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Cost-effectiveness analysis of probiotic peanut oral immunotherapy (PPOIT) versus placebo in Australian children with peanut allergy alongside a randomised trial

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ABSTRACT

Objective To compared the cost-effectiveness of coadministration of a probiotic adjuvant with peanut oral immunotherapy (PPOIT) with placebo (no treatment) in children with peanut allergy.

Design Prospectively planned cost-effectiveness analysis alongside a randomised control trial.

Setting The Royal Children's Hospital, Melbourne, Australia.

Participants 56 children with peanut allergy aged 1–10 years at recruitment.

Intervention A daily dose of probiotic *Lactobacillus rhamnosus* CGMCC 1.3724 (NCC4007) and peanut oral immunotherapy administered for 1.5 years.

Main outcomes measures Costs were considered from a healthcare system perspective and included costs of treatment delivery and adverse events. Effectiveness outcomes included rate of sustained unresponsiveness (SU) and quality-adjusted life years (QALYs). The cost-effectiveness of PPOIT versus placebo was analysed using patient-level data. Time horizon was 10 years from commencement of PPOIT treatment, comprising 1.5 years of treatment (actual data), 4 years of post-treatment follow-up (actual data), and 4.5 years of extrapolation thereafter (modelling).

Results Healthcare cost per patient over 10 years was higher for PPOIT compared with placebo ($A9355 vs $A1031, p<0.001). Over half of the per patient healthcare cost (53%) in the PPOIT group was attributable to treatment delivery, while the remaining cost was attributable to adverse events. Both measures of effectiveness were superior in the PPOIT group: the average SU rate over 10 years was 54% for PPOIT versus 6% for placebo (p<0.001); QALYs over 10 years were 9.05 for PPOIT versus 8.63 for placebo (p<0.001). Overall, cost per year of SU achieved was $A1694 (range $A1678, $A1709) for PPOIT compared with placebo, and cost per additional QALY gained was $A19 386 (range $A19 024, $A19 774).

Conclusions Cost per QALY gained using PPOIT compared with no treatment is approximately $A20 000 (£10 000) and is well below the conventional value judgement threshold of $A50 000 (£25 000) per QALY gained, thus deemed good value for money ($A1= £0.5 approximately).

Trial registration number Australian New Zealand Clinical Trials Registry ACTRN12608000594325; Post-results.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is the first to conduct a trial-based economic evaluation of an oral immunotherapy with the goal of inducing sustained unresponsiveness of peanut allergy in children.
⇒ The cost of probiotic adjuvant with peanut oral immunotherapy (PPOIT), including both the treatment cost and cost associated with adverse events, was estimated using microcosting and trial and follow-up observations.
⇒ The clinical trial and follow-up data on health-related quality-of-life generated direct evidence on the benefits perceived by patients and parents, which was used in making value judgement in conjunction with cost.
⇒ Treatment cost was microcosted based on the study protocol adjusted for trial staff feedbacks and practicality, and thus was not actual use of healthcare resources if PPOIT were the standard care.
⇒ The study did not consider family burdens such as grocery costs, school or job-related opportunity costs, and we hypothesise that including these costs may further favour PPOIT given that it is superior in the remission outcome compared with no treatment.

INTRODUCTION

Prevalence of peanut allergy has been increasing in the past two to three decades,[1] with approximately 1.4%–4.5% of children and adolescents affected in developed countries using stringent diagnostic criteria.[2–5] In the absence of a cure, management centres on allergen avoidance and treating acute reactions following accidental exposure.

Accidental reactions are common, although most are mild and fatality is rare.[6–8] The constant vigilance and lifestyle restrictions together with the unpredictability of reactions cause psychological distress and lead to reduced quality of life for children and their families. Interest in potential treatments is therefore intense.

