Oral Immunotherapy and Viaskin® Peanut for Peanut Allergy: Effectiveness and Value

Response to Public Comments

May 28, 2019

Prepared for

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Manufacturers	
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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. 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).	The net benefit is a balance of benefits and harms. The clear benefits in terms of desensitization have to be balanced with the harms: the challenges with dosing and the frequency of moderate and serious reactions requiring epinephrine use. Part of the uncertainty comes from the short follow-up in the maintenance phase. It is not clear that the rate of serious allergic reactions is decreased compared with ongoing strict avoidance alone over years 2 to 5 and beyond and there are no published data demonstrating improved quality of life / utility while taking AR101.
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 Table 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. Also, not all safety outcomes in PEPITES are reported and are therefore unknown (Appendix D, ICER Draft Evidence Report). 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.	We are comparing AR101 to ongoing strict abstinence, not to Viaskin Peanut. Some could argue that since the rate of epinephrine use with AR101 was more than double that of placebo, AR101 does more harm than good.

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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.	We respectfully disagree. The higher rate of desensitization with AR101 is balanced by a higher rate of adverse events, epinephrine use, and discontinuation of therapy. Only 37% of patients on AR101 in the PALISADE trial enrolled in ARC004, so the results are subject to selection bias. The results of ARTEMIS have not yet been presented nor published in peer-reviewed journals, so we cannot comment on how those results might impact the evidence rating.
ICER must acknowledge – and account for – important limitations in Remington et al. (2018) 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." 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. 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-	We agree that there are limitations to the use of the Remington and Baumert analyses and prefer direct, empirical evidence of benefit and stated as much in the sentence following the one that you highlight. We have added additional text stating that "the generalizability of the modeling predictions to the real world is questionable" and also mentioning the Deschildre results.

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allergic population, as reported in the MIRABEL study. • 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, 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). 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. • In the interest of disclosure, DBV technologies funded the research, which produced both the Baumert and Remington publications. We recommend that ICER remove this biased statement from their report and reconsider this evidence when evaluating the clinical effectiveness of	

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AR101 and Viaskin Peanut for the evidence rating and cost-effectiveness analysis.	
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. 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. 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.	As noted above, only 37% of eligible patients enrolled in ARC004 at the same maintenance dose, so the results are subject to significant selection bias. Thus, they have minimal utility in generalizing the full treated population or those who met the criteria for desensitization at the end of the PALISADE trial. It is likely that those who elected to continue maintenance therapy had higher utilities on treatment than those who elected not to continue. Furthermore, the FAQ-LQ data will not be presented until the first week in June.

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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. We recommend that ICER remove this sentence and reevaluate its modeling approach for the responders from the low-eliciting dose group of PEPITES.	The model does not make any assumptions or calculations to derive eliciting dose from tolerated dose or vice versa. Rather the model calculates the primary efficacy end points from the trials, which are (1) in PALISADE, the proportion of patients able to ingest a dose of 600 mg or more of peanut protein without dose-limiting symptoms at the exit food challenge, and (2) in PEPITES, treatment responders based on eliciting dose of 1000 mg or more after 12 months of therapy.
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).	Thank you for this suggestion, we have updated these estimates in the model.

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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. 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.	Thank you for this suggestion, we have updated these estimates in the model.
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.	We agree with this suggestion, given that only a minority of patients will receive a food challenge in the real world. We recognize that the FDA and/or insurers may eventually require it, but we have dropped this cost from the model until we have more clarity on this point.
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.	We will add an option for reduced complexity to question 6 as it pertains to AR101. ICER's Value Assessment Framework has a standard list of other benefits considerations. For the votes, we select among the considerations that are relevant to the therapy relative to the comparator, in this case, strict peanut avoidance. We initially did not feel an option for 'reduced complexity' was relevant for AR101. But we have reconsidered and will add the option for consideration based on your input.

