May 8, 2019

Aimmune Therapeutics appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER's) Draft Evidence Report as part of the assessment of peanut allergy (PA) immunotherapies. Upon review of the Draft Evidence Report and Draft Voting Questions, we are providing five specific recommendations, with supporting evidence, that would improve the accuracy and utility of this analysis for all stakeholders.

1. **Based on rigorous trial design and robust outcomes, AR101 should receive an evidence rating higher than C+.**

ICER assigned a C+ evidence rating to AR101, which according to the evidence rating matrix, indicates moderate certainty of a comparable or better effect between the drug of interest and its comparator (i.e., allergen avoidance). We contend that this rating should be much higher based on the rigorous design, statistical power, and robust outcomes of PALISADE, the supplementary data from its follow-on study (ARC004), and the recently concluded Phase III ARTEMIS trial.[1-5] A rating of "high certainty" should be considered for AR101, according to the criteria specified in the ICER's Evidence Rating Matrix User Guide (Box 1).[6]

AR101 Clinical Trials: Design and Execution

- Mostly high-quality, larger studies: With 551 enrolled patients (496 from ages 4 to 17 years), PALISADE is the largest double-blind, placebo-controlled, randomized trial, is the only successful Phase III trial conducted for peanut oral immunotherapy and was published in the *New England Journal of Medicine*.[7] ICER recognizes PALISADE to be of "good quality" with "low risk of bias" (page 17).[8]
- Conducted in representative patient populations: PA is one of the most common and persistent forms of food allergy, with approximately 80-85% persistence into adulthood.[9,10] PALISADE enrolled a sensitive, highly atopic peanut allergic population with high rates of prior anaphylaxis, representative of subjects likely to benefit from desensitization therapy. Inclusion of an adolescent population in addition to the younger subjects furthers the relevance and generalizability of the data, as these patients are more likely to have worse outcomes compared to children (more severe reactions, higher risk of death).[11] ARTEMIS provides additional data on a similar cohort, broadening the already robust data from the AR101 study population in PALISADE.[5]
- Direct comparisons available: The PALISADE comparator represents the current standard of practice, allergen avoidance, as there are no FDA-approved therapies for PA.[12]
- Addresses important outcomes or validated surrogate outcomes: PALISADE used tolerated dose as determined by a double-blind, placebo-controlled food challenge (DBPCFC) as its primary outcome. The DBPCFC is the gold standard measure for food allergy testing and is increasingly recognized as a model for accidental exposures.[13] Protection from accidental exposures is the primary goal of allergen desensitization.[12] In the trial, PALISADE achieved its primary endpoint with 67.2% of AR101-treated patients able to tolerate a 600 mg dose of peanut protein compared to 4.0% of placebo patients (between-group difference of 63.2% [$p<0.001$]).[7] PALISADE also met all its key secondary endpoints. Fewer patients in the active group (10%) required epinephrine use during the exit DBPCFC compared to the PBO group (53%). These findings are bolstered by descriptive analyses of patients

experiencing accidental exposures during PALISADE, which suggest that fewer patients from the AR101-treated group experienced peanut-related accidental exposure, resulting in fewer adverse events (AEs), and required less rescue medication compared with the placebo group.[2] The occurrence of accidental exposures during the clinical trial is an indication of the challenge of avoidance, despite high levels of vigilance. Based on these clinical results, it is evident that AR101 provides a substantial treatment benefit.

- Long-term data on benefits/risks available and consistent results: ICER states, "[t]here is considerable uncertainty about the long-term outcomes." Data recently have become available from the AR101 open-label follow-on study, ARC004, which enrolled patients receiving AR101 in PALISADE for an additional 28 weeks following the first year of therapy.[4] The ARC004 study evaluates many of the same endpoints used in PALISADE and provides evidence of continued improvement in patients continuing on therapy. After an additional 28 weeks of daily AR101 therapy at 300 mg, the percentage of completing patients who achieved a tolerated dose of 1000 mg increased from 64.2% (in the first year) to 78.9% (at 18 months), and 48.6% of AR101-treated patients achieved a tolerated dose of 2000 mg.[4] The frequency and severity of AEs in ARC004 were similar to the reduced levels seen during the initial 300 mg dosing period of PALISADE relative to the dose escalation phase.[4] The increasing efficacy and reduced AEs over time is consistent with results of other allergen immunotherapies where treatment effect persists for at least one year following 3-5 years of treatment.[14,15,16]
- Future studies unlikely to change conclusions: Like PALISADE, early findings from the ARTEMIS trial also indicate that a higher proportion of treated individuals were able to tolerate 1000 mg after 6 months of dose escalation followed by three months of therapeutic dosing (i.e., 300mg daily dosing) compared to the placebo group ($p<0.00001$) (Aimmune press release, March 25, 2019).[5] Based on the consistency of results from PALISADE, ARTEMIS and the ARC004 study, the conclusions from PALISADE are not expected to change.

Essential Context for Adverse Events in Immunotherapy

The Draft Evidence Report states that the substantial benefit from treatment with AR101 is balanced by the large numbers of patients with AEs. This statement does not account for the range of severity of AEs associated with AR101 treatment, the vast majority of which were mild to moderate as observed in PALISADE. Additionally, severe treatment-emergent AEs were similar in PALISADE compared to PEPITES, occurring at 4.3% vs. 0.8% for AR101 vs. placebo (Supplement Table S3) and 5.9% vs. 1.7% for Viaskin Peanut vs. placebo patch (Supplement eTable 5). Rates of epinephrine use during PALISADE were 14% for AR101 vs. 6.5% for PBO and 9.2% for Viaskin Peanut vs. 3.4% for PBO. [7,17]Also, not all safety outcomes in PEPITES are reported and are therefore unknown (Appendix D, ICER Draft Evidence Report).[8] We would caution that reporting only AEs deemed to be related to treatment by the investigators rather than all treatment emergent AEs introduces additional bias, which should not be presumed to indicate a low AE profile for Viaskin Peanut.

It is essential to note that in the longstanding practice of immunotherapy, the patient is exposed to increasing quantities of the relevant allergen. Allergic reactions are an expected part of this therapeutic approach, which assumes managed, shorter-term risk of reactions in a controlled setting to minimize the short- and long-term risk of unpredictable, and sometimes fatal, reactions to accidental exposure. ICER recognizes in the Draft Evidence Report (page 20) that the incidence of AEs declined in the therapeutic

dosing phase compared with the dose escalation phase.[8] For example, when looking at the most common AEs in PALISADE, gastrointestinal problems such as abdominal pain, declined in the AR101 group from 43% during dose escalation to 15% in the therapeutic dosing phase, vomiting declined from 35% to 16% and so forth.[7] One case of anaphylaxis was observed over 307 patient-years and 94% of cases of epinephrine use were for mild and moderate AEs.[7] Longer-term data from ARC004 also show that, over time, treatment-related AEs decrease, while the level of peanut allergen tolerated increases.[1] This is consistent with the immune modulation associated with immunotherapy treatment. Therefore, ICER's evaluation of the AE profile for AR101 should be reconsidered.

Evidence Rating Recommendations

Although there can be no true comparison between the PALISADE and PEPITES trials, ICER suggests substantial treatment benefit with AR101 compared to that seen in PEPITES, stating (page 16): "If the study design for the PALISADE trial was the same as that of the PEPITES trial, the between group difference for AR101 compared to placebo would likely have been greater than the 63.2% observed in the PALISADE trial."[8] ICER's observation suggests a greater level of confidence in the PALISADE efficacy outcome, which should be reflected in a higher—and differentiated—evidence rating.

Based on the efficacy and AE data from PALISADE and ARTEMIS, and evidence of improvements in the ARC004 long-term results that are now available, the evidence for AR101 should be classified as having at least a small or substantial net benefit with high certainty ("B/A") and the rating should be at a higher level compared to the evidence for Viaskin Peanut.

2. ICER must acknowledge – and account for – important limitations in Remington *et al.* (2018)[18] when using this study to inform clinical effectiveness assessments of AR101 and Viaskin Peanut.

In the Draft Evidence Report, ICER references Remington *et al.* (2018) stating, "[m]odeling studies suggest that achieving the endpoint in the PEPITES trial will prevent reactions to between 95% and 99.9% of accidental exposures."[8,18] We disagree for the following reasons:

- Remington *et al.* (2018) was based on a previous study by Baumert *et al.* (2018), which used a Monte Carlo simulation to predict the probability of an allergic reaction based on the consumption of certain packaged foods bearing advisory labeling.[18,19] A reaction was predicted to occur if the amount of food consumed contained more peanut protein than the individual could tolerate. The generalizability of this model to a real-life peanut allergic population is questionable. Several inputs used in the model to estimate consumption patterns and allergen concentrations to create exposure scenarios likely do not reflect the reality of the highly peanut-allergic population, as reported in the MIRABEL study.[11,20]
- The packaged foods studied in this research are not meant to contain peanut and therefore will likely have no more than trace amounts of peanut, while reactions to peanut in the real world will often occur in response to larger quantities. Therefore, conclusions about the clinically relevant protection benefits of Viaskin Peanut in PEPITES cannot be drawn from the results from this research. Given that 50% of estimated eliciting dose is ≥125 mg in real life,[11] we question the validity of the modeling study to provide a true reduction in risk associated with accidental exposure in the real world.
- While ICER correctly indicates that there is no uniformly accepted threshold for desensitization, it is important to assess the available data on real-world exposures. Deschildres *et al.* (2016) provide the best available data for the quantity of peanut protein eliciting a reaction in the real world, a median of

approximately 125 mg of peanut protein (interquartile range: 34-177).[11] This would indicate that on average, real-life reactions do not occur from the trace amounts of peanut protein typically expected in packaged foods. A clinically relevant threshold for protection, therefore, would need to meet – or preferably exceed – the levels associated with accidental exposure. Based on the range above, a **tolerated dose** of 300 mg should be the minimum threshold for clinically relevant protection, not merely any improvement relative to the individual patient's threshold.

- Moreover, the PEPITES trial failed to meet its pre-specified primary endpoint. Due to the hierarchical method employed, it also did not meet any of its secondary outcomes and no clinical relevance could be determined.[17]
- In the interest of disclosure, DBV technologies funded the research, which produced both the Baumert and Remington publications.[18,19]

We recommend that ICER remove this biased statement from their report and reconsider this evidence when evaluating the clinical effectiveness of AR101 and Viaskin Peanut for the evidence rating and cost-effectiveness analysis.

3. ICER should assume that utility values increase over time for AR101 treated patients, as suggested by the available long-term data.

As previously discussed, long-term data from ARC004 show an increasing trend in tolerated dose of AR101-treated patients over time.[4] With an increased tolerance threshold, patients can live a more normal life. We therefore request that ICER consider in the base case that desensitized patients who have been on treatment for 5+ years (i.e., after patients turn 12 years old in the model) have a higher utility value that is closer to the utility of the tolerant state. This assumption is also supported by additional data from the ARC004 study, which found self-reported improvements in all domains of the Food Allergy Quality of Life Questionnaire (FAQLQ) (social and dietary limitations, food anxiety, emotional impact and FAQLQ Total Score), when compared to PALISADE baseline.[3] In addition, the once-daily oral administration of AR101 allows for daily confirmation of the ability to tolerate a minimum of 300 mg peanut protein. This is likely to increase patients' sense of well-being, even while continuing to practice avoidance.

4. ICER should remove the assumption regarding derivation of eliciting dose in PALISADE and reevaluate its modeling approach for the responders in PEPITES.

In the effort to interpret the definitions of tolerated and eliciting dose, the report (Page 21) states: "[i]n the PALISADE trial for AR101, successful desensitization was defined by tolerance of a 600 mg dose of peanut protein, which is equivalent to an eliciting dose of at least 1,000 mg." A tolerated dose of 600 mg does not eliminate the possibility that a patient can also tolerate the next higher dose level (i.e., 1000 mg). Therefore, an eliciting dose cannot be derived from a reported tolerated dose. When provided with an eliciting dose, it *is* possible to derive a tolerated dose in the tested series if the challenge is conducted in a stepwise manner according the PRACTALL guidelines. For example, based on a 300 mg eliciting dose, one can assume a tolerated dose of 100 mg.[13] We recommend that ICER remove this sentence and reevaluate its modeling approach for the responders from the low-eliciting dose group of PEPITES.

5. ICER should revise healthcare costs for AR101, as the current model includes overestimates that materially impact the cost-effectiveness results.

- The Year One healthcare cost for AR101 consists of immunotherapy clinic visits and additional outpatient office visits. ICER applies a weekly frequency of 0.50 (i.e., 1 visit to each service every 2 weeks) for a total of 26 for each type of visits. According to the PALISADE study protocol, patients were required to have one physician office visit in the first week for initial dose escalation and another one at the end of the first year. Additionally, an average of 10 bi-weekly visits are required to accommodate the dose escalation process of AR101, making the correct frequency for physician visits a maximum of 0.20 (10 visits / 50 weeks).
- ICER included a separate biweekly cost attributed to "outpatient visit to treat an allergic reaction." In PALISADE, there were 27 episodes of in-clinic epinephrine use reported (Supplement Table S9), none of which required a separate outpatient office visit.[7] To avoid double counting, we suggest ICER include only bi-weekly immunotherapy clinic visits but not additional outpatient office visits to treat allergic reactions. By adjusting the frequency of weekly immunotherapy clinic visits to 0.2 and removing the separate outpatient visits for treating allergic reaction, the updated ICER for AR101 is reduced to $104,898/QALY.
- We appreciate that ICER has included the DBPCFC in the model, consistent with the trial design; however, it is unlikely that the DBPCFC will be employed in clinical practice for every patient who is on AR101, given the oral route of consumption and the ability to determine the patient's capacity to tolerate the current dose amount. Therefore, the cost of the DBPCFC should not be included in either arm of the AR101 model.

