

A novel patient-reported outcomes instrument assessing the side effects of peanut oral immunotherapy

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ARTICLE INFO

Article history:

Received for publication May 14, 2020.

Received in revised form July 16, 2020.

Accepted for publication July 24, 2020.

ABSTRACT

Background: Patients treated with peanut oral immunotherapy (OIT) may experience adverse reactions, particularly during up-dosing.

Objective: To develop the Side Effects of Peanut Oral Immunotherapy Diary (SEPOD), an electronic questionnaire assessing the daily side effects of peanut OIT in clinical trials.

Methods: Content and design of the SEPOD were informed by empirical literature review and meetings with 3 allergy-immunology experts. Interviews to confirm content and inform revisions were conducted in 24 pediatric patients with peanut allergy (14 treated with peanut OIT) aged 6 to 17 years; children aged 6 to 11 years were interviewed with their caregiver.

Results: The SEPOD was drafted after literature review and expert interviews; the initial measurement approach comprised 2 SEPOD versions, a patient-reported outcome (PRO) version for children aged 12 to 17 years, and a caregiver-administered PRO version for children aged 6 to 11 years with instructions for caregiver questionnaire administration. Pediatric patients were expected to respond independently on both versions. Patient interviews indicated that some younger children (ie, aged 6–8 years) had difficulty understanding questions, even when reading aloud; therefore, a caregiver-administered outcome version, identical in content to the caregiver-administered PRO version, was developed for this age group. The final electronic SEPOD covered 23 peanut OIT side effects within the following 7 domains: gastrointestinal, dermatologic, itching, nasal, and respiratory, swelling (eyelid or periorbital, lip, tongue, and throat), pain (tongue, mouth, and throat), and dizziness.

Conclusion: This study yielded the SEPOD, a new clinical outcome assessment instrument with various methods of administration that can be used to assess the side effects of peanut OIT experienced by pediatric patients in a clinical trial setting.

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Introduction

Food allergy is a condition of substantial public health concern that can manifest through various symptoms, ranging from mild skin reactions to potentially life-threatening anaphylaxis.¹ The lifetime self-reported prevalence of allergy to common foods in the overall

population is approximately 6% to 10%,^{2,3} with parent-reported prevalence ranging from 8%^{4,5} to greater than 11%⁴ in the pediatric population. Peanut allergy is the most common type of food allergy in children, with an estimated prevalence between 2% to 5% among pediatric populations in Western countries,^{1,4,6} and the prevalence is

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Disclosures: Dr Nadeau reports receiving grants from the National Institute of Allergy and Infectious Diseases, Food Allergy Research and Education, and End Allergies Together; personal fees from Regeneron Pharmaceuticals, Inc; research sponsorship from Novartis (data and safety monitoring board member), Sanofi,

Astellas Pharmaceuticals, Inc, and Nestlé; is the cofounder of Before Brands, Inc, Alladapt, and Fortra; and was involved in clinical trials with Genentech, Aimmune Therapeutics, and DBV Technologies.

Funding: This study was sponsored by Regeneron Pharmaceuticals, Inc, according to Good Publication Practice guidelines (<http://www.ismpp.org/gpp3>).

<https://doi.org/10.1016/j.anai.2020.07.027>

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estimated to be increasing.^{4,7} Estimated prevalence has increased by 1.2% (± 0.4) per decade in the United States.⁸ Peanut allergy is also responsible for the largest proportion of fatal food-induced anaphylactic reactions in children.⁹

Oral immunotherapy (OIT) is an investigational treatment for peanut allergy that induces desensitization to the allergen over time through daily controlled allergen exposure, thereby increasing the threshold for allergen exposure and subsequently reducing the risk of serious allergic reactions to accidental exposure.^{10,11} In randomized controlled trials (RCTs) of peanut OIT, OIT resulted in increased tolerability to peanut protein and lower symptom severity related to peanut exposure vs placebo among children and adolescents who were highly allergic to peanut.^{12,13} Although peanut OIT side effects, including the increased possibility of reacting to previously tolerated OIT doses,¹⁴ occur most frequently when patients first begin the desensitization process and become less frequent as treatment continues,¹⁵ they may affect treatment persistence and adherence. During the up-dosing phase of the Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization (PALISADE) phase 3 RCT of Palforzia, 53.8% and 2.5% of patients in the treatment arm experienced moderate or severe adverse events, respectively, vs 30.9% and 0.8% of patients in the placebo arm. In addition, withdrawals from the study owing to adverse events were more common in the treatment than the placebo group (11.6% vs 2.4%, respectively), as was the overall study withdrawal rate (21.0% vs 7.3%, respectively).

If patients do not fully adhere to OIT, desensitization will either not occur or will be reduced, which could also lead to a serious allergic reaction to the therapy itself.¹⁶ Therefore, whereas the side effects of daily peanut OIT should be carefully measured and tracked in RCTs, no fit-for-purpose measures existed to assess these outcomes as reported by patients enrolled in the OIT clinical trials. Indeed, such data are necessary for regulatory evaluation¹⁷ and for clinicians to understand the benefits of treatment compared with the risks.^{18,19} Therefore, evaluating such OIT side effects by means of a valid and reliable measure, in addition to physician-reported data and laboratory parameters, is essential for drawing comprehensive conclusions regarding OIT efficacy and safety.