Current peanut oral immunotherapy (OIT) regimens, including the first Food and Drug Administration (FDA) approved treatment Palforzia, can achieve desensitisation but leads to increased reactions including anaphylaxis compared with placebo.[9–12] Desensitisation refers to a temporary increase in reaction threshold that provides protection against accidental peanut ingestion[13 14]; however, patients should continue to avoid peanut and remain on indefinite daily treatment which can continue to cause reactions.[15] Furthermore, indefinite maintenance therapy raises concerns regarding long-term adherence to treatment, particularly during adolescence and young adulthood.[9 15] Consequently and despite the FDA approval, the US Institute of Clinical and Economic Review concluded based on the cost-effectiveness evidence that Palforzia may not provide greater benefit than current standard care due to associated adverse events, and there is the considerable uncertainty surrounding patient quality-of-life improvement.[9] In Australia, the Australasian Society of Clinical Immunology and Allergy also believed that OIT is not ready for routine clinical care.[16] Nevertheless and in the UK, on 2 February 2022, the National Institute for Health and Care Excellence (NICE) recommended Palforzia as an option for inducing desensitisation in children and young people in its technology appraisal guidance TA769,[17] believing that the likely cost-effectiveness estimates are within the range NICE considered acceptable of use of National Health Service resources. Further evidence on the cost-effectiveness of OIT for peanut allergy is urgently needed.

Addition of adjuvants such as immune response modifiers has been suggested to improve the effectiveness and/or safety of OIT.[18] Combined probiotic and peanut oral immunotherapy (PPOIT) was shown in a landmark clinical trial to be effective at inducing sustained unresponsiveness (SU).[19 20] SU (also known as clinical remission) refers to the lack of clinical reactivity that persists after treatment has been stopped for a period of time, allowing patients to stop treatment and introduce peanut into their diet ad libitum.[13 14] SU may offer lasting protection, although 'relapse' can occur. Importantly, children who achieved SU were shown to have fewer reactions and greater quality-of-life than children who were desensitised requiring indefinite maintenance[19 21]; however, whether its overall benefits outweigh the potential risks is unknown.

In this study, we investigated the cost-effectiveness of PPOIT—a treatment aiming to induce SU—compared with placebo, taking into consideration the healthcare cost associated with the delivery of the PPOIT treatment and adverse events. No previous trial-based economic evaluation of PPOIT or other oral immunotherapies that were aiming to induce SU of peanut was available, only one model-based economic evaluation comparing PPOIT with simple avoidance using synthetic evidence.[22 23]

METHODS

Data

This economic evaluation was conducted alongside the PPOIT-001 double-blind, placebo-controlled randomised trial,[20] and aimed to compare the cost-effectiveness of PPOIT versus placebo (no treatment) in children with peanut allergy (Australian New Zealand Clinical Trials Registry ACTRN12608000594325). Details of the trial and long-term follow-up were reported previously.[20 24] Briefly, 62 children aged 1–10 years with peanut allergy were recruited between December 2008 and March 2011 at the Royal Children's Hospital, Melbourne, Australia. The PPOIT intervention was a daily dose of probiotic *Lactobacillus rhamnosus* CGMCC (Chinese General Microbiological Culture Collection) 1.3724 (NCC4007) and a daily dose of peanut OIT administered for 18 months. The peanut OIT schedule comprised a 1-day rush induction phase (1 clinic visit of approximately 8 hours), an 8-month build-up phase (16 clinic visits of approximately 2.5 hours per visit), and a 10-month maintenance phase (1 clinic visit of 0.75 hours every 3 months). The placebo group received products that looked, smelled and tasted similar to the respective active treatments however contain no active treatment. At 18 months (1.5 years from commencing treatment), desensitisation was tested via double-blind, placebo-controlled food challenge. Participants who passed the desensitisation challenge were assessed for SU 2–6 weeks post-treatment via a subsequent double-blind, placebo-controlled food challenge. Participants who achieved SU of peanut allergy were advised to incorporate peanut into the diet freely, while those who did not achieve SU continue with strict peanut avoidance.

Participants who completed the parent trial (n=56) were eligible for follow-up at 4 years post treatment.[24] Six patients (3 PPOIT, 3 placebo) withdrew from the parent trial, and 48 (86%) of the 56 eligible participants enrolled in the follow-up study with information on peanut intake and reactions collected and persistence of SU assessed via a double-blind, placebo-controlled food challenge after 8 weeks peanut elimination.

