Food and Drug Administration
Center for Biological Evaluation and Research (CBER)

Meeting of the

Allergenic Products Advisory Committee

January 21, 2016

FDA White Oak Campus
Great Room
10903 New Hampshire Avenue
Silver Spring, Maryland

CONTENTS

P R O C E E D I N G S

Agenda Item: Call to Order and Opening Remarks, Michael Nelson, M.D., Ph.D.

DR. NELSON: Good morning, ladies and gentlemen, welcome to the 28th Meeting of the Allergenic Products Advisory Committee. I am Dr. Mike Nelson and I am privileged to be your Chair for today's session. At this time I will call the meeting to order.

Let me begin by thanking Dr. Slater, Dr. Kim and Ms. Royster for all of their preparation to make this meeting happen and, in particular, congratulations for choosing today as opposed to tomorrow for the meeting with the incoming weather, and for all the logistical assistance in bringing our subject matter experts from far and wide across the country. We are privileged to have subject matter experts and leaders in their fields as invited speakers, panelists, FDA leadership and presenters among our audience and all here at FDA Headquarters and online, so we welcome you to today's session.

In contrast to our last couple of meetings there are no new products to review; however, the work doesn't get any easier. Today we are tasked with tackling important questions regarding appropriate study design and product considerations for both food immunotherapy and

allergen immunotherapy. The importance of immunotherapy as a potential life-altering form of therapy for patients with food and aeroallergen hypersensitivity cannot be understated. These are two exceedingly common conditions with rising prevalence. The impact on quality of life and healthcare expenditures affects all age groups. For example, food allergy is estimated to affect 8 percent of U.S. children.

Although Dr. Slater and the FDA will provide us with specific questions to address as part of the presentations today, I'm sure that we can anticipate discussing first the appropriate study design and clinical endpoints for food allergen immunotherapy as well as the relative importance of administration route and states of clinical desensitization and tolerance. There are also some unique safety considerations for food allergy when compared to aeroallergen immunotherapy, such as the risk for development or exacerbation of eosinophilic esophagitis.

The second half of today will focus on the role of allergen immunotherapy in the prevention of new sensitization and interruption of the atopic march, as well as the safety considerations for use in young patients.

A few reminders for our panel members -- For the

benefit of our transcriptionist, as well as our national and international audience online, it remains especially important that we identify ourselves each time we speak and toggle our microphones on and off accordingly.

In accordance with the instructions you all received before this and at every meeting and for those in the audience who may be unaware, panel members are prohibited from discussing agenda items in advance or outside of this room and will confine their discussions and deliberations purely within the confines of this room.

Finally, there may be some flexibility with the schedule, especially when it pertains to the public comment period which can vary from a very short period to a full allotted time. So, for those watching online, please stay tuned.

At this time our panel members will now introduce themselves to the audience. Our FDA colleagues will follow I think as part of their introduction and first speech. I would ask the panel members to please state your name, your affiliation and your major area of interest. We'll begin on my far left with Dr. Weber.

DR. WEBER: Richard Weber, National Jewish Health, Denver, Colorado. My expertise is all things allergy and aerobiology specifically. Thank you.

DR. PETERSON: Jane Peterson. I was a public health nurse; I have a doctorate in anthropology. I am very concerned about consumers so I am the consumer rep, and I have done some research on children with asthma.

DR. PLUNKETT: Greg Plunkett. I am with ALK-Abello in Round Rock, Texas. I am the industry rep, and we manufacture allergenic extracts.

DR. GILL: Michelle Gill, UT Southwestern in Dallas. My area of expertise is studying mechanisms -- IGE-mediated mechanisms mainly -- of how allergens interact with antiviral responses and how that relates to pediatric asthma.

DR. FINEGOLD: Ira Finegold, New York, Mt. Sinai Hospital and Mt. Sinai Medical School. My expertise is allergy and immunology.

DR. DYKEWICZ: Mark Dykewicz, Chief of Allergy and Immunology at St. Louis University. Expertise -- allergy and immunology.

DR. KIM: Janie Kim, designated federal officer for APAC.

DR. NELSON: For full disclosure, I'm Mike Nelson, active duty military and work in the Surgeon General's Office for the Army running the Directorate of Medical Education. Allergy and immunology is my clinical

field of interest.

DR. APTER: Andrea Apter, Section Chief, Allergy and Immunology, University of Pennsylvania. My expertise is seeing patients with food allergy and asthma, and my research involves improving outcomes for underserved populations.

DR. KELSO: I'm John Kelso; I'm an allergist from Scripps Clinic in San Diego, California. I see patients with allergic diseases as my main thing that I do. In terms of any specific interest, I have a specific interest in adverse reactions to vaccines.