This article describes the development of the Side Effects of Peanut OIT Diary (SEPOD), a clinical outcome assessment (COA) instrument designed to assess daily side effects of peanut OIT among pediatric patients (aged 6–17 years).

Methods

Development of the SEPOD followed regulatory guidelines¹⁷ and scientific best practices,^{20,21} and was conducted in the following stages: (1) targeted literature review; (2) expert advice meetings (EAMs); (3) concept selection and questionnaire construction; (4) hybrid patient interviews consisting of concept elicitation and cognitive debriefing (with refinement after each wave of interviews); and (5) questionnaire finalization.

Literature Review

The objectives of the empirical literature review were as follows: (1) to identify and describe the existing COAs used to measure the side effects of peanut OIT; and (2) to identify, describe, and substantiate the side effects of peanut OIT that are most important and relevant to pediatric patients (aged 6–17 years). The review was limited to peer-reviewed English language articles published between 2008 and 2018 that described studies in human participants. MEDLINE, Embase, and PsycINFO database searches using the OvidSP platform, in addition to a gray literature search, were conducted to identify potentially relevant articles. Principal investigators of peanut OIT trials were also contacted to identify any COAs used to measure the side effects.

Abstracts were reviewed to identify the relevant COA instruments or whether they reported symptoms of peanut OIT in pediatric patients. Each identified instrument was reviewed, and tables were developed to describe each instrument. Articles were selected for full-text review if they focused primarily on the side effects of peanut OIT among children aged 6 to 17 years. Side-effect concepts were extracted, and a preliminary conceptual model was developed to depict the relevant side effects associated with peanut OIT.

Expert Advice Meetings

The objectives of the EAMs were to identify, describe, and substantiate the side effects of peanut OIT that are most important and relevant to pediatric patients (aged 6–17 years) from the perspective of therapeutic area experts. Each EAM was 60 minutes in length and moderated by 2 trained researchers using a semi-structured EAM guide. The experts were asked questions to spontaneously elicit the important and relevant side effects of peanut OIT treatment for pediatric and adolescent patients and were asked about the words that patients use when describing their treatment-related experiences. Experts were also asked whether they were aware of any existing instruments that could be used to measure the side effects of peanut OIT. Each interview was audio-recorded, after obtaining verbal consent, and then transcribed, coded, and analyzed using a combination of quantitative and qualitative data analytical methods.

To assess the relevance of the side effects of the peanut OIT from the perspective of the experts, concept frequency was evaluated by counting the number of experts reporting a concept at least once during their meeting. In addition to the frequency of the report, the most salient features of each concept, as reported by the experts (eg, time of onset, duration, location) and whether the concept was considered to be “most bothersome” and important by experts, were recorded. The conceptual model of peanut OIT side effects was further refined based on the information obtained through these EAMs.

Concept Selection and SEPOD Construction

The selection of the key OIT side-effect concepts for the SEPOD was conducted on the basis of the analyses of the findings from the literature review and EAMs through collaborative efforts among the co-authors. In total, 20 side-effect concepts were selected for inclusion in the first draft of the SEPOD, including concepts related to itching ($n = 5$), nasal and respiratory functioning ($n = 5$), gastrointestinal (GI) issues ($n = 4$), swelling ($n = 3$), dermatologic issues ($n = 2$), and dizziness ($n = 1$). Instructions, questions, and response options were drafted based on these concepts. Because the SEPOD was intended to be administered daily as an e-diary, the content was programmed for electronic administration.

The following 2 versions of the SEPOD were developed: (1) a self-administered, patient-reported outcome (PRO) version for patients aged 12 to 17 years; and (2) a caregiver-administered PRO (CarePRO) version for patients aged 6 to 11 years (including instructions to the caregiver for questionnaire administration and scripted text to be read verbatim to the child, which was intended for the child to select responses to questions independently). Other than the caregiver instructions, the PRO, and CarePRO content was identical.

Each day the SEPOD is administered and the participants are asked to provide the time the patient took peanut OIT. The diary then prompts the participant to answer questions about the presence, severity, and duration of side effects experienced by the patient 2 hours after the reported ingestion time. The next day, before peanut OIT ingestion, the SEPOD collects information on side effects that did not resolve at the time of the previous day's e-diary entry and any newly occurring GI side effects (ie, that began after the completion of the previous day's e-diary entry).

Table 1
Study Inclusion Criteria

The patient has a clinical history of allergy to peanuts, including a documented sensitivity to peanut allergen (ie, positive skin prick test, or positive in vitro serum IgE).
The patient is currently treated with peanut OIT or was treated with peanut OIT within the previous 6 months (wave 1 only).
The patient is able to speak and comprehend English fluently.
The patient does not have a condition other than peanut allergy that could cause peanut allergy-like symptoms (eg, itchy skin or hives, itching or tingling sensation in or around the mouth or throat, nausea, anaphylaxis).
The patient does not have a condition or situation (eg, cognitive impairment or disorder, alcohol or drug abuse) that would put the individual at considerable risk, may confound the study results, or may interfere significantly with his or her participation in a 90-minute interview.
The patient is not currently receiving a treatment with dupilumab (Dupixent).