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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.	We will add an option for Question 6 for our voting panel to consider if AR101 offers a novel mechanism of action. While we appreciate that AR101 will be the first oral immunotherapy to go through the FDA review process, we did not include it initially because it offers the same mechanism of action as oral immunotherapy as it currently exists in practice. Still, we believe that adding the question allows the panelists to consider the value of the FDA label potentially offered by AR101.
DBV Technologies	
ICER's approach to Viaskin Peanut risk reduction only considers patients who attain the binary primary trial endpoint defined in the PEPITES1 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.	The PEPITES trial was not powered to detect a response. Given the broad uncertainty in these results, we don't think this scenario is warranted.
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 and also a 10-year old chart review study from a large academic practice. ICER models a rate of ER visits per year of 2.7%.	This statement misrepresents the ICER report. On page 8 of the draft report we state "However, up to 40% of those with peanut allergy may experience an accidental exposure with an annual incidence of 10% to 20%.[2,3,7,12] However, that rate appears to have declined significantly according to recent studies (accidental exposures 4.7% per year, epinephrine use 1.1% per year).[13]" Reference 13 is from 782 patients in the United States with a median follow-up of 5.3 years and was published in 2012.

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ICER's model should include costs and disutilities associated with allergic reactions to avoid a material understatement of disease and treatment burden. 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.	The model does include costs and disutilities associated with allergic reactions as well as epinephrine use. Please see Table 4.11 for the associated cost of allergic reactions. Although we mention on p. 27 that disutility decrements were applied based on rates of severe treatment-emergent side effects and the rate of epinephrine utilization, we forgot to include this in a table in the draft report; we'll fix this oversight in the final report.
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 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. 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.	Please see the above response. We agree that disutilities for allergic reaction are warranted, and these were included in the model. We'll make these parameters more explicit in the final version of the report. Thank you for calling this to our attention.

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To enhance the scientific credibility of its assessment, ICER should remove inappropriate comparisons or inferences about or between AR101 and/or Viaskin Peanut. 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.	We respectfully disagree. We think it is essential for patients, providers, and payers to understand the differences in the patient populations studied in the pivotal trials and the differences in the definitions used for the primary outcomes in the trials. There are clear implications from these differences in making indirect inferences about the comparative effectiveness of the two therapies.
Specific examples of these inaccuracies include: 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: 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.	We agree that the protocol differences are important - hence the lack of a network meta-analysis or other quantitative estimates of the relative efficacy of the two therapies.

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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. 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.	There are currently no data to support the hypothesis that a significant proportion (25% to 75% in the Shaker and Greenhawt analysis) of patients treated for 5 years will achieve sustained unresponsiveness. There is hope, but no hard data. We did model that a substantial proportion of the children (>25%) will naturally develop tolerance by adulthood.
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. Given this limitation, and evidence suggesting greater burden than it models, ICER inadequately addresses this uncertainty in its draft report.	As noted in the report, please see the results of the one-way sensitivity analysis for insight on the impact of a higher desensitized utility value on the model results.
Without inclusion of health state utility impact on caregivers, ICERs societal perspective is incomplete. 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	We have added a societal perspective scenario that includes parent/caregiver utility values to the final report.

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substantially offset caregiver burden resulting in increased health state utility.	
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. 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.	As stated above, we have added a societal perspective scenario that includes parent/caregiver utility values to the final report. ICER's reference case defines the health care sector perspective as the base case except for treatments for ultra-rare conditions.
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.	In our report, we compare each treatment against standard care, or strict peanut avoidance. We also state that there is insufficient evidence to compare treatments to one another given lack of head-to-head trials and variations in trial design. Still, as a third party voting panel, it is the role of the CTAF to help decision makers understand if the data are sufficient to compare therapies.
Patient Groups	
Allergy & Asthma Network (AAN)	
Model Structure: 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 cannot 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.	This is correct. The model structure is two separate comparisons of each new technology with peanut avoidance. We do not compare the incremental cost-effectiveness of Viaskin Peanut and AR101