DR. PEDEN: I'm Dave Peden. I'm with the University of North Carolina at Chapel Hill. I'm an allergist immunologist. My research interest is the effect of air pollutants and environmental agents on allergic responses. In the context of that, we do a significant number of allergen and other Phase 1 human challenges.

DR. CHANG: Tina Chang. I'm a medical officer at the FDA in the Division of Vaccines and Related Product Applications.

DR. HISE: Kathleen Hise. I'm an allergist immunologist and a medical officer at the FDA.

DR. SLATER: Jay Slater. I'm the Director of the Division of Bacterial, Parasitic and Allergenic Products.

DR. GRUBER: Marion Gruber. I'm the Director of the Office of Vaccines at CBER, FDA.

DR. NELSON: Thank you all, and again, welcome, and welcome to our audience.

I'm going to turn it over to Dr. Kim who now will read our Conflict of Interest Statement.

Agenda Item: Conflict of Interest Statement, Janie Kim, Designated Federal Officer

MS. KIM: Prior to reading the Conflict of Interest Statement I would like to point out a couple of things. Please check your cell phones and pagers and make sure that they are turned off or in the silent mode during the meeting. Please also refrain from approaching the head table area at any time including before the meeting, during breaks and lunch time or after the meeting. There is no use of any flash photography or TV camera lights while the meeting is in session.

The press officer for this meeting is Ms. Tara Goodin. Her contact information is outside on the table. We ask that all media inquiries be directed to Ms. Goodin. Now for the Conflict of Interest Meeting Statement.

The Food and Drug Administration is convening the January 21st Meeting of the Allergenic Products Advisory Committee under the authority of the Federal Advisory

Committee Act of 1972. With the exception of the industry representative, all participants of the committee are special government employees or regular federal employees from other agencies and are subject to the federal conflict of interest laws and regulations. The following information on the status of the Advisory Committee's compliance with the federal ethics and conflict of interest laws include, but are not limited to, 18 USC Section 208, as provided to the participants at the meeting and to the public.

FDA has determined that all members of this advisory committee are in compliance with the federal conflict of interest laws and regs. Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest. Related to the discussions at this meeting, members and consultants of the meeting have been screened for potential conflicts of interest of their own as well as those imputed to them including those of their spouse or minor child and, for the purposes of 18 USC Code 208, their employers. These interests may include investments, consulting, expert

witness testimony, contracts and grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment.

For Topic 1, the Committee will meet to discuss safety and efficacy data including challenged study endpoints for licensure of food allergy immunotherapy products. For Topic 2, the Committee will meet to discuss the clinical development of aeroallergen immunotherapy products for the prevention of respiratory allergic disease. Based on the agenda and all financial interests reported by members and consultants, no conflict of interest waivers were issued under 18 USC Section 208.

Dr. Greg Plunkett will serve as the industry representative. Dr. Plunkett is employed by ALK-Abello, Inc., and he will act on behalf of all related industry. Industry representatives are not special government employees and do not vote.

There may be regulated industry speakers and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These

individuals were not screened by FDA for conflict of interest.

This Conflict of Interest Statement will be available for review at the registration table. We would like to remind members, consultants and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to exclude himself or herself from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships they may have with any firm, its products or, if known, its direct competitors. Thank you.

Agenda Item: FDA Introduction, Background, and Presentation of Questions, Jay Slater, M.D, FDA

DR. NELSON: Fantastic. I'll turn the podium over to Dr. Slater who is going to do the FDA introduction and get our first speaker onboard.

DR. SLATER: Thank you very much, Dr. Nelson, and thank you for agreeing to chair this important meeting. My job is relatively easy. I'm going to be presenting a very brief introduction to the topics at hand and then we'll get right to it.

The scientific developments that formed the backdrop for this meeting have really been progressing at a very fast rate over the past several years. We have all seen a growth of investigational protocols for immunotherapy of established food allergy, and some of these are by the oral route, some by sublingual route, some are parenteral and some transcutaneous. There has been a dramatic increase in these over the last several years.

In addition, there is a great interest in preventing the development of respiratory allergic disease, and this is prodded by some encouraging early data that also have appeared in the last couple of years. There has been some recent success noted approximately one year ago in preventing peanut allergy in highly at-risk infants. In addition, there has been some claimed success in preventing asthma in children with allergic rhinoconjunctivitis.

In general, there has been a dramatic increase in our understanding of the allergic march, and this is also driving some of the questions that we're asking in this committee meeting.