Abbreviations: IgE, immunoglobulin E; OIT, oral immunotherapy.

Concept Elicitation, Cognitive Debriefing, and Device Usability Testing

Given that the study was conducted in support of the Regeneron clinical trial program (NCT036827770) evaluating the efficacy of peanut OIT among patients aged 6 to 17 years,²² the inclusion criteria of this study were matched to the clinical trial population. Interviews with pediatric patients (aged 6–17 years) and their caregivers were conducted with the following objectives: (1) to identify and confirm the important and relevant side-effect concepts from the patient or caregiver's perspective (ie, concept elicitation); (2) to evaluate the respondent's ability to understand and complete the SEPOD (ie, cognitive debriefing); and (3) to test the usability of the SEPOD on an electronic handheld device.

Participant Recruitment

The sample size estimates for patient recruitment were based on the estimates regarding the number of participants needed to achieve saturation (ie, the point at which no new relevant information is gained from the conduct of additional concept elicitation interviews).²³ After institutional review board approval, 2 waves of recruitment were conducted. Targeted recruitment for wave 1 included 15 patients from the Sean N. Parker Center for Allergy Research (Stanford University, Stanford, California), and for wave 2 included 10 patients from the Global Market Research Group (Chicago, Illinois, and St Louis, Missouri).

Potentially eligible participants who met the study inclusion criteria (Table 1) were identified by site staff patients. Potentially eligible patients and their legal guardians were presented with study information through the participant recruitment letter and the patient outreach e-mail. Interested patients were scheduled to visit the clinic

to provide verbal consent (patient) and written informed consent (parent or guardian), complete screening, and enroll in the study.

Face-to-Face Interviews

Face-to-face interviews, approximately 90 minutes in duration, were conducted following a semistructured interview guide and included the following 3 components: concept elicitation, cognitive debriefing, and usability testing. Wave 1 interviews were conducted with pediatric patients treated with peanut OIT to explore and confirm the relevance of the concepts evaluated by the SEPOD, and to evaluate the participant's ability to read (for patients aged ≥ 12 years), understand, and respond to the SEPOD. Usability testing of the SEPOD was also conducted. Wave 2 interviews were conducted with pediatric patients who were diagnosed as having a peanut allergy but not necessarily treated with OIT. The focus of these interviews was to further evaluate the participant's ability to read (for patients aged ≥ 12 years), understand, and respond to the SEPOD. Further usability testing was also conducted during wave 2. The SEPOD content and e-diary interface features were revised to address the issues identified after each wave of interviews.

The caregivers of patients aged 6 to 11 years participated in the interview and administered the CarePRO version to the patient, whereas the caregivers of patients aged 12 to 17 years did not participate in, but could observe, the interview. All interviews were audio-recorded and subsequently transcribed, anonymized, coded, and analyzed using a combination of quantitative and qualitative data analytical methods.

Concept Elicitation (Wave 1 Only)

During concept elicitation, pediatric patients (aged 6–17 years) were asked open-ended and probing questions about their experiences with peanut OIT. The objectives of this research step were threefold. First, the interviews explored and documented the frequency with which pediatric patients who received peanut OIT reported side effects and the features of these concepts. Second, the interviews documented the words and phrases that patients used to describe the side effects of peanut OIT. Finally, the interviews informed the development of a patient-centric peanut OIT conceptual model to characterize the side-effect concepts.

The comprehensiveness of the SEPOD was assessed by evaluating the data provided by participants regarding whether they thought any side-effect concepts were missing from the SEPOD and, if so, which side effects they recommended for inclusion. In addition, data from the wave 1 interviews were used to evaluate the saturation of concept. A saturation grid was prepared, which presents interview transcripts divided into 4 roughly equivalent groups, based on the

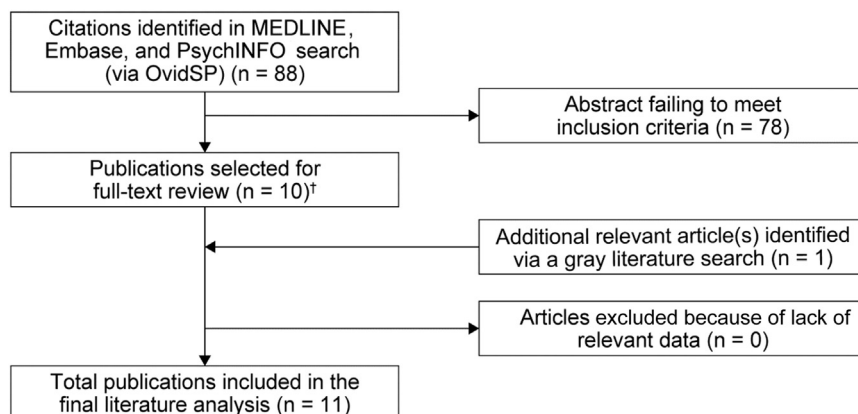


Figure 1. Literature search flow diagram. The dagger indicates abstracts that best met the screening criteria and that presented the strongest likelihood of providing detailed information for full-text review.