Analysis

The cost-effectiveness analysis was conducted from a healthcare sector perspective, whereby the healthcare costs of treatment delivery and adverse events were considered. The effectiveness outcomes were SU rate and quality-adjusted life years (QALYs). We adopted a time horizon of 10 years, which included a period of 1.5 years of treatment, 4 years of post-treatment follow-up, and 4.5 years of extrapolation thereafter. A total of 56 participants who had food challenge assessment outcomes at the end of the trial were included.

Within the trial and follow-up (5.5 years)

The healthcare cost of delivering the PPOIT treatment was microcosted and included five chronological treatment phases: peanut allergy screening, rush phase, build up phase, maintenance phase and food challenge assessments for desensitisation and SU. Medical staff time required during each of the five phases was estimated based on the trial records and the treatment protocol, adjusted as if PPOIT were to be rolled out as standard care so that the economic evaluation results are more relevant in informing decision-making (online supplemental eMethod and eTable 1(a)). Two open food challenge visits were included in costing in this economic evaluation, one to assess desensitisation and the other SU. This differed from the trial where four food challenges were conducted due to the double-blind, placebo-controlled setting. Staff time, pathology tests, medical and pharmaceutical supplies were converted to dollar using the corresponding unit costs, wage rates and on-costs sourced from published standards (online supplemental eTable 1(b)). For participants who withdrew yet received some treatment (n=6), the incurred treatment costs were summed, divided by the number of participants who completed the trial and added to the per patient treatment cost. Number of participants stayed involved at each treatment phase was summarised in (online supplemental eTable (c)).

Healthcare costs for adverse events including those that are treatment-related, other allergic actions and non-allergic events were all included and estimated using study records. Adverse events during the 1.5 years of treatment were costed as per study record. At the 4 years post-treatment follow-up visit, adverse events were self-reported (recall period was 4 years for events related to peanut allergy; 6 months for other events including asthma). Care use and adverse events over the 6-month recall period were multiplied by eight to approximate service use over the 4 years follow-up period. Patient reported medication use such as over-the-counter antihistamine was costed using the cost of a complete package regardless of the actual dose. For medications where a prescription would be required, the cost of a general practitioner visit was added. Emergency department visit was costed by applying relevant unit costs to non-admitted and admitted emergency department stays. Costs of hospital inpatient admissions were estimated matching the primary diagnosis with the Australian Refined Diagnosis Related Groups code, attaching the corresponding national average cost. Unit costs attached to adverse events are summarised in (online supplemental eTable 2).

SU was the primary clinical outcome and was measured at 2–6 weeks and 4 years post treatment. The rates of SU in the intervening years were estimated using linear interpolation as demonstrated in figure 1. The QALYs were estimated using the Food Allergy Quality of Life Questionnaire-Parent Form collected at four time points (end of treatment, 3 months post treatment, 1 year post treatment and 4 years post treatment) and mapped to the