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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.	Thank you for this comment. The challenge with quality of life measurements in all of the trials remains that the instruments used to measure quality of life are not preference-weighted. This means that they cannot be used to calculate an accurate utility value. We have updated the utility gain for desensitization to the median response (60% utility gain), from a recent survey conducted by AAFA, to a survey question that asked "Now assume your child could take a treatment that would make them less sensitive to peanuts. With this treatment, they would have a lower chance of having an allergic reaction. But they would still need to avoid peanuts, carry epinephrine and continue daily treatment. (Assume that the treatment would have a low risk of serious side effects.) How do you think this type of peanut treatment would affect your child's quality of life?"
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.	The incremental QALYs reported are discounted to net present value, which is important to consider when thinking about the results.
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 undue influence the base case substantially. It appears as if a concerted effort was made to show that one or both treatments are not cost effective even in light of no FDA approved therapies.	The price assumption for each treatment was based upon information in the public domain (see page 40 of draft report) and are in the report only to make it easier to understand the cost-effectiveness analyses. How the actual prices compare to ICERs value-based price benchmarks will determine the actual cost-effectiveness of these treatments. Each treatment was evaluated based on the information presented from their individual clinical trial programs. Additionally, no effort was made to attempt to compare the two treatments due to the myriad differences in trial design and outcome measurement.
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	We have added a societal perspective scenario that includes parent/caregiver utility values to the final report.

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case analysis, which represents the health sector perspective. According to the Henry J Kaiser Family Foundation, 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 treatments with little consideration given to the clinical evidence.	
The ICER analysis applies research from Protudjer et al 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.	We appreciate your input on this topic. However, due to the ongoing risk of reactions, need to carry epinephrine, and input from clinical experts, we cannot justify using the same utility value for these two distinct health states.

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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.	The model does include costs and disutilities associated with allergic reactions as well as epinephrine use. Please see Table 4.11 for the associated cost of allergic reactions. Although we mention on p. 27 that disutility decrements were applied based on rates of severe treatment-emergent side effects and the rate of epinephrine utilization, we forgot to include this in a table in the draft report; we'll fix this oversight in the final report.
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.	We have incorporated the quality of life impact to parents/caregivers in the societal perspective scenario analysis, but point out that preference-weighted utility values for parents and caregivers are absent in the literature.
Finally, we would like to offer the follow recommendations as ICER moves forward: 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.	The model's incremental output over the lifetime horizon is not something that can be directly compared to the different health state utility inputs. Furthermore, the Cannon manuscript does not report preference-weighted utility values and thus a direct comparison between the two is not possible
Finally, we would like to offer the follow recommendations as ICER moves forward: 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.	The model does include disutilities associated with allergic reactions as well as epinephrine use. Although we mention on p. 27 that disutility decrements were applied based on rates of severe treatment-emergent side effects and the rate of epinephrine utilization, we forgot to include this in a table in the draft report; we'll fix this oversight in the final report.

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Asthma and Allergy Foundation of America (AAFA)	
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. , 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. 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."	We have added a societal perspective scenario that includes parent/caregiver utility values to the final report.
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. 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. The impact of food allergy extends beyond the individual patient as it changes how the entire family	We have added a societal perspective scenario that includes parent/caregiver utility values to the final report.

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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.	
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, self-care, usual activities, pain/discomfort, and anxiety/depression. 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.	It is true that the EQ-5D is a generic instrument and we encourage the mapping of food allergy quality of life measures to preference-weighted measures, or the development of a food allergy specific preference-weighted measure of quality of life.
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	These reflect differences in placebo groups between the two trials. The underlying patient populations were somewhat different, and we modeled trial-specific rates of epinephrine utilization and the proportion of patients who were

Public Comment	ICER Response
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.	desensitized at 1 year (PALISADE placebo: 4%; PEPITES placebo: 13.6%). The latter is the main driver of the reported QALY differences.
Food Allergy Research & Education (FARE)	
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. 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. 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. 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.	We agree with the concern - the second sentence of the report states "peanut allergy is the leading cause of death from anaphylaxis due to food, particularly in teenagers." In addition, on page 13 of the draft report we note "adolescents may be at the highest risk for death due to both their risk-taking nature and the movement away from environments that can be carefully managed by their parents and other caregivers." We agree, adolescents may be at higher risk due to behavior. However, there are no data available from the trials to inform such an analysis. We are unable to estimate the impact of the hypothesized risk without data to quantify the impact of such behavior on preferences for the model health states. However, we did perform sensitivity analyses around the utility input values as these are limited in the literature as well.