Table 2
Peanut OIT Side-Effect Concepts From EAMs and Patient Interviews

Side effect	Peanut OIT side-effect concepts from EAMs (n = 3)			Peanut OIT side-effect concepts from patient interviews (n = 14)		
	Frequency of report, n ^b	Most bothersome side effects of peanut OIT, n ^c	Most important side effects of peanut OIT, n ^d	Frequency of report, n (%) ^a (N = 14)		
				Spontaneous	Probed	Total
Gastrointestinal						
Abdominal pain	3	—	✓	7 (50.0)	4 (28.6)	11 (78.6)
Nausea	2	—	—	3 (21.4)	5 (35.7)	8 (57.1)
Vomiting	3	—	—	3 (21.4)	3 (21.4)	6 (42.9)
Diarrhea	1	—	—	—	2 (14.3)	2 (14.3)
General gastrointestinal symptoms	1	—	—	—	—	—
Respiratory						
Shortness of breath	3	✓	✓	—	—	—
Wheezing	3	—	—	2 (14.3)	3 (21.4)	5 (35.7)
Coughing	2	—	✓	1 (7.1)	3 (21.4)	4 (28.6)
Stuffy or runny nose	2	—	—	1 (7.1)	1 (7.1)	2 (14.3)
Gagging	1	—	—	1 (7.1)	—	1 (7.1)
Difficulty in breathing	—	—	—	4 (28.6)	2 (14.3)	6 (42.9)
Sneezing	1	—	—	—	4 (28.6)	4 (28.6)
Cardiovascular						
Cardiovascular collapse	1	—	—	—	—	—
Hypotension	2	—	—	—	—	—
Hypertension	1	—	—	—	—	—
Feeling faint	1	—	✓	—	—	—
Fainting	1	—	—	—	—	—
Dermatologic						
Hives	3	✓	✓	6 (42.9)	1 (7.1)	7 (50.0)
Skin itching	—	—	—	3 (21.4)	2 (14.3)	5 (35.7)
Rash	2	✓	—	—	1 (7.1)	1 (7.1)
Redness of skin	—	—	—	—	1 (7.1)	1 (7.1)
Skin swelling	—	—	—	—	1 (7.1)	1 (7.1)
Mouth and throat						
Mouth itching	3	✓	✓	3 (21.4)	2 (14.3)	5 (35.7)
Lip itching	2	—	—	2 (14.3)	1 (7.1)	3 (21.4)
Lip swelling	1	—	—	3 (21.4)	1 (7.1)	4 (28.6)
Mouth swelling	—	—	—	—	1 (7.1)	1 (7.1)
Tongue itching	1	—	—	2 (14.3)	1 (7.1)	3 (21.4)
Itchy throat	3	—	—	5 (35.7)	4 (28.6)	9 (64.3)
Throat swelling	—	—	—	3 (21.4)	2 (14.3)	5 (35.7)
Eyes and ears						
Eye itching	2	—	—	2 (14.3)	4 (28.6)	6 (42.9)
Eye swelling	1	—	—	4 (28.6)	—	4 (28.6)
Watery eyes	—	—	—	1 (7.1)	—	1 (7.1)
Ear itching	1	—	—	1 (7.1)	—	1 (7.1)
Ear warmth	1	—	—	—	—	—
Ear swelling	1	—	—	—	—	—
Other						
General anaphylaxis	3	✓	✓	—	—	—
Feeling warm or hot	1	—	—	4 (28.6)	—	4 (28.6)
Full body swelling	1	✓	—	—	—	—
Incontinence	1	—	—	—	—	—
Urgency to void	1	—	—	—	—	—
Uterine contraction	1	—	—	—	—	—

Abbreviations: EAM, expert advice meeting; OIT, oral immunotherapy.

^aThe side effects most frequently reported to be the “most bothersome” by patients when asked during the concept elicitation portion of interviews were difficulty in breathing (n = 3, 21.4%), mouth itching (n = 2, 14.3%), and stomach pain (n = 2, 14.3%). One participant each (7.1%) reported that hives, rash, itchy tongue, lip swelling, and throat swelling were “most bothersome.”

^bNumber of experts who reported the impact.

^cNumber of experts who reported the impact as being important from the expert and patient perspective.

^dExpert's description of the side effect.

order of interviews conducted. The saturation grid documents when a concept was first mentioned during the interviews (eg, as part of group 1, 2, 3, or 4). Saturation was considered to be achieved if a downward trend in the elicitation of new peanut OIT-related side-effect concepts was observed; that is, whether few-to-no new relevant concepts (ie, pertinent to the research question and not idiosyncratic to an individual participant) emerged in the final group.

Cognitive Debriefing (Waves 1 and 2)

During the cognitive debriefing, patients were asked to complete the SEPOD on an electronic handheld device. During the interview, participants were asked to read each instruction and

question aloud, and while doing so, to think aloud and share their interpretation of what the instruction or question content means or is asking them to do. Data from cognitive debriefing were used to evaluate the participant's understanding of the instructions, items, and response options of the SEPOD (and the CarePRO instructions). The instructions, items, and response options of the SEPOD were evaluated to determine whether the participants interpreted them as intended and for clarity and ease of comprehension on first reading. Participants were also asked whether the content of the SEPOD should be revised or rephrased in any way to promote clarity, whether item concepts were experienced by participants or observed by caregivers, and whether any items were redundant.