Voting Questions

We request that ICER amend Voting Questions 5 and 6 to ensure uniformity in the evaluation of AR101 and Viaskin Peanut.

- Question 5 includes the option *"a. This intervention offers reduced complexity that will significantly improve patient outcomes"* for Viaskin Peanut, but this option is omitted for AR101 in Question 6. As a result, the voting questions presume that oral immunotherapy either cannot offer reduced complexity or significantly improve outcomes, or it should not be assessed.
- Question 5 also includes the option *"d. This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed"* for Viaskin Peanut, but this option is omitted for AR101 in Question 6. AR101 is the first oral immunotherapy to ever go through the FDA review process and, pending approval, it will be the only standardized treatment for oral immunotherapy. The investigational Characterized Oral Desensitization ImmunoTherapy approach for dose escalation, which builds on a century of oral immunotherapy research, is also a novel aspect of AR101 treatment.[21]

In summary, we strongly encourage ICER to reconsider the clinical effectiveness rating and economic evaluation based on the rigorous evidence provided in this letter. PA is a challenging, chronic condition for patients, caregivers and providers, and we look forward to discussing oral immunotherapy further at ICER's public meeting on June 11, 2019.

References

1. Blumchen K, Shreffler W, Griffin N, et al. Extended daily dosing of AR101 for peanut allergy results in higher tolerated doses and continued immunomodulation. Paper presented at: EAACI Annual Meeting 2019; Lisbon, Portugal.
2. Hourihane JO, Lieberman JA, Bird JA, et al. Accidental Exposures to Peanut and Other Food Allergens: Results from a Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial (PALISADE). *Journal of Allergy and Clinical Immunology.* 2019;143(2):AB265.
3. Hourihane J, Johnston D, Lieberman J, et al. Improvements in Disease-Specific Quality of Life for Peanut-Allergic Subjects Receiving AR101 Maintenance Therapy. Paper presented at: EAACI Congress; June 1-5, 2019, 2019; Lisbon, Portugal.
4. Carr TF, Shreffler WG, Griffin NM, et al. Longer-Term Safety and Efficacy Measures of AR101 Oral Immunotherapy for Peanut Allergy: Results from a Phase 3 Follow-On Study. *Journal of Allergy and Clinical Immunology.* 2019;143(2):AB256.
5. Fernandez-Rivas M, Hourihane J, Beyer K, et al. ARTEMIS: A European, Phase 3, Randomised, Double-Blind, Placebo-Controlled Trial of AR101 in Peanut-Allergic Children and Adolescents Aged 4-17. Paper presented at: EAACI Annual Meeting; 1-5 June 2019, 2019; Lisbon, Portugal.
6. Ollendorf DA, Pearson SD. *ICER Evidence Rating Matrix: A User's Guide* ICER;2017.
7. Vickery B, Vereda A, Casale T, et al. AR101 Oral Immunotherapy for Peanut Allergy. *New England Journal of Medicine.* 2018;379(21):1991-2001.
8. ICER. *Oral Immunotherapy and Viaskin Peanut for Peanut Allergy: Effectiveness and Value [Draft]*. Institute for Clinical and Economic Review; April 9, 2019
9. Iweala OI, Choudhary SK, Commins SP. Food Allergy. *Current gastroenterology reports.* 2018;20(5):17-17.
10. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. *The Journal of allergy and clinical immunology.* 2001;107(2):367-374.
11. Deschildre A, Elegbede CF, Just J, et al. Peanut-allergic patients in the MIRABEL survey: characteristics, allergists' dietary advice and lessons from real life. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology.* 2016;46(4):610-620.
12. Casale TB, Haselkorn T, Ciaccio CE, Sriaroon P, Chipps BE. Harmonization of Terminology for Tolerated and Reactive Dose in Food Allergy Immunotherapy. *The Journal of Allergy and Clinical Immunology: In Practice.* 2019;7(2):389-392.
13. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *The Journal of allergy and clinical immunology.* 2012;130(6):1260-1274.
14. Didier A, Malling HJ, Worm M, et al. Post-treatment efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet in adults with grass pollen-induced allergic rhinoconjunctivitis. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology.* 2013;43(5):568-577.
15. Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy.* 2007;62(8):943-948.

16. Eng PA, Borer-Reinhold M, Heijnen IAFM, Gnehm HPE. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. *Allergy.* 2006;61(2):198-201.
17. Fleischer DM, Greenhawt M, Sussman G, et al. Effect of Epicutaneous Immunotherapy vs Placebo on Reaction to Peanut Protein Ingestion Among Children With Peanut Allergy: The PEPITES Randomized Clinical TrialEffect of Epicutaneous Immunotherapy vs Placebo on Reaction to Peanut Protein in Children With Peanut AllergyEffect of Epicutaneous Immunotherapy vs Placebo on Reaction to Peanut Protein in Children With Peanut Allergy. *JAMA.* 2019;321(10):946-955.
18. Remington BC, Krone T, Koppelman SJ. Quantitative risk reduction through peanut immunotherapy: Safety benefits of an increased threshold in Europe. *Pediatr Allergy Immunol.* 2018;29(7):762-772.
19. Baumert JL, Taylor SL, Koppelman SJ. Quantitative Assessment of the Safety Benefits Associated with Increasing Clinical Peanut Thresholds Through Immunotherapy. *The journal of allergy and clinical immunology In practice.* 2018;6(2):457-465.e454.
20. Crepet A, Papadopoulos A, Elegbede CF, et al. Mirabel: an integrated project for risk and cost/benefit analysis of peanut allergy. *Regulatory toxicology and pharmacology : RTP.* 2015;71(2):178-183.
21. Aimmune Therapeutics. Developing an orally administered biologic immunotherapy for the treatment of peanut allergy. 2019; https://www.aimmune.com/ar101-peanut-allergy/. Accessed April 29, 2019.

May 8, 2019

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RE: DBV Technologies Suggestions and Comments to the ICER Draft Report on Peanut Allergy

To whom it may concern,

On behalf of DBV Technologies, I appreciate the opportunity to comment on ICER's draft peanut allergy assessment. DBV Technologies is dedicated to improving the lives of patients with food allergies and other immunologic diseases. Despite allergic reactions to peanut being unpredictable and potentially severe/life-threatening, there are no FDA approved therapies. Through our research into peanut allergy treatment, DBV Technologies aspires to reduce the significant burden that peanut allergy has on patients, caregivers and their healthcare providers.

Given the absence of reliable Quality of Life (QoL), Health State Utility and long-term efficacy and safety outcomes in the literature, DBV Technologies believes ICER's draft report cannot reliably capture potential treatment value. These variables are the key determinants of economic value, so conclusions of the draft report should be interpreted with caution. The draft report does not adequately characterize the impact of these uncertainties and limitations. Therefore, we recommend the following:

1. Develop a base case model that more comprehensively captures the treatment risk reduction of allergic reactions and the costs and disutility of either accidental reactions or treatment of adverse events.
2. Remove/Eliminate scientifically inappropriate and clinically irrelevant comparisons and inferences about or between AR101 and/or Viaskin Peanut.
3. Transparently address assessment limitations due to data gaps by expanding the evaluation of key variable sensitivities and evaluation scenarios.

In addition, we include an appendix to this letter with suggestions for corrections and clarifications to the draft report.

1. DBV Technologies disputes that ICER's risk reduction model is a complete approach. ICER's methods fail to include all clinically relevant responses from PEPITES and the full cost and consequences of significant allergic reactions.
   1.1 ICER's approach to Viaskin Peanut risk reduction only considers patients who attain the binary primary trial endpoint defined in the PEPITES[1] study. It does not consider the risk benefit conferred to patients who have a clear clinical response (improved eliciting dose (ED) with decreased sensitivity), but who did not meet one of the two primary endpoint thresholds. We encourage ICER to include a scenario model in its final report with reaction risk model states that includes all threshold changes in ED as measured in PEPITES.

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1.1.1 In clinical practice, because of the risks and potential consequences of a provoked reaction in a real-world setting, Oral Food Challenges (OFC) are infrequently used and primarily administered only to rule-out peanut allergy when patient history, skin prick test and/or IgE levels are inconclusive.[2] Given the practical challenges of OFC, additional measures, beyond surrogate endpoints, are needed to measure patient-centered outcomes such as the risk of allergic/anaphylactic reactions.[3] Considering the limitations in assessing reaction risk and clinical relevance of interventions, a model evaluation of risk reduction is needed to project the potential population impact of Viaskin Peanut.

1.1.2 To capture the relevance of clinical risk reduction from the PEPITES study, a Quantitative Risk Assessment model was applied by Dr Benjamin Remington to the PEPITES active and placebo populations. The results were recently presented at the American College of Allergy, Asthma & Immunology 2018 Annual Scientific Meeting. In his model, using national databases of consumption and contamination amounts, Dr Remington found that, when compared to baseline, there was a 75-97% reduction in the reaction risk predicted among Viaskin Peanut patients exposed to possible peanut contamination through four common packaged food categories, while in the placebo treated group, no change in risk was observed.[4,5]

1.1.3 A methodology for an economic model of peanut allergy risk reduction was developed by Dr. Daniel Ollendorf of the Center for Economic Value and Research and was shared with ICER by DBV Technologies.

1.2 ICER underestimates the frequency, cost and impact of allergic reactions in its assessment.

1.2.1 DBV Technologies disputes ICER's conclusion that the rate of inadvertent allergic reactions is low and decreasing. To arrive at this conclusion, ICER extrapolated findings from a 20-year old 83 patient Canadian survey[6,7] and also a 10-year old chart review study from a large academic practice.[8] ICER models a rate of ER visits per year of 2.7%.

1.2.2 More recent national surveys suggest a much larger burden on the healthcare system. Recently, Gupta et al report that 22.9% of peanut allergy patients visit the ER each year due to a food allergy reaction.[9] Further, in another study of peanut allergy, patient claims from a large commercial database showed that the annual rate of ER visits due specifically to peanut allergic reaction was 14.3%.[10]

1.3 ICER's model should include costs and disutilities associated with allergic reactions to avoid a material understatement of disease and treatment burden.

1.3.1 Considering that the primary objective of food allergy treatment is to reduce the risk of allergic reactions, transparently tracking all allergic reactions that occur during peanut allergy clinical trials, both related to the therapy and not, is essential to understanding both the benefits and risks of these interventions. DBV Technologies believes that allergic reaction costs and disutilities and their associated duration should be assigned as follows:

1.3.1.1 In clinical trials, instructions for epinephrine use are consistent with the FDA prescribing information;[11] without knowing more details about the nature of the preceding reactions, episodes of study epinephrine utilization are a reliable predictor for the frequency of clinically significant allergic reactions.

1.3.1.2 Guidelines and epinephrine prescribing information recommend emergency room care after administration. As such, in its model ICER should include ER costs for each use of epinephrine.[11,12]

1.3.2 Allergic reactions have a negative impact on QoL. A recent meta-analysis of 1,000 patients across 12 oral immunotherapy (OIT) trials by Chu et al, suggest that, of those studies where QoL was evaluated, that when compared to untreated patients, OIT did not improve quality of life, likely due to a greater than three-fold increase in anaphylaxis risk (RR 3.12) and other adverse events.[3]

1.3.3 There are multiple approaches to assign disutilities to the rate of allergic reactions to a model. To support its exclusion of allergic reactions disutilities, ICER suggests that the length of time patients are impacted by allergic reactions due to inadvertent peanut exposure or to treatment is unknown but is expected to be relatively short-lived. DBV Technologies is not aware of any evidence that supports this conclusion. There are, however, resources that can be used to assign a utility decrement to the incidence of allergic reactions in its assessment:

1.3.3.1 Carroll et al[13] describes disutilities of allergic reactions that can be applied to the rate of epinephrine use in its base case model.

1.3.3.2 NICE may also be a source for obtaining the utility decrement associated with anaphylactic reactions and the estimated number of days necessary to apply disutility.[14]

1.3.3.3 Another example of the application of anaphylaxis disutilities to a peanut allergy health economic model may be found in the recently published manuscript by Shaker and Greenhawt.[15]

2. To enhance the scientific credibility of its assessment, ICER should remove inappropriate comparisons or inferences about or between AR101and/or Viaskin Peanut.

2.1 In the draft report, ICER's evaluation of the PALISADE and PEPITES studies includes efficacy and safety comparisons between Viaskin Peanut and AR101. These inferences and comparisons are not informed by evidence. Given the difference in underlying immunologic mechanisms of action, different study populations, methods and clinical trial endpoints, these analyses are scientifically and clinically flawed. Specific examples of these inaccuracies include:

2.2 Key protocol differences exist between the studies, invalidating head-to-head comparisons. Differences in study design, their endpoints as well as how endpoints were measured make comparisons impossible. ICER relates the measurement of the clinical trial allergic reaction endpoint Eliciting Dose (ED) used in the PEPITES study to Tolerated Dose (TD) in the PALISADE study, suggesting that a TD can be extrapolated from an ED which is not possible. Additionally, each study used different stopping criteria and OFC measurement scales:[16,17]

2.2.1 PALISADE considers mild reactions as tolerated in its definition of TD while;

2.2.2 PEPITES defines ED as the dose, based on the accumulation of enough predefined points on a scoring system requiring objective signs of a reaction, where a reaction occurs.