Public Comment	ICER Response
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..., Child and family social limitations..., Marriage and relationship strain..., Physical care...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...., Loss of work productivity and career impact.	We have added a societal perspective scenario that includes parent/caregiver utility values to the final report.
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.	We agree that the availability of FDA approved treatments may lead to more testing to identify children with peanut allergy - a potential harm from overdiagnosis and overtreatment of children who would never know about the "diagnosis" and would naturally develop tolerance. There is the potential for an epidemic of pseudo-disease as skin tests and serologic tests have poor specificity (lots of false positives) and these tests rather than OFC are likely to be used. It is unclear whether this would translate into a net benefit or net harm to children and their families.

Public Comment	ICER Response
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.	We have added the sentence "Both AR101 and Viaskin Peanut were granted “Breakthrough Therapy” designation by the FDA in 2015 to expedite the development and review of these therapies." However, we would caution that recent analyses suggest that therapies approved with breakthrough status have a less robust evidence base at approval, hence lower certainty about the magnitude of the net clinical benefits (Puthumana et al, JAMA 2018).
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 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.	The one year evaluation of desensitization is based on the clinical trial designs for the two products being evaluated. While we appreciate the concern being raised, this decision was driven by the available evidence. We also note that the spontaneous tolerance transition continues for the entire time horizon.

Public Comment	ICER Response
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. 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.	We appreciate your input on the topic of adverse events. We followed standard health economic practices of modeling severe events (typically grade 3/4 as measured in clinical trials), as those high cost events are those that influence the incremental costs of technologies. The actual treatment costs and variability of those costs for mild reactions are uncertain and thus we did not include them in the model.
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. 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.	The use of publicly available Medicare fee schedules is standard in health economics when private payers' actual reimbursement amounts for services are not available. Furthermore, these medical cost inputs have minimal impact on the incremental cost-effectiveness ratios from the model, even when increased to extreme values. We will update the model with CMS' 2019 values for the final report.

Public Comment	ICER Response
Patients Rising Now	
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. 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," 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.	ICER staff worked collaboratively with a patient group to collect survey data which helped us to understand the impact of peanut allergy on patients and their families. We have revised several portions of the report to reflect this new data, including key assumptions in our model. Unfortunately, the survey was not completed in time to include in the draft report.
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.	Patient groups and specialists supported the inclusion of OIT as currently practiced because it is currently offered by some Allergists and because it is well represented in the published literature. We believe that including OIT adds important context to the evidence base for the two therapies likely to be approved by the FDA.

Public Comment	ICER Response
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" And, "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: - Withdrawal rates due to adverse events: (11.6% vs. 2.4%) for AR101 and (1.7% vs. 0%) for Viaskin 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.	These adverse events are included in the model, but they are balanced by the much larger proportion of patients who attain desensitization with AR101 than with Viaskin, despite the population studied in the PALISADE trial being more sensitive to peanut protein at baseline.

Public Comment	ICER Response
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." 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), since that may be the basis for the adverse event profiles of the two experimental treatments.	We recognize that the food allergy literature is very limited in reporting preference-weighted health related quality of life measurements and that such measures specifically for peanut allergy do not exist. Not only did we note this in the limitations section, but we also explored ranges of utility estimates in the sensitivity analysis section.
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. 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.	Thank you for the citations. We have added the racial and socioeconomic disparity data from this publication to the first paragraph of the Introduction and highlighted it in the Other Benefits section (5.1) of the report.