Table 3
Demographics of Patient Interview Participants

	Overall sample total (N = 24) ^a	Wave 1: peanut OIT total (N = 14) ^a	Wave 2: peanut allergy total (N = 10)
Age (y)			
Range	6.0–17.0	6.0–17.0	6.0–17.0
Mean (SD)	10.2 (3.9)	11.4 (3.8)	8.6 (3.8)
Sex, n (%)			
Female	12 (50.0)	8 (57.1)	4 (40.0)
Male	12 (50.0)	6 (42.9)	6 (60.0)
Race, n (%)			
White	10 (41.7)	6 (42.9)	4 (40.0)
Asian	8 (33.3)	8 (57.1)	0 (0.0)
Black	4 (16.7)	0 (0.0)	4 (40.0)
Hispanic	1 (4.2)	0 (0.0)	1 (10.0)
Puerto Rican	1 (4.2)	0 (0.0)	1 (10.0)

Abbreviation: OIT, oral immunotherapy.

^aAlthough 15 participants were recruited for wave 1, 1 participant was excluded from analysis as English was their second language.

Analysis

Concept elicitation and cognitive debriefing data were coded using Atlas.ti (Atlas.ti Qualitative Data Analysis, Berlin, Germany) and analyzed using descriptive methods. For the concept elicitation data, the frequency with which each participant reported a side-effect concept was tallied. For the cognitive debriefing data, the frequency with which each participant reported issues with, or understanding of, the item content was tallied. The results were summarized in a tabular format.

Results

Literature Review

A total of 11 full-text articles were reviewed (Fig 1), from which 50 side-effect concepts were identified. The following were the most frequent side-effect concepts: (1) hives (n = 9, 81.8%); (2)

Table 4
Saturation Analysis Summary: Side Effects of Peanut Oral Immunotherapy

Concept	Group 1 ^a (~29%) of interviews	Group 2 ^b (~57%) of interviews	Group 3 ^c (~79%) of interviews	Group 4 ^d (~100%) of interviews
Difficulty in breathing	P			
Ear itching		P		
Eye itching	P			
Eye swelling	P			
Feeling hot	P			
Gagging		P		
Hives	P			
Lip itching		P		
Lip swelling	P			
Mouth itching	P			
Nausea	P			
Skin itching	P			
Stomach pain	P			
Stuffy or runny nose		P		
Throat itching	P			
Throat swelling	P			
Tongue itching	P			
Vomiting	P			
Watery eyes	P			
Wheezing		P		

Abbreviation: P, present.

^aParticipants included in Group 1 of interviews were as follows: 01-01, 01-02, 01-03, 01-05.^bParticipants included in Group 2 of interviews were as follows: 01-06, 01-07, 01-08, 01-09.^cParticipants included in Group 3 of interviews were as follows: 01-10, 01-11, 01-12.^dParticipants included in Group 4 of interviews were as follows: 01-13, 01-14, 01-15.

abdominal pain (n = 8, 72.7%); (3) nausea, vomiting, and wheezing (n = 7, 63.6% each); (4) cough, diarrhea, and itchy mouth (n = 6, 54.5% each); (5) anaphylaxis and rash (n = 5, 45.5% each); and (6) nasal congestion and upper respiratory symptoms (n = 4, 36.4% each). A total of 9 COA measures were identified and reviewed, but none evaluated relevant concepts comprehensively or in a way that could quantify treatment benefit in a clinical trial setting.

Expert Advice Meetings

Meetings were conducted with 3 clinical experts, based in Boston, Massachusetts; Houston, Texas; and Stanford, California. Each clinician saw 15 to 100 patients with peanut allergy per month, and all 3 experts worked in an academic medical setting, had practiced medicine for more than 21 years, and specialized in allergy-immunology.

The experts reported 35 side-effect concepts experienced by pediatric patients treated with peanut OIT (Table 2). All 3 experts reported abdominal pain, anaphylaxis, hives, mouth itching, shortness of breath, vomiting, and wheezing as side effects of the peanut OIT experienced by pediatric patients. In addition, 2 experts reported coughing, eye itching, itchy throat, lip itching, hypotension, nausea, rash, and stuffy or runny nose. According to the experts, the most frequent side effects reported by patients were mouth itching (per 3 experts); hives (per 2 experts); and abdominal pain, coughing, or vomiting (per 1 expert). Wheezing was reported by all 3 experts as the most severe among all peanut OIT side effects.

Patient Interviews

Participant Demographics

A total of 25 interviews were conducted across wave 1 (n = 15) and wave 2 (n = 10), but 1 interview from wave 1 was excluded because English was not the primary language of the participant. The mean age (SD) of patients in wave 1, consisting of patients treated with peanut OIT, was 11.4 (±3.8) years; 43% were male, and 43% were White. In wave 2, consisting of patients with peanut allergy, mean age (SD) was 8.6 (±3.8) years; 60% were male, and 40% were White (Table 3).