2.2.3 The study baseline OFC challenges are adjudicated differently; the signs/symptoms that would stop an entry challenge in PALISADE would not necessarily allow an investigator to discontinue in PEPITES.

2.3 Finally, ICER characterizes Viaskin Peanut efficacy as modest, which is a subjective term used without basis. In the PEPITES study, Viaskin Peanut treated patients were 4X more likely than placebo to have a measured improvement in ED.[18]

3. ICER acknowledges the absence of long-term efficacy and safety outcomes, as well as quality of life data, as key limitations in its assessment. To transparently address these limitations, it needs to expand its evaluation of key variable sensitivities and scenarios.

3.1 Emerging data raise interesting questions for the future study of treatment duration for Viaskin Peanut. The answers to these questions are not yet known, but based on preliminary findings, DBV Technologies suggests that ICER at least consider more scenario alternatives for treatment and benefit duration:

3.1.1 We suggest that ICER model and report scenarios where most patients receive lifetime benefit after only having been treated for up to 5 years. While the below findings involve small numbers of patients in an open-label phase, they suggest potential Viaskin Peanut long-term treatment response. Such a response could be similar to immunotherapy for airborne and venom allergies. With these treatments, some patients experience the benefit of remission of their allergic disease after a period of 3-5 years of treatment or are often able to successfully extend the interval between doses.[19]

3.1.2 While conclusions from an open label extension study are not possible, in the OLFUS-VIPES study there was a suggestion of a potentially progressive effect of Viaskin Peanut with increased desensitization rates beyond 12 months of treatment. In addition, following study medication discontinuation after 24 or 36 months of active treatment, a subset of 25 eligible patients were monitored for peanut sensitivity for two months off therapy, during which time they were untreated and continued to avoid peanut before being re-challenged with an OFC. 80% of the subjects demonstrated sustained unresponsiveness, with all 25 subjects maintaining immunologic changes in the absence of continued treatment.[20,21]

3.1.3 ICER may also consider the approach Greenhawt and Shaker take in modeling scenarios that evaluate the potential health economic impact of shorter than lifetime treatment, with sustained peanut sensitivity threshold.[15]

3.2 ICER needs to better characterize the impact of uncertainties of health state utility outcomes.

3.2.1 ICER should include scenarios with higher estimates of desensitization utility. ICER states that there is a paucity of health-related QoL evidence. In its model, patient utility is the key determinant of value. Despite its significance to the model, ICER relies on a study of Swedish food allergy patients to project patient utility. ICER appropriately acknowledges that peanut allergy patients may have a different preference set than non-peanut food allergy patients. Indeed, Dunn

Galvin et al found that peanut allergy patients 0-12 years of age, had worse health-related QoL than patients allergic to single foods or multiple foods other than peanut[22]. Given this limitation, and evidence suggesting greater burden than it models, ICER inadequately addresses this uncertainty in its draft report.

3.3 Without inclusion of health state utility impact on caregivers, ICERs societal perspective is incomplete.

3.3.1 ICER acknowledges that caregivers of pediatric food allergy patients suffer significant financial and psycho-social burden and may be a predominant beneficiary of treatment. Improvements in patients' health and QoL outcomes resulting from new therapies may substantially offset caregiver burden resulting in increased health state utility.

3.4 ICER should include societal impact in the base case as employers, the ultimate payer for the majority of peanut allergy care, bear much of this societal burden in lost productivity and unfilled opportunities.

3.4.1 The health care sector perspective should represent the actual payers of pediatric care, the majority of which are employers in the US. As most of the societal burden is caused by lost caregiver productivity and foregone opportunities, employers have much to gain in pediatric peanut allergy treatment.[23]

DBV Technologies applauds ICER's considerations of other benefits and context:

- By potentially reducing the risk of allergic reactions Viaskin Peanut may help reduce important economic disparities in medical services, emergency room and hospital utilization within lower income households.
- We are also pleased that ICER acknowledges the distinct approach of Viaskin Peanut Epicutaneous Immunotherapy (EPIT). Through this approach, Viaskin Peanut may offer patients effective treatment with low risk of significant adverse events.

Suggestions for voting questions:

- DBV Technologies believes it is premature to ask the panel any of these questions prior to FDA approval. Further, we have significant concerns about questions 3 and 4 which ask the panel to compare investigational treatments. We reemphasize our concern of the scientifically inappropriate, clinically irrelevant and flawed comparisons. Given ICER's acknowledged limitations of this assessment, using it to answer these questions may result in poorly informed healthcare system choices.

DBV Technologies appreciates the opportunity to share our comments on ICER's treatments for the peanut allergy draft report. In this letter we have sought to highlight some of the key limitations and concerns that we believe critically impact the report. DBV Technologies respectfully requests that ICER acknowledge this feedback and take the necessary effort to address these concerns so that patients, families, doctors and other stakeholders have an informed and unbiased perspective from which to evaluate these first potential treatments for peanut allergy.

Sincerely,

Emmanuel M. Mahlis, MD
Senior Vice President, Global Medical Affairs

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References

1. Fleischer D, Greenhawt M, Sussman, G. Effect of Epicutaneous Immunotherapy vs Placebo on Reaction to Peanut Protein Ingestion Among Children with Peanut Allergy: The PEPITES Randomized Clinical Trial
   JAMA. 2019;321(10):946-955
2. Waserman S, Begin P, Watson, W. IgE-mediated food allergy
   Allergy, Asthma, and Clinical Immunology 2018 14 (Suppl 2):55 September 12, 2018
3. Chu D, Wood R, French S, Fiocchi S, Jordana M, Waserman S, Brożek J, Schünemann H
   Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety
   Lancet Published online April 25, 2019 Accessed April 30, 2019
   Http://dx.doi.org/10.1016/S0140-6736(19)30420-9
4. Remington BC, Krone T, Koppelman SJ. Quantitative risk reduction through peanut immunotherapy: Safety benefits of an increased threshold in Europe. Pediatr Allergy Immunol 2018;29(7):762-772.
5. Remington BC. Quantitative risk reduction through epicutaneous immunotherapy (EPIT): Results from the PEPITES Phase III trial. Slide presentation.
   Accessed January 2019.
6. Shaker M, An Economic Analysis of a Peanut Oral Immunotherapy Study in Children
   J Allergy Clin Immunol 2017;5(6):1707-1716
7. Vander Leek T, Liu A, Stefanski K, Blacker B, Bock A The natural history of peanut allergy in young children and its association with serum peanut-specific IgE
   The Journal of Pediatrics 2000; 137(6)749-756
8. Neuman-Sunshine D, Eckman J, Keet C, Matsui, E, Peng D, Lenehan P, Wood, R
   The natural history of persistent peanut allergy
   Ann Allergy Asthma Immunol 108 (2012) 326 –331
9. Gupta R, Warren C, Smith B, Blumenstock J, Jiang J, Davis M, Nadeau, K
   The Parent Reported Public Health Impact of Childhood Food Allergy in the United States
   Pediatrics 2018; 142 (6):e20181235 Accessed April 30, 2019
10. Chalil J, Vlahiotis A, Tran O, Shah H, Prinz M, Barrett C
    Healthcare Resource Use (HCRU) And Costs associated with peanut allergy (PA)
    Accepted Poster Presentation, 2019 ISPOR annual Meeting
11. Epi-Pen and Epi-Pen Jr. Prescribing information
    Https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019430s074lbl.pdf
    Accessed April 30, 2019
12. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update.
    Journal of Allergy and Clinical Immunology. 2011;127(1):S1-S55.
13. Carroll A, Downs S, Improving Decision Analyses: Parent Preferences (Utility Values) for Pediatric Health Outcomes

Journal of Pediatrics 2009; 155:21-5

14. NICE Clinical Guidelines, No. 134 Centre for Clinical Practice at NICE (UK) National Institute for Health and Clinical Excellence (UK); 2011 Dec.
15. Shaker A, Greenhawt M. Estimation of Health and Economic Benefits of Commercial Peanut Immunotherapy Products – A Cost Effectiveness Analysis JAMA Network Open 2019;2(5):e193242 accessed May 3rd 2019
16. Vickery B, Vereda A, Casale, T et al. AR101 Oral Immunotherapy for Peanut Allergy NEJM 2018;379(21) 1991-2001; PALISADE Study Protocol
17. Fleischer D, Greenhawt M, Sussman, G. Effect of Epicutaneous Immunotherapy vs Placebo on Reaction to Peanut Protein Ingestion Among Children with Peanut Allergy The PEPITES Randomized Clinical Trial JAMA. 2019;321(10):946-955; Supplement 1: Clinical Study Protocol and SAP
18. Fleischer D, Greenhawt M, Sussman, G. Effect of Epicutaneous Immunotherapy vs Placebo on Reaction to Peanut Protein Ingestion Among Children with Peanut Allergy The PEPITES Randomized Clinical Trial JAMA. 2019;321(10):946-955; Supplementary Online Content
19. Cox L. Nelson, H, Lockey, R Allergen immunotherapy: A practice parameter third update. JACI: 2011; 127 (1): Supplement January 2011: S1-S55
20. Sampson H, Shreffler W, Yang W, Sussman G et al. Effect of Varying Doses of Epicutaneous Immunotherapy vs Placebo on Reaction to Peanut Protein Exposure Among Patients With Peanut Sensitivity: A Randomized Clinical Trial. JAMA 2017; 318(18):1798-1809
21. Brown-Whitehorn T, de Blay F, Sampson HA. Sustained unresponsiveness following long-term epicutaneous immunotherapy (EPIT) with VIAKSIN® Peanut: Results of the OLFUS-VIPES Phase IIb study. Poster presentation. EAACI Congress, Munich Germany, May 2018.
22. DunnGalvin A, BlokFlokstraw B, Burks A, Dubois A, Hourihane J. Food allergy QoL questionnaire for children aged 0–12 years: content, construct, and cross-cultural validity Clinical and Experimental Allergy 2008, 38, 977–986
23. Gupta R, Holdford D, Bilaver L, Dyer A, Holl J, Meltzer D. The Economic Impact of Childhood Food Allergy in the United States JAMA Pediatrics 2013 167(11) 1026-1031

Appendix Recommendations and Corrections	
Section 1.1 Decline in the incidence of accidental reactions	Without longitudinal research tracking population reactions, it is more accurate to say that the true annual incidence is unknown. Indeed, Gupta et al and Chalil et al suggest much higher rates of reaction than ICER describes[9,10]
Section 1.1 Description of Viaskin Peanut	We suggest: Viaskin Peanut is based on epicutaneous immunotherapy, or EPIT. It works by delivering biologically active compounds to the immune system through intact skin
Section 1.3 Definitions within DBPCFC	It is important to note that PEPITES was conducted with the PRACTALL protocol to measure the outcome of patients at study baseline and 12 months. The PALISADE study used Modified PRACTALL protocol. These are two different approaches to measuring response and both approaches should be defined.[16,17]
Section 3.3 Page 15	• Line 3: Patients were required to have an eliciting dose of 300mg (not grams) or less on DBCFC at study entry. • Tolerated dose (TD)was not assessed in PEPITES so the ICER suggestion that 300mg eliciting dose (ED) equates to 100mg tolerated dose (noted in parentheses) is unsubstantiated.
Section 3.3 Page 21 Controversies and Uncertainties	Tolerated dose was not assessed in PEPITES so the ICER suggestion that 300mg ED equates to 100mg TD or 1,000mg ED equates to 300mg TD is unsubstantiated
Section 4.2 Model Inputs Page 29	Please note the correct the PEPITES primary study endpoint should read: Treatment response was defined as a post- treatment eliciting dose of 300 mg or more or 1000 mg or more of peanut protein for the low– or high–eliciting dose subgroups, respectively[1].
Section 4.3 Prior Economic Models Page 45	ICER should update its report to acknowledge the recently published study by Shaker and Greenhawt:[15] "The Estimation of Health Economic Benefits of Commercial Peanut Immunotherapy- A Cost Effectiveness Analysis"
Section 4.4 Summary and Comment	The suggestion that the incidence rate reactions due to accidental exposure is very low is subjective and misleading. The real-world frequency of these reactions cannot be known with certainty.

Limitations Page 47	Considering more recent evidence suggests significantly more occurrences of Emergency Room use due to peanut allergy reactions.[9,10], ICER should modify this inference.

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Allergy & Asthma NETWORK

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May 6, 2019

Steven Pearson, MD, MSc
Institute for Clinical and Economic Review
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Boston, MA 02109

RE: ICER Draft Evidence Report for Evaluation of "Oral Immunotherapy and Viaskin® Peanut for Peanut Allergy"

Dear Dr. Pearson,

On behalf of the >30 Million Americans living with life-threatening allergies, we submit the following letter to the Institute for Clinical and Economic Review (ICER) and the opportunity to comment on the Draft Evidence Report for ICER's review of peanut allergy treatments.

We commend ICER for making minor adjustments from the original scoping document to the draft evidence report. The most notable change on behalf of patients was the decision to use a fifty-year treatment window versus an eighty-year treatment window for the lifetime treatment cost. This improved the overall lifetime cost effectiveness of treatments; however, it still did not result in achieving the QALY thresholds established by ICER.

Below is a list of our concerns with the model previously documented but not fully addressed:

<u>Model Structure</u>
ICER employed standard cost effectiveness methodology to develop the model structure. It is a decision analytic model utilizing a Markov model design. Because of the significant differences in the design of the Viaskin Peanut and AR101 clinical trials, data from the two studies can not be compared to one another; therefore, there will be no attempt to compare the two products to one another. Rather, clinical and cost effectiveness will compare each product to its placebo arm.

