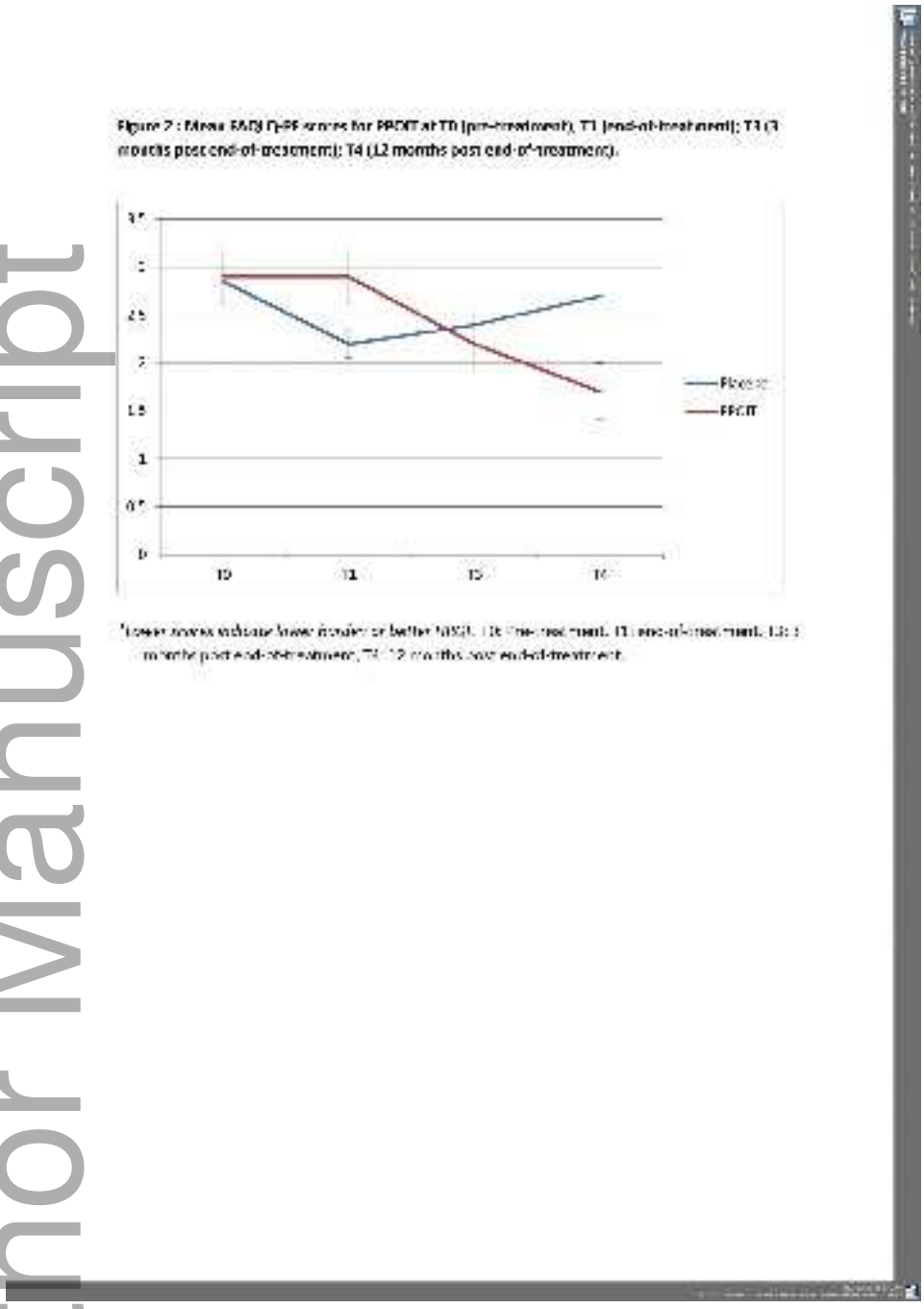

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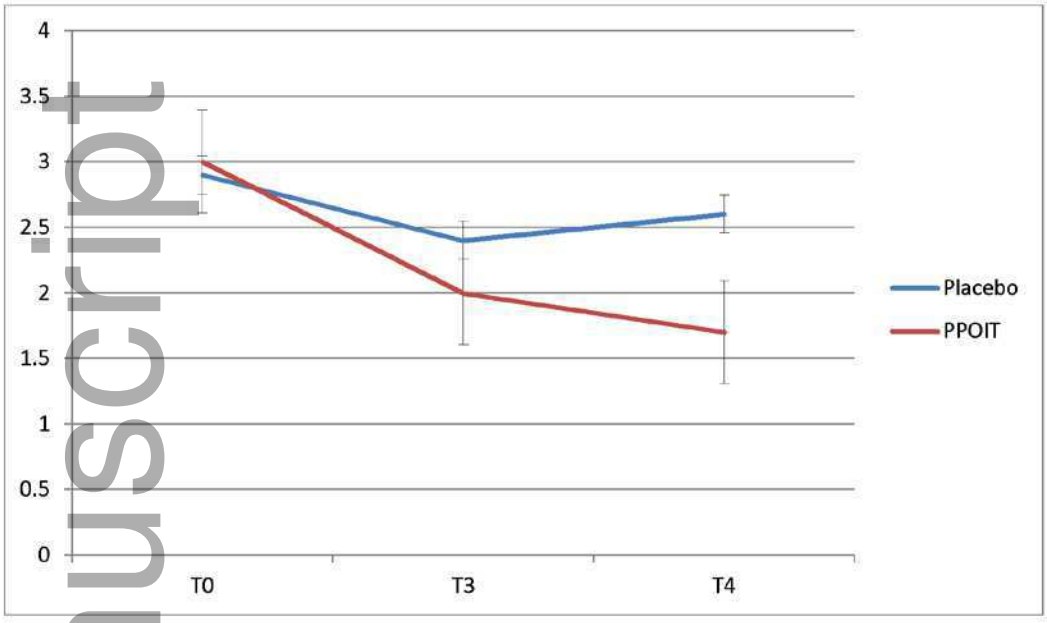
Figure 3 : Mean Food Anxiety (FA) subscale scores for PPOIT and Placebo groups at T0 (pre-treatment); T3 (3 months post end-of-treatment); T4 (12 months post end-of-treatment).



**Lower scores indicate lower burden or better HRQL.* T0: Pre-treatment, T3: 3 months post end-of-treatment, T4: 12 months post end-of-treatment.