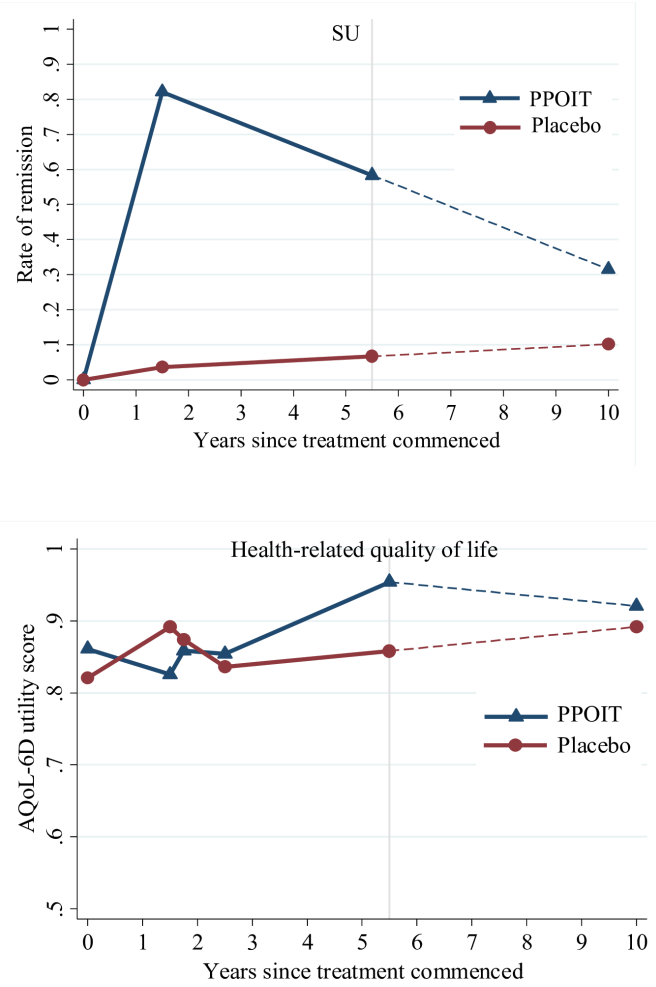

Figure 1 SU and health-related quality-of-life outcomes over the 10-year time horizon. Dashed lines represented the period where extrapolation was applied. AQoL-6D, Assessment of Quality-of-life-6D; PPOIT, combined probiotic and peanut oral immunotherapy; SU, sustained unresponsiveness.

Assessment of Quality-of-life-6D utility scores, then multiplied by the duration of life years.

For participants who had results at the end of the trial but not at the 4-year post-treatment follow-up, we assume that their costs and effectiveness outcomes would follow a pattern similar to patients with observations available within each treatment arm as the characteristics of these patients were shown to be comparable previously.[24] A random draw from the observed cost and outcome distributions within each arm was used to fill in the missing observations to preserve maximum uncertainty. A sensitivity analysis was conducted excluding participants with no 4-year post-treatment follow-up data available (n=8).

Extrapolation beyond trial follow-up (4.5 years)

A direct extrapolation of 4.5 years was included given the substantial differences observed between the two treatment groups at the last available follow-up (figure 1), as these differences are unlikely to converge immediately after the final follow-up. The extrapolation period

of 4.5 years was chosen because this timeframe allows the observed differences between groups to converge, leaving any further extrapolation beyond this timeframe unimportant.

In terms of outcomes, we assumed that the proportion of patients who achieved SU would rise at the same rate as the trend observed during the 4-year post-treatment follow-up for the placebo group (figure 1). Similarly, health-related quality-of-life for the placebo group was assumed to rise following the previously observed trend. For the PPOIT group, we assumed that the proportion of patients with SU would continue to fall as seen during follow-up (figure 1). Health-related quality-of-life was assumed to drop which is against the observed trend; this assumption is conservative and is made so that the two groups would have converged quality of life given the possible adaptions to health states, or regression to the mean. For simplicity, the speed at which quality-of-life drops for the PPOIT group was assumed to be the same as the speed at which quality-of-life increases for the placebo group. For both SU and quality-of-life outcomes, variations around the means were assumed to be the same as what was observed during the 4-year post-treatment follow-up.

In terms of cost, total healthcare costs of adverse events over the extrapolation period were assumed to follow the same mean and distribution as was seen over the 4-year post-treatment follow-up, and a random draw from the observed distributions of costs was used for individual patients to preserve the uncertainties.

Cost-effectiveness and uncertainty

The incremental cost-effectiveness ratio, defined as the difference in cost (PPOIT vs placebo) divided by the difference in effectiveness (PPOIT vs placebo), was calculated and presented as the cost per year of SU achieved, and cost per additional QALY gained, respectively. Uncertainty around the cost-effectiveness ratio was estimated using probabilistic sensitivity analysis of 5000 simulations, and the range of the simulations was reported. One-way sensitivity analysis was performed to test the methodological assumptions and sampling variability for each of the following independent scenarios, presented using a tornado graph: (1) exclusion of adverse events that are highly unlikely to be related to peanut allergy such as dental surgeries and bone and joint injuries; (2) doubling of the cost of the PPOIT product (total treatment cost thus $A6096); (3) applying a discount rate of 3.5% for all costs and outcomes beyond the treatment period of 1.5 years to account for time preference; (4) including only participants who completed both the trial and 4 years post-treatment follow-up (n=48); (5) treating adverse events reported for the past 6 months at the last follow-up as for the past 12 months to counter for potential recall bias due to telescoping (pulling in important events that fall outside the recall period[25]); and (6) dropping adverse events that are specifically related to asthma occurring beyond the 1.5-year treatment period. We also tested our results adding extra family cost of restricting diet, assuming that children who did not achieve SU would require an additional food cost of $A3000 per year based on a previous Canadian study.[26]