<u>Data Inputs</u>
Disutilities due to treatment emergent adverse events are not incorporated into the model. Furthermore, the utility calculation clearly lacks sufficient data to be accurate. The Swedish study using the EQ-5D was never validated for use in food allergy and has not been studied in peanut allergy. Furthermore, the healthy utility gain of 50% between the allergic vs nonallergic state is completely arbitrary. In our opinion, the QOL benefit from the STOPII trial was well known and should serve as a more objective measure of potential benefit.

<u>Results</u>
There was no difference in life years gained due to either treatment compared to their placebo arm in the base case analysis. The difference in quality-adjusted life years (QALYs) gained ranged from 0.21 to 0.63, a very small difference. "The face validity of the model is in question when these results suggest that the impact of these new treatments adds only 0.21 to 0.63 years of quality-adjusted life on average.

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Cost Inputs/Model Perspective

We would like to understand how the pricing assumptions were made on each treatment. If this estimate was not made objectively and validated then it could undult influence the base case substantially. It appears as if a concerted effort was made to show that one or both treatments are not cost effecrive even in light of no FDA approved therapies.

ICER has indicated that impact of caregiver productivity loss will be considered in a scenario analysis that examines the societal perspective. We believe that caregiver productivity loss should be included in the base case analysis, which represents the health sector perspective. According to the Henry J Kaiser Family Foundation[1], in 2017, 49% of the US population was covered by employer-sponsored health insurance. Since employers carry a large burden of health care costs in the US, the health sector perspective should also represent the US employer perspective. Therefore, in the modeling exercise it is more appropriate to include caregiver productivity loss in the base case analysis rather than a scenario analysis.

The Modified Societal Perspective achieved a more realistic incremental cost per QALY gained for AR101; however, this has no impact on the draft questions for deliberation and voting by the CTAF. Moreover, the draft questions are heavily focused on the clinical evidence with the exception of two on the long-term value of the proposed treatments. Ironically, the draft report is heavily focused on the long-term value of the proposed treaments with little consideration given to the clinical evidence.

Health State Utilities Input

The ICER analysis applies research from Protudjer et al[2] to assign a utility value for the peanut sensitive and peanut tolerant states. However, since there are no published utility values available for the peanut desensitized state, an average between the two states from Protudjer is applied. This implies that the utility of a desensitized patient is halfway between the peanut sensitive and peanut tolerant state. We recognize that in developing economic models, when no data exist, assumptions are made. We believe in order for the model to better reflect the real-world experience of patients, that ICER should use the utility for peanut tolerant patients to represent peanut desensitized patients in the base case analysis. Much of the reason patients would seek desensitization is to eliminate the risk of anaphylactic reaction when accidentally exposed to peanut allergen. When successfully desensitized, patients no longer worry that small amounts of accidental peanut exposure will lead to a reaction. When coupled with continued avoidance of peanut, the quality of life of a desensitized patient is similar to the quality of life of a peanut tolerant patient. There may be an ongoing small utility decrement due to inability to enjoy peanut product, but we believe this is small relative to the utility gain related to desensitization.

ICER did not assess any disutility to the reactions incurred during AR101 therapy, this is an egregious error. Epi use and anaphylaxis occurred at high rates vs. avoidance and people dropped out due to other treatment related side effects. There is no plausibility or validity to the assumption that there is no disutility here. While no one is arguing that there may be more benefit at 1 year with OIT than EPIT given the trial outcomes, the difference is artificially inflated by not subtracting out the harm from the buildup events.

Finally, we would like to offer the follow recommendations as ICER moves forward:

- Accept data regarding the quality of life impact of peanut allergy on the caregiver or family – worry, anxiety, day to day disruption of school or work activity, change in employment status, etc… Key is to incorporate data as it becomes available.

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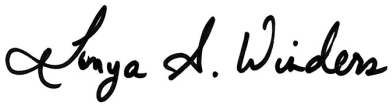
- Reconsider the face validity of the minimal impact to quality of life with treatment, as represented by the minimal QALY difference between the treatment and its placebo arm. ICER's own reference, Cannon 2018, shows the discrepancy between true quality of life impact and what the model results show.
- Reconsider the disutility assessment to the reactions incurred during the AR101 trials. Epi use and anaphylaxis occurred at high rates versus avoidance and consequently patients discontinued the trial due to adverse events.

Allergy & Asthma Network stands ready to partner with ICER to support the value assessment and ensure cost-effectiveness of these treatment solutions. We implore the committee to consider true patient-centered outcomes rather than simply QALYs. We advocate for appropriate use of these innovative treatments and believe that when the right treatment is selected for the right patient at the right time, it benefits both the individual patient and the healthcare system.

It is truly a promising time for those in the peanut allergy community. Significant scientific advancements in diagnosis and treatment are exciting. We look forward to the opportunity to provide additional insights and/or patient testimonies. Please do not hesitate to contact me should you have any questions.

All my best,



Tonya A. Winders
President & CEO

References

1. Henry J Kaiser Family Foundation 2017, accessed March 8, 2019, https://www.kff.org/other/state-indicator/total-population/?currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7Dhttps://www.kff.org/other/state-indicator/total-population/?currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D

2. Protudjer JL, Jansson SA, Heibert Arnlind M, et al. Household costs associated with objectively diagnosed allergy to staple foods in children and adolescents. *The journal of allergy and clinical immunology in practice.* 2015;3(1):68-75.

3. Cannon HE. The economic impact of peanut allergies. *The American journal of managed care*

Asthma and Allergy Foundation of America

May 8, 2019

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
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Boston, Massachusetts 02109

Dear Dr. Pearson:

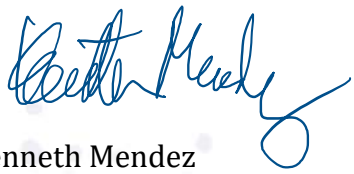
Outlined below are comments from The Asthma and Allergy Foundation of America ("AAFA") on the draft questions for deliberation by the CTAF at its June 11, 2019 meeting on Oral Immunotherapy and Viaskin® Peanut for Peanut Allergy: Effectiveness and Value.

- Why doesn't question 6 have the same available answers as question 5?
- Why isn't ICER asking if AR101 offers reduced complexity (as compared to other OIT)?
- Question 5e and 6c should include the **caregiver's** ability to return to work/school/productivity (not just the patient's)
- Questions 5 and 6 should also ask about quality of life. The questionnaire covers "burden," but quality of life is different. For example:
    - Emotional and mental health from reduced anxiety/fear/isolation/depression,
    - Financial impact resulting from the ability to consume more types of products (e.g. products made on shared equipment with peanut products),
    - Social impact allowing visits to certain restaurants, ability to attend sleepovers/baseball games/birthday parties, air travel etc.

- Questions 5 and 6 should include these additional choices:
    - This intervention will have a significant impact on broadening patients' diets
    - This intervention will have a significant impact on reducing patients' and caregivers' social isolation

We hope that these comments are helpful as you finalize your voting questions.

Sincerely,



Kenneth Mendez
President and Chief Executive Officer
Asthma and Allergy Foundation of America

Asthma and Allergy Foundation of America

May 8, 2019

Steven D. Pearson, MD, MSc
President
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Dear Dr. Pearson:

The Asthma and Allergy Foundation of America ("AAFA") thanks the Institute for Clinical and Economic Review ("ICER") for the Draft Evidence Report "Oral Immunotherapy and Viaskin Peanut for Peanut Allergy: Effectiveness and Value" (April 9, 2019) and the work that went into developing it.

While AAFA questions some of the methodology in ICER's analysis, we agree with the general conclusion of ICER's main finding:

- **Both AR101 and Viaskin Peanut can yield benefits for people with peanut allergy, largely due to the improved subjective quality of life improvements for patients and caregivers.**
- **The cost of these therapies once introduced into the marketplace will have an impact on their long-term effectiveness for patients**.

We appreciate that ICER is calling attention to the prevalence of peanut allergy among children in the United States, the $24.8 bn economic cost to the United States, and the challenges families and caregivers must live with in managing this disease.

However, we believe that ICER understated or overlooked some important points in its analysis, specifically that

- **The absence of a societal perspective in the base case scenario misrepresents the value of these treatments.**
- **The analysis does not adequately account for potential "Spillover Benefits" from the therapies.**
- **Health utility assumptions used in the analysis are flawed.**
- **Incremental vs. "Avoidance Alone" QALYs are understated resulting in an undervalue of the cost effectiveness of the two therapies.**

On the surface, ICER solicits patient feedback and expresses a desire to include the patient perspective in its analyses. ICER's modeling is sophisticated enough to include the patient perspective in the base case of its models. However, it does not. Until ICER includes the societal perspective in base case analyses, ICER will continue to claim outcomes that are unrealistic and will ultimately do more harm than good for patients.

Societal Perspective Reference Case

Solely focusing on direct medical costs for the "base case" analysis with a modified societal perspective in the sensitivity analysis seriously misrepresents the *value* of a treatment for any food allergy. In the case of food allergy, families impacted have consistently reported that food allergy significantly impacts meal preparation and social activities.[1,2] Because there is little credible economic data nor are either of these products launched commercially, the societal perspective is perhaps the most important factor in this analysis. Moreover, methodologically, while we understand that the direct medical costs are of interests to many stakeholders (particularly payers) and should be explicitly reported, The Second Panel on Cost Effectiveness recommends that economic models should report both perspectives (societal and heath sector) and produce an impact inventory to aid in decision making.[3,4]

Additionally, we find it concerning that ICER would choose a paper focusing on household costs only as a citation for the health state utility estimates in the model, but ignore the primary purpose of the paper which was stated clearly in the title: "Household Costs Associated with Objectively Diagnosed Allergy to Staple Foods in Children and Adolescents."[5]

"Spillover Benefits"

ICER's utility analysis does not seem to fully account for the benefits caregivers' experience. While the societal perspective analysis attempts to capture costs important to caregivers (co-payments, special diets, childcare, and opportunity costs due to caregiver productivity losses), the utility gains do not account for potentially quality of life gains attributed to the caregiver – potentially underestimating the true societal value.[6] A recent review of cost-utility analyses for Alzheimer's Disease found that incorporating spillover effects improved the cost-effectiveness ratio below the accepted threshold in 1/3 of the cases.[7] The impact of food allergy extends beyond the individual patient as it changes how the entire family must live to accommodate a peanut-sensitive child. In addition to the missed costs described above, we are unable to determine whether the ICER model formally accounts for potential spillover benefits in the denominator for the parents. The methods state a scenario analysis was conducted in which "caregiver utility added to the societal perspective" but the disclaimer in the impact inventory (Table E1) suggests otherwise.

Health Utility Assumptions

The use of the Protudjer study and the EQ-5D utility data as an anchor for the utility assumptions in the ICER peanut model are flawed. There are 5 domains in EQ-5D: mobility,

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[1] Bollinger ME et al. *Ann Allergy Asthma Immunol*. 2006;96:415–21.
[2] Springston EE et al. *Ann Allergy Asthma Immunol*. 2010;105:287-294.e3.
[3] Weinstein MC et al. *J Am Med Assoc*. 1996;276:1253–8.
[4] Sanders GD et al. *J Am Med Assoc*. 2016;316:1093–103.
[5] Protudjer JLP et al. *J Allergy Clin Immunol Pract*. 2015;3:68–75.
[6] Brouwer WBF. *Pharmacoeconomics*. 2018;37:451–6.
[7] Lin P-J et al. *Pharmacoeconomics*. 2019;37:1–12.

self-care, usual activities, pain/discomfort, and anxiety/depression.[8] However two of the five; mobility ("walk about") and self-care ("wash or dress myself"), have little to do with outcomes related to whether a child can or cannot eat peanuts. If two of the five measures in EQ-5D do not apply then is EQ-5D the correct instrument to use for such a fundamental part of ICER's analysis?

In the use of EQ-5D as part of the Protudjer study, there are statistically significant differences in perceived health status between case (food allergy) and control (general population) groups. This difference will influence the resulting EQ-5D utility scores in those groups. Because the case (food allergy) group has much higher perceived health status than the control (general population) group in the study, this beginning difference in perceived health status suggests that the two are not unbiased comparisons. Any difference in EQ-5D utility scores between the two groups would be an underestimate. Since ICER is using this relative difference as a proxy for the difference in HRQoL for people 'cured' (effectively treated) and those not cured in its peanut allergy model, this means the net value of any treatment in the ICER model will be an underestimate.

AAFA has conducted its own basic utility research including in Appendix A. We appreciate ICER's willingness to engage AAFA in contributing some utility questions. Since the availability of utility estimates is sparse, modelers acknowledge this assumption as an "average utility of the untreated with peanut sensitivity and peanut tolerant health states." We hope ICER uses some of our findings to develop more realistic utility estimates.

Incremental vs. "Avoidance Alone"

Upon review of the model's base case findings, we noted a discrepancy between the quality-adjusted life year (QALY) results reported in tables 4.13 and 4.14. We would expect the total cost, QALY, and life years results to be consistent. However, "Avoidance Alone" provides 26.43 QALYs in Table 4.13 compared against AR101 and "Avoidance Alone" provides 26.53 when compared to Viaskin. This difference would have the impact of overestimating the QALYs gained in Table 4.13 or underestimating the QALYs gained in Table 4.14.