Concept Elicitation

During wave 1 interviews, 28 peanut OIT side-effect concepts were elicited (Table 2). The most frequently reported concepts were abdominal pain (n = 11/14, 78.6%), throat itching (n = 9/14, 64.3%), nausea (n = 8/14, 57.1%), and hives (n = 7/14, 50.0%). The side effects most frequently reported to be the “most bothersome” were difficulty breathing (n = 3/14, 21.4%), mouth itching (n = 2/14, 14.3%), and stomach pain (n = 2/14, 14.3%). One participant (7.1%) reported that hives, rash, itchy tongue, lip swelling, and throat swelling were “most bothersome.”

All 20 spontaneously elicited peanut OIT side effects were elicited in approximately the first 57% of interviews, indicating achievement of saturation (Table 4). The conceptual model, triangulating findings from the literature review, EAMs, and patient interviews, was then finalized (Fig 2).

Cognitive Debriefing

Cognitive debriefing with patients in wave 1 indicated that caregivers of patients aged 6 to 11 years understood the CarePRO instructions. In addition, patients' understanding of the side-effect concepts in wave 1 was high (>90%), with the exceptions being swelling, runny or stuffy nose, dizziness, and wheezing. In most cases (80%; 16/20), when the concept was not interpreted as intended, the patient was aged 8 years or younger (Table 5). Most participants understood instructions and response options, except for some patients aged 8 years or younger.

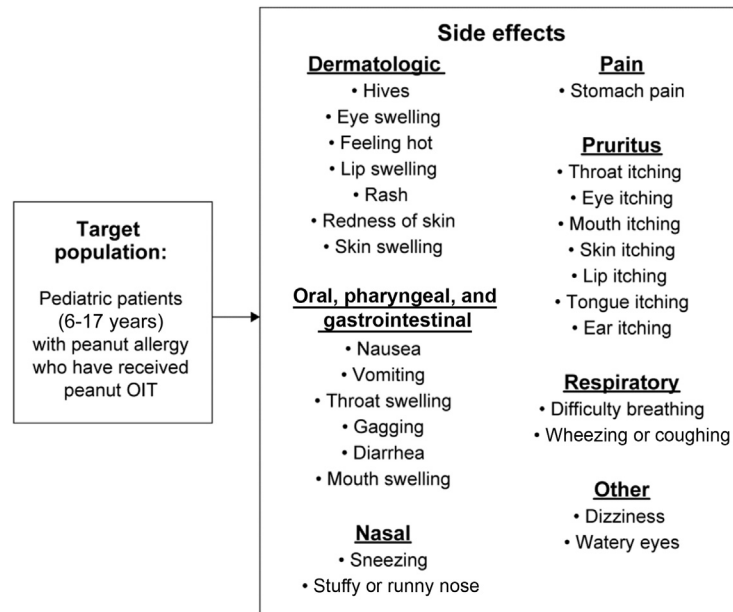


Figure 2. Patient-centric peanut OIT conceptual model. OIT, oral immunotherapy.

Regarding the overall usability of the electronic handheld device, participants (including both patients and caregivers) reported a positive experience in terms of ease of use ($n = 12/13$, 92.31%), acceptability of the device ($n = 9/9$, 100.0%), selecting responses by tapping ($n = 10/12$, 83.3%), and moving from screen to screen ($n = 9/9$, 100.0%). However, some participants reported, and interviewers observed, usability issues related to tapping or scrolling on the screen.

After wave 1, minor revisions were made to simplify some content of the SEPOD to improve understanding of the instructions, side-effect concepts, and response options. Clarifying parenthetical text was added to some side-effect concepts. For example, “lip itching” and “itching in your mouth” were merged, and the text was added to indicate the area of the mouth to which was being referred (ie, “itching in or around your mouth [lips, tongue]”). Furthermore, the order of concepts was revised to minimize

confusion (eg, some participants reported including “nausea” in their assessment of “vomiting;” thus, nausea was indicated before vomiting).

During wave 2, participants were cognitively debriefed on the revised draft SEPOD, and although most patients understood all side-effect concepts, 10% to 20% had difficulty understanding nausea, itching, swelling, and wheezing concepts. All instances of concept misunderstanding ($n = 13$) occurred in patients aged 8 years or younger (Table 6). Similar findings were observed for the cognitive debriefing of the instructions and response options.