All costs were presented in 2020 Australian dollars (A$) prices ($A1= £0.5 approximately, based on the 2020 Purchasing Power Parity published by the Organisation for Economic Co-operation and Development Statistics). Analyses were conducted and reported as per established guidelines.[27–29] The Stata statistical software package (V.14.0) was used. Patient written consent was provided at recruitment.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

There were no statistically significant differences in the baseline characteristics between the two groups at trial entry (table 1). Cost of treatment over the 1.5-year treatment period was $A4972, of which 71% ($A3543) was attributable to medical staff time, 23% for PPOIT product and 6% for pathology tests. During the treatment period, healthcare costs associated with adverse events were higher for the PPOIT group; however, the difference was not statistically significant.

Cost of adverse events during the 4-year post-treatment follow-up was higher for the PPOIT group compared with placebo ($A1739 vs $A169, p<0.001). The difference was primarily driven by asthma events. Patients in the PPOIT arm had statistically significantly higher SU rates and health-related quality-of-life at the 4-year post-treatment follow-up. The extrapolated cost and effectiveness outcomes beyond follow-up were also summarised in table 1.

The cost-effectiveness outcomes over the time horizon of 10 years are summarised in table 2. Overall, PPOIT is more costly and more effective. The incremental cost per QALY gained of $A19 327 (range $A19 024–19 774 thus approximately $A20 000) for PPOIT compared with placebo is well below the conventional value judgement threshold for funding which may be as high as $A50 000 (£25 000) per QALY gained in Australia.

One-way sensitivity analysis (figure 2) suggested that the results are most sensitive to how asthma events post-treatment were handled; however, our conclusion remains under different scenarios. PPOIT appeared to be slightly more expensive when a conventional discounting rate of 3.5% was applied, which is as expected as treatment cost occurred upfront and made up over half of all healthcare costs over the 10-year period. When adding family burden of food cost for children who did not achieve SU, PPOIT is cheaper and more effective thus the dominant strategy. This is as expected as children in the PPOIT group have higher SU rates (the cost effectiveness ratio is negative

Table 1 Patients characteristics, costs and outcomes

Characteristics	PPOIT (n=28)	Placebo (n=28)	Difference	P value
At trial entry				
Age in years, mean (SD)	6.0 (2.6)	5.8 (2.8)	0.3	0.70
Females, % (n)	36% (10)	32% (9)	4%	0.78
History of doctor-diagnosed asthma (ever), % (n)	57% (16)	50% (14)	7%	0.59
Costs, A$ ($A1=£0.5 approximately)				
Costs, 1.5 years of treatment				
Treatment cost	4972	0	4972	–
Doctor	2442	0	2442	–
Nurse	1101	0	1101	–
PPOIT	1124	0	1124	–
Pathology tests and epinephrine autoinjector	305	0	305	–
Adverse events, mean (SD)	905 (656)	719 (528)	186	0.25
Cost, 4 years of post-treatment follow-up				
Adverse events, mean (SD)	1739 (672)	169 (141)	1570	<0.001
Peanut allergy events	4 (21)	35 (128)	–31	0.20
Asthma events*	1735 (674)	133 (29)	1602	<0.001
Cost, post follow-up over 4.5 years (extrapolation)†				
Adverse events, mean (SD)	1739 (672)	169 (141)	1570	–
Outcomes, mean (SD)				
SU rate, end of 1.5 years of treatment	0.82 (0.39)	0.04 (0.19)	0.79	<0.001
SU rate, 4-year post-treatment follow-up	0.58 (0.51)	0.07 (0.26)	0.52	0.002
SU rate, end of 10 years (extrapolation)‡	0.32 (0.51)	0.10 (0.26)	0.21	–
AQoL-6D, baseline	0.86 (0.09)	0.82 (0.11)	0.04	0.19
AQoL-6D, end of 1.5 years of treatment	0.83 (0.10)	0.89 (0.10)	–0.07	0.022
AQoL-6D, 0.25-year post-treatment follow-up	0.86 (0.12)	0.87 (0.11)	–0.02	0.66
AQoL-6D, 1-year post treatment follow-up	0.85 (0.09)	0.84 (0.14)	0.02	0.65
AQoL-6D, 4-year post-treatment follow-up	0.95 (0.04)	0.86 (0.13)	0.10	0.004
AQoL-6D, end of 10 years (extrapolation)‡	0.92 (0.04)	0.89 (0.13)	0.03	–