Conclusion: How ICER Reports the Results—It Matters

Throughout this process, ICER staff has reminded us that the "contextual considerations" and sensitivity analyses are taken very seriously in the final determination. While we appreciate ICER's commitment to go beyond the "Cost/QALY" in making recommendations, we must urge ICER to consider our highlighted concerns. If ICER's final conclusion from this report is just a single base case built solely on the health sector perspective for a disease with significant indirect and non-medical costs then ICER will be presenting an inaccurate assessment of the utility of these new therapies. While we believe that ICER wants to establish the true value of these new technologies, we fear that how ICER results are reported will miss a large piece of the value proposition for those kids, caregivers, and families who have peanut allergies. We

[8] Whitehead SJ, Ali S. *B Med Bull*. 2010;96:5–21.

urge you to follow the recommendations of the Second Panel at a minimum and report both health sector and societal cost perspectives in your primary results table.[9]

ICER's work opens a much needed dialogue about issues that have a direct impact on our lives and have implications for patients who need innovative, life-enhancing therapies to address conditions like peanut allergies. However, this assessment acknowledges (pg. 21) a significant amount of uncertainty in developing ICER's findings:

> …The primary benefit of desensitization to peanuts in patients with peanut allergy is likely to be the improvements in quality of life for both the patient and caregivers. However, the quality of life outcomes for the phase 3 trials have not yet been published. *It is challenging to fully evaluate the impact of these therapies without placebo-controlled assessments of the change in quality of life*….

We encourage ICER to act responsibly, especially if good data does not exist to pursue a reasonable analysis. If this assessment is like ICER's recent Asthma Review, ICER will summarize the final assessment and output from the voting meeting into two pages with little reference to the patient perspective and to critiques provided by comment letters like this one. We appreciate ICER bringing attention to peanut allergies, but we hope that ICER leadership acknowledges the significant shortcomings of this peanut analysis.

Again, I thank you for your willingness to engage with our organization and our patient community.

Sincerely,

Kenneth Mendez,
President and Chief Executive Officer
Asthma and Allergy Foundation of America

[9] Sanders GD et al. *J Am Med Assoc*. 2016;316:1093–103

APPENDIX A

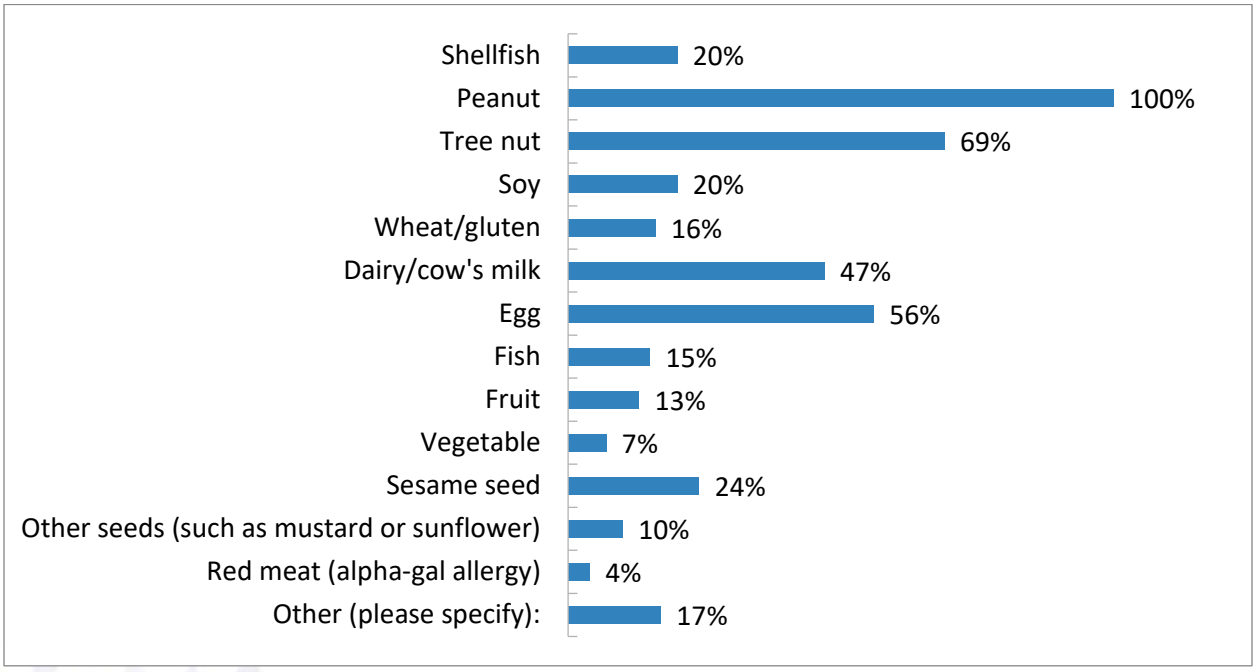
In April 2019, the Asthma and Allergy Foundation of America (AAFA) conducted an online survey to gather information about the patient and caregiver experience with food allergy. A total of 2,223 responses were recorded; 1,234 from caregivers of children with diagnosed food allergy and 989 from patients (age 13 and over) with diagnosed food allergy.

Among the caregivers, 853 respondents confirmed that their child had been diagnosed with a peanut allergy. The following data relate only to those 853 caregivers of children with peanut allergy.

Demographics: The ages of the child with peanut allergy ranged from infant to young adult: 1% were between 0-11 months old, 19% were between the ages of 1 to 4 years old, 51% were between the ages of 5 to 12 years old, 26% were between the ages of 13 to 17 years old and 4% were between the ages of 18 and 23 years old. We also provided the opportunity for respondents to tell us the race of the child with food allergy; 69% were white, 12% were Latino, 5% were Asian, 4% were black/African American and 9% preferred not to answer.

Comorbidities: Nearly all (93%) of respondents indicated that their child had multiple food allergies. In addition to peanut allergy, 69% also had a tree nut allergy, 56% also had an egg allergy and 47% had a milk allergy. (Figure 1)

Figure 1: Overlapping Food Allergies



Base: Which of the following food allergies has your child been diagnosed with (by a health care professional)? N=853

Most respondents also identified other comorbid conditions that their children had been diagnosed with: 56% had seasonal allergy, 49% had non-seasonal allergy, 53% had atopic dermatitis and 49% had asthma.

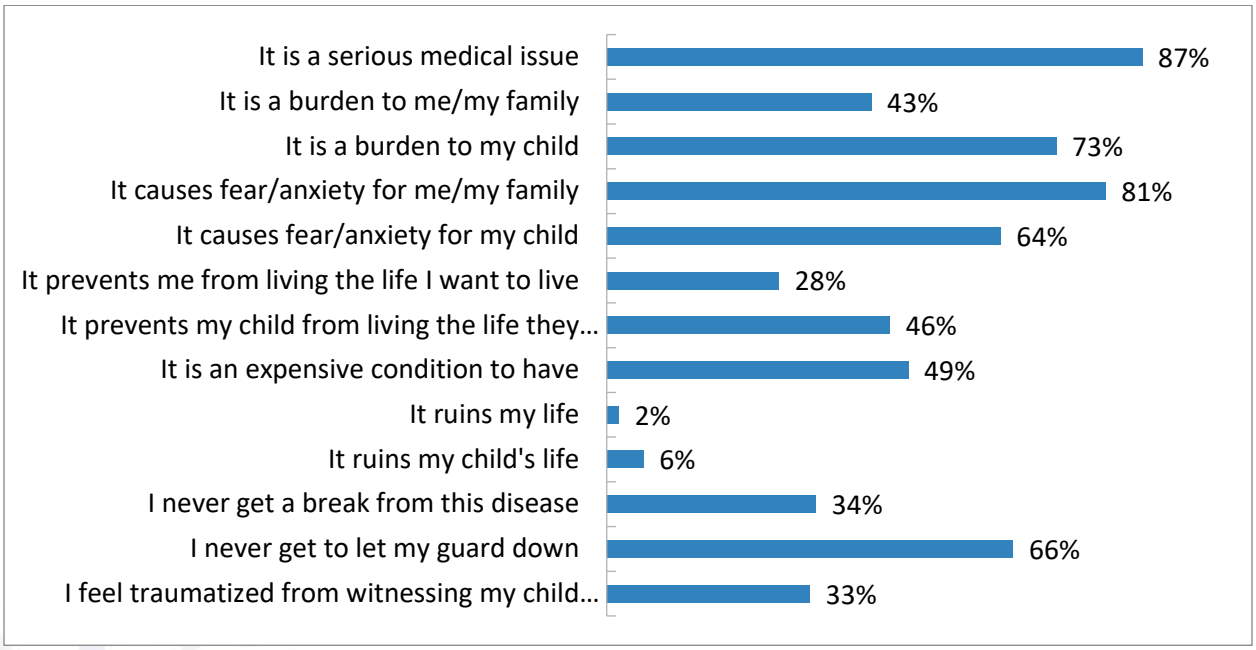
Clinical Experience: Experience with food allergy varied among respondents, with 4% diagnosed less than a year ago, 34% diagnosed 1-5 years ago, 37% diagnosed 6-10 years ago and 25% diagnosed more than 10 years ago. When asked how many "severe" allergic reactions the child has had to the best of the caregiver's knowledge, 13% said zero, 21% said one, 26% said two, 20% said three, 10% said four, 7% said 5-10 and 4% said more than ten. We did not confirm which of these reactions caused by exposure to peanut specifically.

Quality of Life: When asked how often the child with peanut allergy skips or limits daily tasks or social activities because of food allergy, 20% said often, 46% said occasionally, 25% said rarely and 9% said never.

Additionally, 51% said they have avoided airline travel due to food allergy, 94% have avoided certain restaurants, 21% have changed schools, 84% have changed family traditions to accommodate for food allergy, 36% have stopped talking to friends/family because of their lack of empathy with/understanding of food allergy and 81% have volunteered to host certain events in order to ensure food is safe.

Caregiver burden: Food allergy is often at the top of mind for caregivers; when asked how often they think about their child's food allergy, 86% of respondents said "always/always in the back of my mind." Respondents also said they could never let their guard down (66%) and could never get a break from this disease (34%). Thirty-three percent felt traumatized from witnessing their child have a severe allergic reaction. (Figure 2)

Figure 2: Caregiver Beliefs About Their Child's Food Allergy

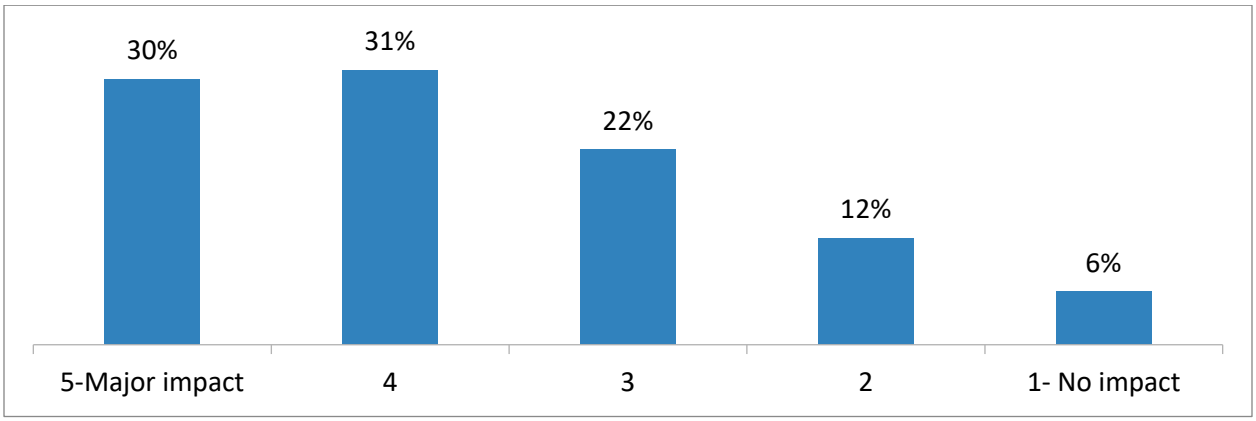


Base: In thinking about your child's food allergy, which of the following do you believe? N=853

The survey identified common themes of fear, anxiety, isolation and depression among caregivers of food-allergic children. Fifty-eight percent of respondents said they always feel fearful of accidental exposure to a known food allergen and 57% said they always feel fearful of cross contamination with a known food allergen.,

About a quarter of respondents (26%) said they are seeing (or have seen in the past five years) a mental health professional related to their child's food allergy. Additionally, Figure 3 captures the extent to which respondents felt that their child's food allergy impacted their own mental health.

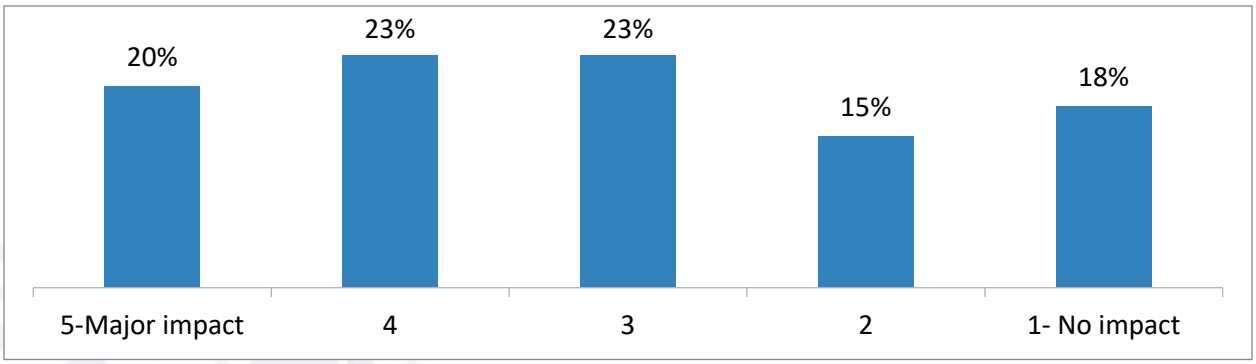
Figure 3: Mental Health Burden for Caregivers



Base: On a scale of 1 to 5, how much of an impact do you think your child's food allergy has on each of the following aspects of YOUR life? (MENTAL HEALTH) N=853

Financial burden: Forty-one percent of respondents said they or their spouse have had to make a career choice (such as quitting or changing jobs) in order to care for a child with food allergy. More than half (55%) have missed at least one day of work in the past year because of their child's food allergy (12% had missed more than 5 days). Additionally, Figure 4 captures the extent to which respondents felt that their child's food allergy impacted their finances.