Refinement and Finalization of the SEPOD

Based on the findings from cognitive debriefing and input from the United States Food and Drug Administration during the review of the sponsor’s phase 2 study protocol,²⁴ the content and strategy for SEPOD administration were refined and finalized. Based on the

Table 5
Patient Interpretation of the Side-Effect Concepts in Wave 1

Concept	Interpreted as intended, n/N (%) ^a	Patient unfamiliar with the concept, n (%)	Not interpreted as intended, n (%)	Age of respondent who incorrectly interpreted the concept, y
Stomach pain	14/14 (100)	0 (0)	0 (0)	—
Skin itching	14/14 (100)	0 (0)	0 (0)	—
Trouble breathing	14/14 (100)	0 (0)	0 (0)	—
Hives (lumps on skin)	13/14 (92.9)	1 (7.1)	0 (0)	6
Vomiting (throwing up)	13/13 (100)	0 (0)	0 (0)	—
Nausea (feeling like you might throw up)	13/14 (92.9)	1 (7.1)	0 (0)	6
Lip itching	13/13 (100)	0 (0)	0 (0)	—
Itching in your throat	13/14 (92.9)	0 (0)	1 (7.1)	17
Eye itching	13/13 (100)	0 (0)	0 (0)	—
None of these things	13/13 (100)	0 (0)	0 (0)	—
Eye swelling	12/14 (85.7)	2 (14.3)	0 (0)	Both 6 y
Lip swelling	12/14 (85.7)	2 (14.3)	0 (0)	Both 6 y
Swelling in your throat	12/13 (92.3)	0 (0)	1 (7.7)	6
Runny or stuffy nose	12/14 (85.7)	1 (7.1)	1 (7.1)	Both 6 y
Itching in your mouth	12/12 (100)	0 (0)	0 (0)	—
Coughing	12/12 (100)	0 (0)	0 (0)	—
Rash (red, itchy, bumpy skin)	11/12 (91.7)	0 (0)	1 (8.3)	9
Diarrhea (runny, loose poop)	11/12 (91.7)	1 (8.3)	0 (0)	6
Sneezing	11/12 (91.7)	0 (0)	1 (8.3)	6
Dizziness	10/14 (71.4)	3 (21.4)	1 (7.1)	2 aged 6 y, 1 aged 9 y, 1 aged 11 y
Wheezing	9/12 (75.0)	2 (16.7)	1 (8.3)	2 aged 6 y, 1 aged 8 y

^aInterpretation of results presented have been calculated with varied denominators based on the total number of participants who provided responses. In cases in which the denominator is less than 14, data were missing for some participants.

Table 6
Patient Interpretation of Side-Effect Concepts in Wave 2

Concept	Interpreted as intended, n/N (%) ^a	Patient unfamiliar with the term, n (%)	Not interpreted as intended, n (%)	Age of respondent who incorrectly interpreted the concept, y
Rash (red, itchy, bumpy skin)	10/10 (100)	0 (0)	0 (0)	—
Vomiting (throwing up)	10/10 (100)	0 (0)	0 (0)	—
Runny or stuffy nose	10/10 (100)	0 (0)	0 (0)	—
Sneezing	10/10 (100)	0 (0)	0 (0)	—
Skin itching	10/10 (100)	0 (0)	0 (0)	—
Eye itching (itching around the eye or eyelid)	10/10 (100)	0 (0)	0 (0)	—
Coughing	10/10 (100)	0 (0)	0 (0)	—
Dizziness (spinning feeling)	9/9 (100)	0 (0)	0 (0)	—
Hive(s) (lumps on skin)	9/10 (90.0)	1 (10.0)	0 (0)	6
Eye swelling (puffiness around the eye or eyelid)	9/10 (90.0)	1 (10.0)	0 (0)	6
Lip swelling (lip puffiness)	9/10 (90.0)	0 (0)	1 (10.0)	6
Stomach pain (pain in your belly)	9/10 (90.0)	1 (10.0)	0 (0)	6
Trouble breathing	9/9 (100)	0 (0)	0 (0)	—
Nausea (feeling like you might throw up)	8/10 (80.0)	1 (10.0)	1 (10.0)	6, 8
Diarrhea (runny, loose, watery poop)	8/9 (88.9)	1 (11.1)	0 (0)	8
Itching in or around your mouth (lips, tongue)	8/10 (80.0)	1 (10.0)	1 (10.0)	7
Itching in your throat	8/10 (80.0)	2 (20.0)	0 (0)	Both 8 y
Wheezing (noisy, squeaky breathing)	8/10 (80.0)	2 (20.0)	0 (0)	6, 8
Swelling in your throat (throat feeling like it is tight or closing)	5/7 (71.4)	1 (14.3)	1 (14.3)	6
None of these things	7/7 (100)	0 (0)	0 (0)	—

^aResults of interpretation presented have been calculated with varied denominators based on the total number of participants who provided responses. In cases in which the denominator is less than 14, data were missing for some participants.

feedback received from the Food and Drug Administration, the following additional items were included: (1) tongue or mouth pain; (2) throat pain; (3) tongue swelling; and (4) nose itching. The final SEPOD includes 23 peanut OIT side effects as follows: (1) GI (4 items); (2) dermatologic (2 items); (3) itching (5 items); (4) nasal or respiratory (5 items); (5) swelling of the eye, lip, tongue, and throat (4 items); (6) pain on the tongue or mouth and throat (2 items); and (6) dizziness (1 item).

A caregiver-administered outcome (CareO) version of the SEPOD was developed for administration in patients aged 6 to 8 years, which consists of additional caregiver instructions allowing caregiver observer report (if the patient cannot understand or choose an answer on their own) and a question to specify the source of report (child only or child and caregiver; collected for 1 week at baseline, 1 week at the midpoint of the trial, and 1 week at the end of the trial). The PRO, CarePRO, and CareO items are identical, including the expectation that the patient responds independently.