Public Comment	ICER Response
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."	This simply means that although the utilities for the younger age group were lower than those for the older age group, the differences between the utilities for peanut sensitivity (age 0-11: 0.84; age 12+: 0.91) and peanut tolerant (age 0-11: 0.94; age 12+: 1.00) were similar (age 0-11 difference: 0.10; age 12+ difference: 0.09). Therefore, the two sets of age-based utilities do not notably impact the incremental QALY results.
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.	Thank you for this comment. During the period between the draft report and the updated report, one new cost-effectiveness model in this therapy area has been published. We have added a description of that manuscript and model to the report, including key differences and rationale for our approach.

Public Comment	ICER Response
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. 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). Is this not a conflict of interest that is not disclosed?	We believe it is important for our authors to be able to objectively review evidence in a way that is unbiased and free from financial conflicts. Dr. Tice is an expert in evidence-based medicine and has been an evidence author on reviews for CTAF for over a decade. In his capacity as lead author on reviews evaluated by the CTAF panel, he also sits on the CTAF Advisory board to advise them on the results of our evaluations and meetings.
The FDA had granted both investigational agents Fast Track and Breakthrough status. This should be described in the draft report and discussed at the CTAF meeting.	We have added "The FDA granted Fast Track Designation to Viaskin Peanut in 2012 and to AR101 in 2014. Both AR101 and Viaskin Peanut were granted Breakthrough Therapy Designation by the FDA in 2015 to expedite the development and review of these therapies." to the section describing the therapies in the Introduction.
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.	This cost is listed in Table 4.10.
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.	These reflect differences in placebo groups between the two trials. The underlying patient populations were somewhat different, and we modeled trial-specific rates of epinephrine utilization and the proportion of patients who were desensitized at 1 year (PALISADE placebo: 4%; PEPITES placebo: 13.6%). The latter is the main driver of the reported QALY differences. Rounding accounts for the 0.01 difference, we will add a note to the table.

Public Comment	ICER Response
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 is the source of health insurance for 39% of children 0-18 in the U.S., and that up to 60% of children may be covered by Medicaid at any point during the year. In addition, we noted that in other draft reports ICER has used a discounted price, e.g., 7.4%.B50	The discounting referred to in the budget impact section is in reference to the discounting of future costs to net present value, which is not typical for budget impact analyses. Thus, we utilized undiscounted (actual) costs across all 5 years in the budget impact analysis. However, this comment appears more related to manufacturer price discounts (or rebates) that are offered to payers. Because we do not have an actual published wholesale price, it is difficult to apply a Medicaid discount. The price sources for the two products may have already accounted for their expected market share and discounts.
Partnership to Improve Patient Care (PIPC)	
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.	The challenge with existing quality of life metrics is that they are not preference-weighted. This means that they cannot be used as utility values and thus cannot be utilized to calculate quality adjusted life years. The creation of a preference-weighted quality of life measure in food allergy represents a substantial opportunity
In this study, ICER chose to use a patient-reported outcome (PRO) tool that is known to be insensitive to allergies. Peer-reviewed literature is replete with examples of where the use of this particular tool, the EQ-5D, has underestimated treatment effect and differences. 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.	In order for a cost-effectiveness analysis to use quality adjusted life years as an outcome, a preference-weighted measure of health state utility is needed. While we appreciate that the EQ-5D instrument may be insensitive to changes, there are no published preference-weighted or mapped utility values in the food allergy literature.

Public Comment	ICER Response
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). 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.	We have added a scenario analysis that explores the impact of patient age when entering the model. This analysis indicates that patient age does not notably impact the model results. We recognize that the efficacy of treatment may vary by age, but we are limited by the available trial data in this regard.

Public Comment	ICER Response
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. 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. 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.	Health technology assessment frequently requires making decisions with the data that are available. All decision makers, including patients, families, and clinicians, must decide based on available evidence. Otherwise, no informed decision could be made at all.