Figure 4: Financial Burden



Base: On a scale of 1 to 5, how much of an impact do you think your child's food allergy has on each of the following aspects of YOUR life? (FINANCES) N=853

FARE
Food Allergy Research & Education

May 8, 2019

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

RE: Oral Immunotherapy and Viaskin® Peanut for Peanut Allergy: Effectiveness and Value Draft Evidence Report

Dear Dr. Pearson:

FARE thanks the Institute for Clinical and Economic Review (ICER) for engaging with the peanut allergy community to inform its Peanut Allergy assessment. We aim to ensure that the Peanut Allergy Assessment reflects the value that breakthrough therapies can offer to patients, their families and caregivers who face significant care challenges and psychosocial burdens every day from managing peanut allergy and its potentially life-threatening effects upon exposure.

In this light, FARE appreciates the opportunity to comment on ICER's Peanut Allergy: Effectiveness and Value Draft Evidence Report In particular, we respectfully request the following refinements to the Draft Evidence Report to better reflect the value these therapies can provide to patients:

1. Better quantify the life-long costs of the physical and psychosocial burden children and adolescents with peanut allergy face in their daily lives.
2. Increase the annual costs in the societal perspective analysis to more accurately account for family and caregiver psychosocial and physical burden in caring for children and adolescents with peanut allergy.
3. Reflect the potential for reduction in care disparities for children and adolescents with peanut allergy across racial, ethnic, gender, socio-economic, and geographic categories as a result of new access to previously unavailable treatment options.
4. Recognize the two breakthrough therapies considered in the analysis offer significant and meaningful value to patients and their families by giving treatment options to patients where no treatment currently exists.
5. Implement further distinctions in health state utilities to better reflect the varied, individual outcomes that patients with peanut allergy experience.
6. Incorporate costs for ongoing primary care and mild reactions to peanut exposure that occur in everyday life.
7. Use private commercial insurance rates to more accurately reflect direct medical care costs borne by patients, their families, and insurers in treating children with peanut allergy.

FARE's comments reflect our strong desire to continue working with ICER and other stakeholders to ensure that all patients with peanut allergy have affordable access to breakthrough therapies that treat this potentially life-threatening disease and better enable them to live safe, productive lives with less anxiety and burden over potential exposure.

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1. Child and Adolescent Physical and Psychosocial Disease Burden

Research clearly shows that children and adolescents with peanut allergy face ongoing daily challenges and disruption in their lives due to the potentially life-threatening disease such as:

- Social isolation;
- Depression;
- Difficulty in school performance;
- Difficulty in leisure activities; and

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- Fear of allergic reaction.[1] [2] [3]

These persistent physical and psychosocial burdens can negatively impact a child or adolescent's quality of life in meaningful ways, unfortunately inhibiting their social interactions and school performance. Moreover, U.S. adolescents can perceive their food allergy as a burden to others, further adversely affecting the family and social interactions in their daily lives.[4]

Of significant concern is that some adolescents with food allergies may underestimate the severity of their disease, thinking they generally will not "die from any cause," which may result in risk-taking behaviors that can increase the risk of dying from food allergy.[5] For example, adolescents may not always carry epinephrine due to burden or the incorrect view that they do not need it, placing themselves in potentially life-threatening situations.[6] Further, in the case of some adolescents, parents may not recognize the adverse social impact of food restrictions or annoyance at having to carry epinephrine, potentially causing disruption in the relationship between parents and their children with food allergy.[7]

FARE appreciates that the Draft Evidence Report incorporates Quality of Life inputs for children and adolescents with peanut allergy. However, we urge ICER to better quantify these costs in the Final Evidence Report to more appropriately recognize the physical and psychosocial burden and risk that individuals with peanut allergy face on an ongoing basis.

2. Parent and Caregiver Psychosocial and Physical Care Burden

Research visibly demonstrates that parents and caregivers of children with peanut allergy experience ongoing psychosocial burden and anxiety that others simply do not face. Parents and caregivers must constantly ensure that their children adhere to a special diet to avoid preventable peanut exposure, have immediate access to epinephrine when accidental peanut exposure occurs, and receive appropriate ongoing medical care for peanut allergy. Research further shows that continuous psychosocial and physical care burden can result in meaningfully reduced quality of life for parents and caregivers of children with peanut allergy, as well as negatively impact work productivity and career continuation and advancement. As such, FARE appreciates that the societal analysis perspective in the Draft Evidence Report accounts for some costs associated with parent and caregiver burden, but urges ICER to increase the assumed amounts in the Final Evidence Report to more accurately affect the costs of the oftentimes significant burden they face, particularly including:

- **Persistent anxiety and stress:** Research broadly shows that parents and caregivers can have substantially lower quality of life due to persistent anxiety over potential child peanut exposure. In a study of more than 850 parents of children with food allergy, researchers found that mothers experienced significant adverse impact on quality of life primarily due to concern over accidental allergen exposure in environments like school and daycare where parents cannot control child access to potential foods allergens.[8] Similarly, another study found 41 percent of caregivers reporting significant impact on their stress levels as a result of their child's food allergy.[9] In a separate survey of parents of children with peanut allergy in the United Kingdom, nearly one-third of participants reported levels of anxiety indicating "probable clinical caseness" on the Hospital Anxiety and Depression Scale (HADS) – almost double the prevalence in the UK population overall.[10] Notably, a survey of 1,126 U.S. parents found that caregivers who were more knowledgeable

[1] Antolin-Amerigo D, Manso L, Caminati M, et al. Quality of life in patients with food allergy. Clin Mol Allergy. 2016:14:4.
[2] Walkner M, Warren C, Gupta RS. Quality of life in food allergy patients and their families. Pediatr Clin North Am. 2015 Dec;62(6):1453-61.
[3] Stensgaard A, Bindsley-Jensen C, Nielsen D, Munch m, DunnGalvin A. Quality of life in childhood, adolescence and adult food allergy. Patient and parent perspectives. Clinical and experimental allergy; journal of the British Society for Allergy and Clinical Immunology. 2017:47(4):530-539.
[4] Antolin-Amerigo D, Manso L, Caminati M, et al. Quality of life in patients with food allergy. Clin Mol Allergy. 2016:14:4.
[5] *Ibid.*
[6] *Ibid.*
[7] *Ibid.*
[8] Warren C, Gupta R, Sohn, M et al. Differences in empowerment and quality of life among parents of children with food allergy. Annals of Allergy, Asthma & Immunology. 2015 Feb;114(2):117-125.
[9] Bollinger ME, Dahlquist LM, Mudd K, Sonntag C, Dillinger L, McKenna K. The impact of food allergy on the daily activities of children and their families. Ann Allergy Asthma Immunol. 2006 Mar;96(3):415-21.
[10] Acaster S, Gallop K, Andrea V, de Vries J. The parental burden of caring for a child with peanut allergy in the UK. ISPOR Europe 2018; Barcelona, Spain.

about food allergy and those whose children who had been to the emergency department in the past year, had multiple food allergies, or were allergic to specific foods were significantly more likely to experience poor quality of life.[11]

Further, research demonstrates that parental and caregiver anxiety generally worsens relative to the severity of their child's allergy. One study illustrated, for example, that parental anxiety measured by EuroQoL-5-Dimension responses correlated substantially with the proxy-reported severity rating (mild, moderate, severe) of their child's peanut allergy; in other words, the more severe the proxy-reported peanut allergy, the worse the parent scored on health-related quality of life (HRQL). [12]

- **Child and family social limitations:** Parents of children with peanut allergy have heightened concern that their child's risk of death impairs daily living activities and disrupts the family/social dimension of family relations.[13] [14] In one study, 49 percent of parents indicated that food allergy affected family social activities.[15] A separate survey of 1,126 U.S. parents of children with food allergy found that most parents had concern about their child's social limitations due to food allergy and 40 percent of parents of children with food allergy reported experiencing hostility from other parents when trying to accommodate their child's food allergy.[16]

- **Marriage and relationship strain:** Peanut and other food allergies can significantly negatively impact parent and caregiver adult relationships. For example, one study found that 25 percent of U.S. parents of children with food allergy reported food allergy caused a strain on their marriage or relationship. [17] Unfortunately, such strains can adversely affect the children with food allergies, as well as the adults who care for them.

- **Physical care:** Parents and caregivers of children with peanut allergy must take physical care of their children in ways that others do not. In certain cases, for instance, the anxiety from food allergy can cause parents to home school their children, substantially increasing the physical care and educational support parents provide for these children.[18] Moreover, parents and caregivers must ensure their children follow strict diets free of peanut exposure. One study concluded, for example, that food allergy significantly impacted meal preparation.[19] FARE notes here that the Draft Evidence Report appropriately recognizes that children with peanut allergy require special diets, but does not appear to explicitly include a cost for such preparation.[20]

- **Loss of work productivity and career impact:** Ongoing burden and anxiety can negatively impact family member and caregiver work productivity and careers. In one survey of U.K. parents of children with peanut allergy, parents reported an average of 1.5 days off work in the prior 12 months due to their child's peanut allergy and that their productivity at work was impacted for an average of two days in the last year, with over half reporting a more than 50 percent

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[11] Springston EE, Smith B, Shulfruff J, Pongracic J, Holl J, Gupta RS. Variations in quality of life among caregivers of food allergic children. Annals of Allergy, Asthma & Immunology. 2020 Oct;105(4):287-294.
[12] *Ibid*.
[13] Primeau MN, Kagan R, Joseph L, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology. 2000:30(8): 1135-1143.
[14] Stensgaard A, Bindsley-Jensen C, Nielsen D, Munch m, DunnGalvin A. Quality of life in childhood, adolescence and adult food allergy. Patient and parent perspectives. Clinical and experimental allergy; journal of the British Society for Allergy and Clinical Immunology. 2017:47(4):530-539.
[15] Bollinger ME, Dahlquist LM, Mudd K, Sonntag C, Dillinger L, McKenna K. The impact of food allergy on the daily activities of children and their families. Ann Allergy Asthma Immunol. 2006 Mar;96(3):415-21.
[16] Springston EE, Smith B, Shulfruff J, Pongracic J, Holl J, Gupta RS. Variations in quality of life among caregivers of food allergic children. Annals of Allergy, Asthma & Immunology. 2020 Oct;105(4):287-294.
[17] Gupta RS, Springston EE, Smith B, Kim JS, Pongracic JA, Wang X, Joll J. Food allergy knowledge, attitudes, and beliefs of parents with food-allergic children in the United States. Pediatric Allergy Immunology. 2010 Sep;21(6):927-34.
[18] *Ibid*.
[19] Bollinger ME, Dahlquist LM, Mudd K, Sonntag C, Dillinger L, McKenna K. The impact of food allergy on the daily activities of children and their families. Ann Allergy Asthma Immunol. 2006 Mar;96(3):415-21.
[20] ICER. Oral Immunotherapy and Viaskin® Peanut for Peanut Allergy: Draft Evidence Report, page 36.

reduction in work productivity.[21] Further, 24 percent reported an impact on their careers as a result of their child's peanut allergy, including job change (10 percent), job given up (7 percent), career choice restricted (7 percent), and job loss through dismissal (1 percent).[22]

Again, while FARE appreciates that the Draft Evidence Report includes annual out-of-pocket costs and productivity loss in the societal perspective analysis, we urge ICER to include the additional costs for each of the aforementioned psychosocial, physical, and work burdens that substantially impact the quality of life of parents and caregivers of children and adolescents with peanut allergy.

3. Potential Reduction in Care Disparities

Research illustrates that disparities in the diagnosis of peanut allergy persist despite physicians diagnosing the allergy in nearly 75 percent of patients.[23] Specifically, in a cross sectional survey administered to 38,480 U.S. parents from 2009 to February 2010, 3,218 children were identified with food allergy and, of those, 754 (24.8 percent) were reported to have a peanut allergy.[24] Peanut allergy was reported most often among 6- to 10-year old children (25.5 percent), white children (47.7 percent), and children from households with an annual income of $50,000 - $99,999 (41.7 percent).[25] Notably, research also shows that childhood peanut allergies are twice as prevalent in urban environments (2.8 percent) compared to rural communities (1.3 percent) in the U.S.[26] Research demonstrates that children from non-white and lower income U.S. households have lower rates of peanut allergy diagnosis than their peers and there is a reasonable likelihood that they are undiagnosed at even higher rates in urban areas given the increased prevalence of the disease in urban environments.

With the anticipated Food and Drug Administration (FDA) approval of breakthrough therapies for peanut allergy, heightened attention to childhood peanut allergy likely will occur and children who otherwise may not have been diagnosed may receive peanut allergy diagnosis and gain new access to care and avoid preventable adverse outcomes. FARE very much hopes that increased focus and attention will lead to improved rates of appropriate diagnosis and new availability of treatment options for children with previously undiagnosed peanut allergy who need this critical access to care, ultimately reducing gaps and disparities in care for often disadvantaged and underserved children. FARE urges ICER to formally recognize the value in the Final Evidence Report of this important reduction in care disparity that likely will result because of the availability of breakthrough therapies for peanut allergy.