Student's t-test for continuous outcomes and χ^2 tests for dichotomous outcomes were used.
*Last available follow-up survey was used whereas the recall period was 6 months. The estimated cost for 6 months was multiplied by 8 to approximate the cost over the 4 years post treatment.
†Assumed to follow the same pattern as seen for the 4 years post treatment.
‡Mean values were estimated using assumed trends while SD were assumed to be the same as the previous observable point.
AQoL-6D, Assessment of Quality-of-life-6D.

thus not presented in figure 2 given it is uninterpretable). When the additional family burden of extra food cost is half of what was reported in the literature thus $A1500 per year, the total cost of PPOIT is the same compared with no treatment while the PPOIT group have higher SU rates and better quality-of-life outcomes.

DISCUSSION

Using data collected alongside a clinical trial evaluating a limited course of treatment for children with peanut allergy, this study found that cost per QALY gained is approximately $A20 000 (£10 000) comparing PPOIT with no treatment. The estimated cost to achieve one additional QALY is thus well below the conventional value judgement threshold of $A50 000 (£25 000) per QALY gained, suggesting that PPOIT is very good value for money. We estimated that just over half (53%) of the total healthcare cost was attributable to treatment delivery, while adverse events accounted for the remaining half. This deviates from the previous opinion that adverse events may be the most important cost driver for peanut OIT treatments.[9] This may be due to that the addition of a probiotic to the OIT treatment is associated with fewer adverse events, or that the cost of delivering the treatments is not as negligible as people thought.[19] We estimated that one full course of PPOIT treatment

Table 2 Cost-effectiveness outcomes for a time horizon of 10 years

	PPOIT	Placebo	Difference, P value or range
Cost, A$ ($A1= £0.5 approximately)	9355	1031	8324, p<0.001
Treatment	4972	0	4972, p<0.001
Adverse events	4383	1031	3352, p<0.001
Outcome			
Average SU rate per year	54%	6%	48%, p<0.001
Average QALYs per year	0.905	0.863	0.042, p<0.001
Cost-effectiveness*			
Incremental cost per year of SU achieved	–	–	$A1694 (range $A1678, $A1709) Or £847 (range £839, £855)
Incremental cost per QALY gained	–	–	$A19 386 (range $A19 024, $A19 774) Or £9693 (range £9512, £9887)

*Cost-effectiveness ratios and ranges were produced using simulation.

costs approximately $A5000 which includes medical staff time and PPOIT product. This is comparable to a 1-year treatment cost assumed by the US Institute of Clinical and Economic Review for two peanut allergy treatments which are Palforzia and Viaskin (US$4200 and US$6500, respectively)[9]; however, the two treatments may involve indefinite maintenance dosing. The observed QALY gains comparing PPOIT with placebo are reassuring, implicating not only the improved patient quality of life but also the relatively mild impact of the adverse events. Cost per year of SU achieved using PPOIT was estimated to be $A1694. This may be acceptable even if required as out-of-pocket costs for certain families, as a previous US study reported that caregiver willingness-to-pay for food allergy treatment was on average around US$3504 per year per child.[30] Note that willingness-to-pay values may vary between countries due to a range of factors, and there is currently no available evidence from Australia.