Discussion

The SEPOD, which was developed in accordance with regulatory guidelines¹⁷ and scientific best practices,²⁰ is a new questionnaire that can be used to assess daily allergic side effects of peanut OIT among pediatric patients (aged 6–17 years) in a clinical trial setting. The instrument development process comprised a literature review and meetings with experts to develop a conceptual model and draft questionnaire followed by hybrid qualitative interviews with pediatric patients and caregivers to carry out concept elicitation, cognitive debriefing, and device usability testing. The final electronic SEPOD measures 23 peanut OIT side effects covering GI, dermatologic, itching, nasal and respiratory, swelling, pain, and dizziness domains. The SEPOD consists of different administration instructions, modes of administration, and reporting approaches that consider pediatric developmental differences.

Although the literature review confirmed the lack of an appropriate COA instrument to measure peanut OIT side effects, a preliminary list of peanut OIT side-effect concepts was derived and was then confirmed during the EAMs. Concept elicitation and cognitive debriefing interviews with patients or caregivers provided evidence that the SEPOD-evaluated concepts are relevant to pediatric patients and that these participants (and caregivers when applicable) were able to interpret the instructions, items, and response

options as intended. The results of these interviews also indicated that the usability of the electronic handheld device was satisfactory, with participants noting that completing the SEPOD on the device was easy.

There are numerous challenges in choosing, developing, and implementing self-report or proxy-report PRO instruments in pediatric patients,²⁵ especially those in younger age groups,²⁶ including age-relevant vocabulary, comprehension of health concepts, the need to determine the lower age limit at which children can provide reliable and valid responses, and appropriate use of reports by informants other than the patients themselves.²⁷ The SEPOD was developed in consideration of these issues and encourages self-report by children aged 6 to 17 years. Although an age cutoff for self-report for children aged 6 years was first considered for the SEPOD, cognitive debriefing revealed that there might be issues in understanding among patients aged 6 to 8 years. Hence, the SEPOD includes different administration instructions, modes of administration, and reporting approaches that consider developmental differences but also allows and encourages patient self-report and allows for observer report if the patient cannot reliably self-report his or her side effects (with data collected to document who has reported). Such innovative pediatric COA measurement approaches, with flexible administration and reporting options, provide the potential to avoid proxy reporting, minimize missing data, and improve overall data quality.

The SEPOD development process should be understood in the context of a few limitations. First, although recruitment targets for the interviews aimed at including a diverse group of patients in terms of age, sex, and race, participating patients and their caregivers were recruited from only 2 research sites in the United States. Second, although a recent meta-analysis³ found that patient characteristics such as age and co-existing conditions do not seem to be related to the peanut OIT adverse event risk, our sample size was too small to assess whether the experience of peanut OIT symptoms differed by age, sex, or race. Future studies are warranted to assess how the experience of peanut OIT may differ across patient subgroups. Third, owing to the challenges in identifying or recruiting pediatric patients treated with peanut OIT, an unapproved treatment in the United States at the time of study conduct, wave 2 interviews were conducted with pediatric patients with a history of peanut allergy. As such, it was challenging, especially for younger patients, to understand the hypothetical situation of participating in

a trial and taking peanut OIT, or to understand the concepts that they may not have experienced (or remember experiencing). However, as a result of addressing this challenge in younger patients, the SEPOD may be even easier to comprehend for patients of all ages.

Finally, although content validity was clearly demonstrated for the SEPOD versions for patients aged 9 to 17 years, the findings regarding content validity for the CareO are less clear. The CareO SEPOD version, however, does collect data on who responded to the questionnaire, which allows for sensitivity analyses to be conducted based on the respondent (child or caregiver). This strategy also accounts for the ability of the child to answer independently to the questionnaire to change during the course of the study as they age, or become more familiar with the SEPOD.

Evaluating side effects is important for informing clinical decision-making for all treatments, but especially critical in peanut OIT, given the particularly high incidence during OIT up-dosing.^{15,16} For example, as observed in the up-dosing phase of the PALISADE RCT, adverse events for the treatment group involved the GI tract (85.8%), respiratory tract (81.2%), skin (66.9%), and immune system (16.9%).¹² In phase 3 and phase 2 OIT clinical trials, adjustments were made to the biweekly up-dosing OIT schedule according to the side effects.^{12,13} The evaluation of non-life-threatening side effects is also evidence that the treatment is active in the body and possibly increasing desensitization.²⁸

Because peanut OIT is administered daily, with most doses given at home,^{14,29} uncomfortable side effects can induce patient anxiety, leading to skipping doses or discontinuing treatment entirely.²⁸ By engaging the patient and caregiver in collecting daily side-effect data, a sense of self-management may also be provided,^{30–33} potentially enhancing treatment persistence and adherence to maximize benefit from the OIT.^{19,28}

Acknowledgments

The authors would like to thank the patients, their families and all investigators involved in this study. Medical writing and editorial assistance, under the direction of the authors, was provided by Gauri Saal, MA Economics and Ian Norton, PhD of Prime (Knutsford and London, UK) and Saba Choudhary, PhD, (Prime, New York).

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