4. Recognition of Breakthrough Therapies for Life-Threatening Disease With No Treatment Options

Patients currently do not have any available therapies approved by the FDA to treat peanut allergy. The current standard of care – avoidance followed by epinephrine and visit to the emergency department in the event of exposure – is not treatment. Hence, FARE and the broader peanut allergy community are very excited for anticipated patient access to multiple FDA-approved therapies that treat this potentially life-threatening disease.

Recognizing the innovative nature of Viaskin® Peanut and AR101, FARE urges ICER to formally consider the value of the breakthrough status of both of these therapies in the Final Evidence Report. We further respectfully request that ICER fully factor this into the written Assessment, particularly given the ongoing burden of disease for patients and their families and the potential for life-threatening adverse events from exposure.

5. Refining Health Utility States to Reflect Varied Individual Patient Outcomes

Children and adolescents with peanut allergy can experience very different levels of treatment responsiveness, de-sensitization and outcomes depending on their individual characteristics. To reflect the varied patient experiences, FARE

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[21] Acaster S, Gallop K, Andrea V, de Vries J. The parental burden of caring for a child with peanut allergy in the UK. ISPOR Europe 2018; Barcelona, Spain.

[22] *Ibid*.

[23] Dyer AA, Rivkina V, Perumal D, Smeltzer BM, Smith BM, Gupta RS. Epidemiology of childhood peanut allergy. Allergy Asthma Proc. 2015 Jan-Feb;36(1):58-64.

[24] *Ibid*.

[25] *Ibid*.

[26] Gupta RS, Springston EE, Smith B, Warrier MR, Pongracic J, Holl JL. Geographic variability in childhood food allergy in the United States. Clin Pediatr (Phila). 2012 Sep;51(9):854-61.

respectfully requests that ICER refine the Draft Evidence Report to incorporate more distinctions in the various health states modeled in the Final Evidence Report.

For example, the Draft Evidence Report assumes that patients become desensitized to peanut allergy or not after year one and does not account for the potential for increased tolerance over time (e.g., the ability of the patient to tolerate a higher dose). A patient who is desensitized after year one receives a utility value under the current model, while others who do not achieve this level of tolerance do not. FARE believes a one year timeframe simply is arbitrary and does not reflect the experiences of individual patients. Thus, FARE requests revising the model to formally consider the utility to a patient of an increased tolerance of a higher dose over a specified time period, even if that period is less than one year.

6. Incorporation of Medical Costs for Ongoing Primary Care and Mild Reactions to Peanut Exposure

While FARE strongly supports inclusion of the significant direct medical costs of severe adverse events (AEs) associated with peanut exposure, we further respectfully request that the model incorporate other medical costs for mild reactions to exposure as well as ongoing increased primary care costs associated with the disease. For example, patients with peanut allergy can experience dermatological, respiratory, and gastrointestinal reactions from peanut exposure that, while not life-threatening, can result in the need for medical care.[27] FARE believes the Final Evidence Report should reflect the value to patients, their families, and insurers that these breakthrough therapies offer through helping to avoid the medical costs associated with more mild reactions to peanut allergy exposure and ongoing medical care to treat to the disease.

7. Reflection of Commercial Reimbursement Rates in Patient Direct Medical Care Costs

The Draft Evidence Report incorporates unit prices for AE direct medical costs based on the Centers for Medicare and Medicaid Services (CMS) Medicare Physician Fee Schedule Final Rule and Correction Notice Tables for 2018. Rather than the Medicare rates, however, FARE urges that the Final Evidence Report to include private commercial insurance rates for medical care. Given that Medicare primarily covers seniors and not children, private commercial reimbursement rates for medical costs are more appropriate for inclusion in the Final Evidence Report.

Analyses by the Congressional Budget Office and others notably indicate that private sector rates generally are higher than Medicare rates.[28] [29] [30] Hence, FARE urges ICER to include these higher commercial rates in the Assessment to more accurately reflect the costs that patients, their families and insurers experience in treating children with peanut allergy. Additionally, while FARE disagrees with this approach, if ICER opts to use the Medicare Physician Fee Schedule rates, FARE requests that the Peanut Allergy Assessment include the reimbursement amounts for 2019, which are now available.

Conclusion

FARE again wishes to thank ICER for engaging with the peanut allergy community on this critically important advancement in treatments for individuals with peanut allergy and specifically for the opportunity to comment on the Peanut Allergy: Effectiveness and Value Draft Evidence Report. We look forward to our ongoing dialogue on this important assessment to make sure that patients and their families have affordable access to innovative therapies that for the first time have the potential to treat the potentially life-threatening condition of peanut allergy.

Sincerely,

Lisa Gable
Chief Executive Officer
Food Allergy Research & Education

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[27] *Ibid*.

[28] Congressional Budget Office. "An Analysis of Private-Sector Prices for Physician Services." June 26, 2017.

[29] Baker L, Bundorf M, Royalty A. Private insurers' payments for routine physician office visits vary substantially across the United States. Health Affairs. 2013:32(9).

[30] Berenson R, Ginsburg P, Kemper N. Unchecked provider clout in California foreshadows challenges to health reform. Health Affairs. 2010:29(4).

May 8, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Draft Evidence Report "Oral Immunotherapy and Viaskin® Peanut for Peanut Allergy"

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with life-threatening conditions and chronic diseases for them to have access to vital therapies and services. Access is a matter of survival and quality of life for those patients, and it spans affordability, insurance coverage, and physical access. To support improved access, we engage all stakeholders to foster realistic, patient-centered discussions for particular conditions and the U.S. health care system. That is, our goal is a balanced dialogue that illuminates the truth about health care in a just and equitable way.

We appreciate the opportunity to provide our comments on ICER's April 9th Draft Evidence Report, "Oral Immunotherapy and Viaskin® Peanut for Peanut Allergy."

As the draft report makes clear, there is very limited evidence about patient perspectives and quality of life concerning the two investigational treatments described in the report, i.e., "No data on participant quality of life were reported."[i] There is also extremely limited data about existing, unapproved oral immunotherapy preparations. We will return to this analytical conundrum in our comments below, which are organized into sections concerning: Patient Perspectives and Issues; Data Challenges; Uncertainties and Limitations; QALYs; and Other Matters.

Patient Perspectives and Issues

We are encouraged that ICER investigated patient concerns and perspectives about peanut allergies by having discussions with patients and patient group, and noted these observations: [ii]

- "Patients and their caregivers often lead a lifestyle that may be heavily impacted by fear and anxiety."
- "An important goal for patients is to be able to live and eat more freely."
- "Patients and their caregivers experience tremendous anxiety, stress, and report poor quality of life."
- "Caregivers frequently miss time from work."
- "Patients with peanut allergy may feel they are restricted in where they live"
- "patients and families may choose not to travel via airplane or travel abroad."

We also want to note the very important patient perspectives related to access and affordability that are critical concerns for patients:[iii]

- "Unregulated OIT [oral immunotherapy] that is practiced now may not always be reimbursed by insurance since it can be viewed as experimental...patients who pursue OIT often pay out of pocket, which can limit access to those who can afford it."
- "Out of pocket expenses are a major issue for patients."

We completely agree that the "primary benefit of desensitization to peanuts in patients with peanut allergy is likely to be the improvements in quality of life for both the patient and caregivers." And to provide ICER with more data, we would have hoped ICER would have worked with the patient groups to develop data similar to the survey ICER conducted with the MS Coalition.[iv] We would encourage ICER to do more of that type of primary data development. However, as the draft report also notes, "the quality of life outcomes for the phase 3 trials have not yet been published. It is [therefore] challenging to fully evaluate the impact of these therapies without placebo-controlled assessments of the change in quality of life,"[v] Given the reality of such limited data – particularly about patient perspectives and quality – we believe it is too early for ICER to conduct this assessment.

Another critical concern for patients is the level of assurance that a treatment will work and that they have an accurate understanding of potential adverse reactions. Therefore, we question ICER's decision to include information from reports about the non-FDA approved OIT peanut protein extracts without such caveats because OIT preparations have uncertain quality assurance and batch-to-batch variability.

In that vein, we also noted the significant adverse event differences described in the draft report, e.g., "the adverse events associated with AR101 appear to be significantly greater than those of Viaskin Peanut"[vi] And,[vii] "The patch was well tolerated with low rates of adverse events – mostly cutaneous and few serious." As well as the specific data cited in the draft report:[viii]

- Withdrawal rates due to adverse events: (11.6% vs. 2.4%) for AR101 and (1.7% vs. 0%) for ViraSkin Peanut
- Serious adverse events were more common in the active treatment group (2.2% vs. 0.8%) for AR101 and (1.3% vs. 0%) for Viaskin Peanut
- Overall withdrawal rates: (21.0% vs. 7.3%) for AR101 and (10.5% vs. 9.3%) for Viaskin Peanut
- Systemic allergic reactions (14.2% vs. 3.2%) for AR101 and (3.8% vs. 1.7%) for Viaskin Peanut

Despite citing those adverse event differences, the draft report's incremental cost-effectiveness ratios do not appear to adequately consider them, which as we've pointed out, can be of considerable importance to patients. Ignoring this very important patient concern and perspective undermines the validity of the draft report's conclusions.

Another area we believe ICER should have further explored is the differences between peanut allergies and other food allergies, since as draft report notes, "peanut allergy is the leading cause of death from anaphylaxis due to food," which indicates the seriousness of peanut allergies compared to other food allergies or intolerances. This is an important consideration, but the draft report's Clinical Guidelines section does not fully distinguish between food allergies generally and peanut allergies, and the draft report's Limitations section explores this problematic merging of peanut and other food allergies: "utility estimates used for the base case model come from a food allergy, but not necessarily peanut allergy, patient population. It is possible that peanut allergy patients specifically hold slightly different preferences for treatment."[ix] Noting this difference in the

Limitations section - but not addressing it in a substantive way in the actual analysis - is very strange given that peanut allergy specific information is the fundamental basis for determining both clinical and economic value of the potential new therapies. We also suggest that ICER discuss the physiological and immunological differences in antigen presentation (i.e., oral versus transdermal routes[x]), since that may be the basis for the adverse event profiles of the two experimental treatments.

And lastly, given the changes in access and affordability that will result from FDA approval of treatments for peanut allergies, we question why racial and socioeconomic differences in rates of peanut allergies (as opposed to the rate of accidental exposures for people with peanut allergies) are not discussed.[xi] With all the uncertainties and assumptions in the draft report's data inputs and modelling, ICER should try and be more comprehensive in elucidating the problems of peanut allergies, who it affects, and actual projections for the composition of what the patient population might look like in the future.

Data Challenges, Uncertainties and Limitations

The draft report's entire modeling process is muddled and very imprecise because of lack of data and extreme assumptions. For example:

- The draft report notes that there is essentially only data for a single year, but the modeling projects out to lifetime effects.
- "We also assumed that participants in the peanut desensitized health state had utility equal to the average of the utilities for the untreated with peanut sensitivity and peanut tolerant health states."[xii]
- "The preference-weighted health-related quality of life literature in food allergy is extremely limited."[xiii]

The draft reports' citations about price projections used to establish the placeholder prices are misleadingly cites as from "analysts." However, the one source cited is a Kaiser Health News article, but that article's sources are two other articles. The first is a February 2018 LA Times story citing the projected price for AR101 from the company CEO.[xiv] The second is a 2015 Reuters news story that states, "Analysts estimate a year's supply of Viaskin at about $6,500 and of Aimmune's treatment [AR1010] at $5,500."[xv] Given that those numbers are from secondary sources (i.e., not from analysts directly), and that they are old reports - and in the case of AR101 provide contradictory numbers - those sources should be provided accurately and with disclaimer that they are secondary sources that have not been directly verified, i.e., not "publicly available analysts' reports." This is a serious deficiency in the draft report.

We also would like to point out the inherent uncertainties and challenges of researching allergies since the symptoms – and physiological responses – can be affected (and sometimes dramatically) by factors other than the exposure to a potential allergen. For example, at the extreme, a patient with Dissociative Identity Disorder (DID, formerly called Multiple Personality Disorder) was found to have different (or no) food allergies among their different personalities.[xvi] This indicates a clear mind-gut-immune system symptomatic connections that in the Western mechanistic perspective of human biology ignores the more realistic systemic and evolutionary reality of the human organism. We bring up this issue, because it calls into question almost all of the results from the unblinded OIT studies, and it also raises questions about the socio-

psychological-environmental aspects of treating peanut allergies and how those factors were either controlled or accounted for in the trials.

We are also confused by the following, and request ICER explain it in plain language since we are concerned it is obfuscating something important: "We also noted that the utility values for ages 12+ were higher than those for the same health state for children age 0-11, which is difficult to reconcile. However, the differences between the health states within each age group are approximately equal. Thus, for the purpose of the model, this difference in absolute utility values between the age groups does not result in differences in incremental QALYs. Using the 0-11-year-old utility values for the entire model time horizon or switching values at age 12 results in the same incremental difference in QALYs between the two treatments. The assumptions for the utility values were explored in the one-way sensitivity analysis using broad ranges for all three utility input values. Uncertainty in the utility values, where overlap occurs between the bounds and the next health state, were programmatically handled in the probabilistic sensitivity analysis. Forcing health states assumed to be ordinal to each other was accomplished by selecting the larger of either a) the maximum drawn from the health state's utility distribution, or b) the value drawn for the next worse health state."[xvii]

On page 37 of the draft report it states that as part of the Model Validation process, "we compared results to other cost-effectiveness models in this therapy area." What other cost-effectiveness models are there in this therapy area given that there are currently no approved therapies? Please specify and explain how such comparisons are meaningful.