Our results are based on a trial comparing PPOIT with placebo (no treatment), where no treatment or peanut avoidance is the standard care in Australia thus the most appropriate comparator when evaluating the new

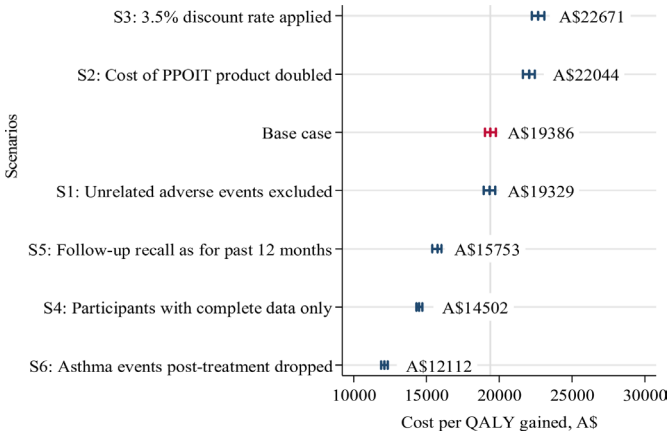

Figure 2 One-way sensitivity analyses. Cost-effectiveness ratio and range are shown. PPOIT, combined probiotic and peanut oral immunotherapy; QALY, quality-adjusted life year.

treatment PPOIT.[27] Although it is beyond the scope of this study to judge how PPOIT would compare with the standard peanut OIT (ie, with no probiotic), a recent trial showed that PPOIT had similar SU rate compared with standard OIT in the short run but was associated with fewer gastrointestinal events.[19] The results of this study thus may be relevant for both OIT and PPOIT given the similar primary clinical outcome and we hypothesise that PPOIT may be slightly better due to the reduced minor adverse events.

Several limitations were identified. Adverse events during the 4 years post-treatment follow-up were costed based on the final follow-up survey whereas participants were asked to report asthma events for the previous 6 months and peanut allergy events for the past 4 years. Based on the survey data collected, we found that the PPOIT group had higher adverse event cost but this is solely due to asthma-related healthcare use instead of peanut allergy. An examination of the asthma events over the 6-month survey period revealed that there were three cases of hospitalisation due to asthma ($A1807 per admission), all reported by participants in the PPOIT group. The remaining asthma events all cost less than $A100. We are uncertain if the three asthma hospitalisations in the PPOIT group are due to the treatment or chance. Speculating on the basis of three observations is not practical. Nevertheless, the numbers of children with doctor-diagnosed asthma at baseline and trial completion were similar comparing the two treatment groups, and we are unable to make further inference. We have extrapolated conservatively and assumed all benefit of PPOIT would disappear over time. This includes the assumption that health-related quality of life would continue to rise for the placebo group and drop for the PPOIT group given the possible adaptation. This is more conservative compared with existing studies including the economic evaluation evidence of Palforzia made available by NICE[17] and as a result we may have underestimated the value of PPOIT. This is because while people may revise rating of quality

of life after adapting to the condition, this does not imply that they are unwilling to pay for treatments that could potentially improve their condition.

CONCLUSIONS

In conclusion, PPOIT appears cost-effective for children with peanut allergy compared with placebo (no treatment). Our findings provide evidence for stakeholders and policy-makers to consider PPOIT as a limited-course treatment for peanut allergy.

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Contributors LH designed the study, participated in data cleaning, analysis and interpretation, and drafted the manuscript. KD and MT conceptualised and designed the study, participated in data acquisition and interpretation, critically reviewed and revised the manuscript. ML designed the study, participated in data acquisition and interpretation, critically reviewed and revised the manuscript. PL and ACL participated in data acquisition and interpretation, critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. MT accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests MT holds shares/share options in Prota Therapeutics, is an inventor on patents owned by Murdoch Children's Research Institute related to food immunotherapy and has received grant funding from the NHMRC (Australia), Prota Therapeutics and the Allergy Immunology Foundation Australia (AIFA).

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained from parent(s)/guardian(s)

Ethics approval The economic evaluation was approved by the Royal Children's Hospital Human Research and Ethics Committee (HREC 27086U), Melbourne, Australia. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Not applicable. Data required to reproduce the base case analysis results of this study are reported in the manuscript and the supplement.

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