Ongoing Concerns about Quality Adjusted Life Years (QALYs)
First, doesn't the lack of quality of life data undermine the analytical validity of calculations for determining QUALITY as part of QALYs? And second, we want to reinforce the widespread concern about QALYs by sharing a quote from an expert in the area from a recent Congressional briefing about Comparative Effectiveness Research:

"The QALY is **extremely problematic,** but it's highly functional for decision making, and you see that. So I'm not saying that to defend it, because I think it's **hugely flawed**, in that it sort of **assumes certain homogeneity** and parallels of what matters to which patient groups. And I do think that for elderly, disabled, etc. etc, it, it's - to the extent it actually informs decision making about what's paid for and how much things are paid for, it's really got some kind of **flimsy underpinnings**."[xviii] [emphasis added]

Other Matters
- Dr. Tice is the lead author, but his clinical expertise seems to be focused on medical treatment of people with cancer and he doesn't have background in allergies or immunology.[xix] How does his background make him an appropriate author for a report on peanut allergies? Why couldn't ICER find someone with expertise or experience directly related to this topic? In addition, according to ICER's website, Dr. Tice is an Advisor to the California Technology Assessment Forum (CTAF).[xx] Is this not a conflict of interest that is not disclosed?[xxi]
- The FDA had granted both investigational agents Fast Track and Breakthrough status.[xxii] This should be described in the draft report and discussed at the CTAF meeting.
- The price used for epinephrine autoinjectors is not given, but rather a citation to a proprietary, non-public database. Given that the price patients have been paying for those

epinephrine delivery devices has been a topic of great public interest, the draft report should list the specific dollar amount it is using for its model – or declare why that price is proprietary and cannot be disclosed.

- In Tables 4.13, 4.14, 4.15 and 4.16, the QALYs in the Avoidance row are different numbers yet the life years in those rows are the same. Is this due to the different age ranges used in the phase 3 clinical trials for the two investigational agents? Also in tables 4.13 and 4.15, the math seems incorrect, the Incremental QALYs should be .21 rather than .22, unless there is a rounding issue not discussed. And we do note that if the QALY number for Avoidance from 4.14 was used in tables 4.15, then the Incremental QALY would be .31, which is an almost 50% increase. Please explain those numbers and how they were derived in detail.
- We note the significant changes between the base case and the modified societal perspectives figures in the draft report, and congratulate ICER for recognizing the importance of societal factors for the value of these potential treatments to patients and society. However, we are very disappointed that despite those findings, the draft report ignores them in reaching its final conclusions and assessments.[xxiii]
- The prices used in the Potential Budget Impact section are "undiscounted," but why is that the case when Medicaid receives a minimum statutory discount, and Medicaid[xxiv] is the source of health insurance for 39% of children 0-18 in the U.S.,[xxv] and that up to 60% of children may be covered by Medicaid at any point during the year.[xxvi] In addition, we noted that in other draft reports ICER has used a discounted price, e.g., 7.4%.[xxvii]

Conclusions

This draft report is based on extremely limited data without patient quality perspectives, and uses many weak assumptions for its modeling. It also takes a very anti-patient perspective about what is value, i.e., ignoring clinical and patient value and solely focusing on economics. For example, the final concluding sentence of "The ultimate value of these products will be determined by the prices that are set by the manufacturers and their long-term effectiveness."[xxviii] confirms ICER's focus on economics. Overall, this may be the worst ICER report so far.

We are optimistic that the general trend of incorporating more patient perspectives and concerns into health care coverage, payment and care decisions – such as is happening at the FDA, CMS and other respectable organizations – will continue, and ICER's impact on patients' lives will continue to decline.

Sincerely,

Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

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[i] Draft Report pp 14-15
[ii] Draft Report pp. 6-7
[iii] Draft Report pp. 6-7
[iv] "Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Effectiveness and Value: Draft Evidence Report," ICER, March 14, 2019.
[v] Draft Report p 21

[vi] Draft Report p. 17
[vii] Draft report p 16
[viii] Draft report p. 14
[ix] Draft Report p. 47
[x] "Dendritic Cells and Their Role in Allergy: Uptake, Proteolytic Processing and Presentation of Allergens," Int. J. Mol. Sci. 2017, 18, 1491 (See section 3. "Different Dendritic Cell Subsets Identified in Skin, Respiratory, and Gastrointestinal Tract and Their Role in Allergy")
[xi] "National prevalence and risk factors for food allergy and relationship to asthma: Results from the National Health and Nutrition Examination Survey 2005-2006," Journal of Allergy and Clinical Immunology, Vol. 126 (4), October 2010, p. 801 - "Food sensitization and PFA/LFA were more prevalent in non-Hispanic black subjects and least prevalent in non-Hispanic white subjects…. these distinctions were greatest for shrimp and peanut."
[xii] Draft Report p. 32
[xiii] Draft Report p. 32
[xiv] "Peanut allergy treatment succeeds in study," LA Times, February, 20 2018, https://www.latimes.com/business/la-fi-peanut-allergy-treatment-20180220-story.html
[xv] "Biotech companies chase elusive peanut allergy treatment," Reuters News, October 27, 2015, https://www.reuters.com/article/us-biotech-peanuts/biotech-companies-chase-elusive-peanut-allergy-treatment-idUSKCN0SL2LK20151027
[xvi] "Dissociative Identity Disorder," Cleveland Clinic, https://my.clevelandclinic.org/health/diseases/9792-dissociative-identity-disorder-multiple-personality-disorder; and "Probing the Enigma of Multiple Personality, New York Times, June 28, 1988, https://www.nytimes.com/1988/06/28/science/probing-the-enigma-of-multiple-personality.html.
[xvii] Draft Report p. 32
[xviii] "Right Care, Right Patient, Right Time: The Role of Comparative Effectiveness Research," Sean Tunis, M.D., M.Sc, Alliance for Health Policy Congressional Briefing, April 17, 2019, www.allhealthpolicy.org/publicbriefing-4172019/
[xix] https://www.ucsfhealth.org/jeffrey.tice
[xx] https://icer-review.org/people/jeff-tice-md/
[xxi] Draft Report p. i
[xxii] Viaskin Peanut and AR101 have both been granted Fast Track and Breakthrough Therapy designation (https://www.dbv-technologies.com/pipeline/viaskin-peanut/), and http://ir.aimmune.com/news-releases/news-release-details/us-fda-accepts-bla-filing-aimmune-therapeutics-ar101-peanut
[xxiii] Draft Report p.46 and 47.
[xxiv] For the purposes of this discussion the term "Medicaid" includes both state Medicaid programs and State Children's Health Insurance Programs (CHIPs).
[xxv] "Health Insurance Coverage of Children 0-18," Kaiser Family Foundation, Timeframe = 2017, www.kff.org/other/state-indicator/children-0-18/?
[xxvi] "Unduplicated Number of Children Ever Enrolled in CHIP and Medicaid," CMS, www.medicaid.gov/chip/downloads/fy-2017-childrens-enrollment-report.pdf
[xxvii] "Draft Evidence Report "Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value," ICER, August 23, 2018
[xxviii] Draft Report p. 47

PIPC Partnership to Improve Patient Care

May 8, 2019

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson,

On behalf of the Partnership to Improve Patient Care (PIPC), I am writing to provide comments on the Institute for Clinical Economic Review's (ICER) draft evidence report on treatments for peanut allergy. Our concerns are largely consistent with previous comments and we continue to urge ICER to evolve its methodology to be patient-centered and incorporate outcome measures that matter to patients and people with disabilities. Unfortunately, ICER's assessments continue to be conducted in a manner that, if used by insurers to make coverage and reimbursement decisions, would be dangerous to patient access and outcomes.

As you may know, researchers estimate that 32 million Americans have food allergies, including 5.6 million children under the age of 18. Caring for children with food allergies costs U.S. families nearly $25 billion annually. The prevalence of childhood nut allergy is estimated to have more than tripled between 1997 and 2008.[1] Peanut reactions can be unpredictable, and even small amounts of peanut contact can cause a severe and potentially life-threatening reaction.[2] Peanut allergy can be particularly anxiety-provoking, as there is no proven way to determine which patients are at risk for life-threating anaphylaxis reactions.[3]

We would like to highlight the following concerns with ICER's draft evidence report:

ICER Overlooks Patient Input and Preferences in Favor of Discriminatory QALYs

Despite the availability of validated quality of life metrics specific to patients with peanut allergy, ICER chose not to incorporate these metrics and instead used quality-adjusted life years (QALYs) in its assessment.

Patients with peanut allergies and their caregivers overwhelmingly look for reduced complexity and reduced caregiver burden. For example, reduced complexity of lifestyle and treatment

[1] Food Allergy Research Network. Facts and Statistics. https://www.foodallergy.org/life-with-food-allergies/food-allergy-101/facts-and-statistics. Accessed April 18, 2019
[2] Food Allergy Research Network. Peanut Allergy. https://www.foodallergy.org/common-allergens/peanut-allergy. Accessed April 18, 2019.
[3] Cianferoni A, Muraro A, Food induced anaphylaxis. Immunol Allergy Clin North Am. 2012; 32(1):165-195.

would be of huge benefit to the nearly 40% of individuals with peanut allergies who experience accidental exposure or reaction.[4] The Allergy and Asthma Network highlighted this lack of patient-centricity in their comments to ICER, stating, "We implore the evaluators to consider patient-reported outcomes rather than simply QALYs. We advocate for appropriate use of these innovative treatments and believe that when the right treatment is selected for the right patient at the right time it inevitably saves the system and the individual patient."

ICER Uses a Faulty Model that Does Not Account for Complexities of the Condition

In this study, ICER chose to use a patient-reported outcome (PRO) tool that is known to be insensitive to allergies.[5, 6] Peer-reviewed literature is replete with examples of where the use of this particular tool, the EQ-5D, has underestimated treatment effect and differences.[7] Yet, ICER continues to choose a PRO tool that is insensitive to the outcome of interest solely because it can easily be cross-walked into a QALY. Doing so is both illogical and deliberately discriminatory to those suffering from disabilities and serious health conditions. As the Asthma and Allergy Foundation of America (AAFA) stated in their comment letter related to ICER's recent review of asthma biologics, "when real-world healthcare data is available, real-world healthcare data should be used to estimate the potential patient population and treatment effectiveness."

An additional flaw in ICER's model is the assumption that everyone begins treatment at seven years of age. The two trials each have broad age ranges, from four to eleven years of age and from four to seventeen years of age. Based on ICER's own assessment, there is some evidence that the younger the treatment recipient, the more effective the intervention (page 16, para 2).[8] With this information, assuming an older age of treatment, and selecting one age for the entire population, minimizes the observed benefits that could be captured if the assessment took a more realistic perspective. It is an overly simplistic choice to address just one single age archetype. Treating patients earlier in life may significantly improve patient quality of life and increase the effectiveness of both interventions, an essential consideration that is not incorporated into ICER's model.

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[4] Panel N.I.-S.E., Boyce J.A. Assa'as A., et al. Guidelines for the diagnosis and management of food allergy in the United States; report of the NIAID-sponsored expert panel. J. Allergy Clin Immunol. 2010;126(6 Suppl):S1-58.
[5] Marklund B, Ahlstedt S, Nordström G. Health-related quality of life among adolescents with allergy-like conditions–with emphasis on food hypersensitivity. Health and quality of lifeoutcomes. 2004 Dec;2(1):65. Flokstra-de Blok BM, Dubois AE. Quality of life in food allergy: valid scales for children and adults. Current opinion in allergy and clinical immunology. 2009 Jun 1;9(3):214-21.
[7] Flokstra-de Blok BM, Van der Velde JL, Vlieg-Boerstra BJ, Oude Elberink JN, DunnGalvin A, Hourihane JO, Duiverman EJ, Dubois AE. Health-related quality of life of food allergic patients measured with generic and disease-specific questionnaires. Allergy. 2010 Aug;65(8):1031-8.
[8] Page 16, para 2 of draft evidence report

ICER Continues Concerning Pattern of Premature Studies

ICER's rush to judgment has significant real-life implications for allergy patients. Because of the very low mortality rates for those with peanut allergies, most of the benefit accrued from these interventions will be seen in improved quality of life. Yet, ongoing studies measuring health-related quality of life (HR-QOL) in these interventions have not been published yet, which ICER acknowledges.[9] By ICER's own valuation of the available evidence for these therapies, evidence on their effectiveness is currently only marked as inconclusive due to a lack of both head-to-head studies and HR-QOL data.[10] This raises the question of why this report is being undertaken at this time when waiting for HR-QOL data would allow for a much more complete, and potentially more accurate, analysis. By conducting the assessment at this time, payers that reference ICER's reports to make coverage decisions will not receive a comprehensive understanding of the treatment's value and could rely on incomplete information to make decisions detrimental to patients' access to care.

Conclusion

ICER continues to use one-size-fits-all models and limited data that do not capture the complexities of different patient populations in their assessments of innovative medical products. PIPC echoes the Asthma and Allergy Network, the Asthma and Allergy Foundation of America, and other patient advocacy groups that have implored ICER to acknowledge that patients are unique individuals with different preferences who respond differently to treatments. Publishing reports that make one-size-fits-all judgements of value is harmful to patients and the health care system as a whole.

Thank you for your consideration of our comments.

Sincerely,

Tony Coelho
Chairman, Partnership to Improve Patient Care

[9] Page 21 of draft evidence report
[10] Pages 22-23 of draft evidence report