For the food allergy therapy question we have a number of different issues, and those will be reviewed in detail in the presentations to come. We have issues regarding the assessment of efficacy in these studies, and

trial design issues including questions of field trials, challenged trials and possible surrogates for the assessment of efficacy. In general, there's an interest in discussing the appropriate endpoints for these kinds of trials.

And, of course, we have safety issues as well. We have short-term safety issues, long-term safety issues, and safety issues that are associated with both the treatment itself, the challenge procedures that are used to assess the treatment, and field exposure situations.

I just wanted to briefly point out that this actually isn't the first time that we've touched on this in this committee. In 2011, in the course of a discussion on the use of environment challenge chambers in the assessment of allergen immunotherapy, Dr. Rabin presented this slide in which he noted that, at least at the time, our thinking was that food allergen immunotherapy would be best assessed under controlled situations, not during a field trial. But this was in the context of a number of other considerations, and it didn't get much discussion either by Dr. Rabin or by the committee in the following discussion.

We are also the committee to discuss issues regarding the prevention of the development of asthma in children. This includes a number of issues, and this slide

isn't nearly complicated enough to cover the complexity of the subject, but it includes issues regarding inclusion criteria, endpoints and the duration of these studies and the duration of follow-up.

You're going to be hearing three excellent presentations today. The first will be from Dr. Kathleen Hise, a medical officer in the Office of Vaccines. She'll be talking about clinical development of allergen immunotherapies for the treatment of food allergy.

That will be followed by a discussion by Dr. Thomas Platts-Mills from the University of Virginia, who accepted our invitation to talk to us today about the subject, can we control the atopic march; how do we design and assess relevant intervention studies.

Finally, Dr. S. Tina Chang, another medical officer in the Office of Vaccines, will discuss the prevention of respiratory allergic disease with allergen immunotherapy.

In terms of the questions and discussion, I'm going to go through the questions very quickly for you, but before I get to that I want to point out, as Dr. Nelson has already pointed out, that the committee is not being asked to address any product-specific questions. We're asking questions regarding broadly the field of food allergy

therapy, immunotherapy and, broadly, the prevention of the development of asthma. And I wanted to point out that although there may be some scientific overlap between the two agenda items, the clinical and regulatory issues are distinct, and, therefore, the FDA requests a separate treatment of each of the questions.

For the treatment of food allergy the three questions are: Question 1, Regarding food challenge studies to assess effectiveness of immunotherapy in allergic individuals, please discuss the objective criteria for determining the eliciting dose, particularly in children less than 5 years of age, and clinically meaningful parameters including amplitude of response and duration of time off-therapy that could be used to demonstrate the effectiveness of immunotherapy for desensitization or for sustained unresponsiveness; that is, the maintenance of desensitization off-therapy, and finally, safety considerations for the food challenge.

Question 2, Please discuss approaches other than food challenge studies to demonstrate effectiveness of immunotherapy products intended for use in food-allergic individuals.

Question 3, Taking into account the route of administration of immunotherapy in food-allergic

individuals and the age of study subjects, please discuss specific safety monitoring for signs and symptoms of allergic reactions.

For the prevention of development of asthma the two questions are: Question 1, Studies to demonstrate effectiveness of allergy immunotherapy to prevent the development of asthma will likely enroll a population at increased risk for the development of asthma including children 6 months of age and older. Please discuss factors to consider in the identification of subjects at increased risk for development of asthma, the diagnosis of asthma in infants and young children, and factors to consider regarding the timing of the assessment of asthma endpoints. For example, age, time on therapy, time off therapy and others.

Question 2, Please discuss the assessment of safety in infants and young children receiving aeroallergen immunotherapy to prevent the development of asthma.

Dr. Nelson, that ends my presentation.

DR. NELSON: Thank you very much for that outstanding introduction and some pretty tough questions for this group to tackle in the few hours ahead of us today.

Next on the agenda is Dr. Kathleen Hise, medical

officer, Division of Vaccines and Related Product Applications. She is going to start us off by providing an overview of clinical considerations for food allergen immunotherapy.

Agenda Item: Clinical Considerations for Food Allergen Immunotherapy, Kathleen Hise, DVRPA

DR. HISE: Thank you. I am going to talk about the clinical development of allergen immunotherapies for the treatment of food allergy. My presentation topics will include a brief introduction, investigational treatments, a section on the demonstration of efficacy focusing on food challenges and study models, safety monitoring, and a brief summary.

Allergen immunotherapy is used to treat sensitivity to aeroallergens and hymenoptera venoms. There are no licensed immunotherapy products that are available for food allergies. Several different routes of allergen immunotherapy for food allergy are currently being investigated.

Food allergy affects up to 15 million people in the United States. About 6 million of those are children. The prevalence has been increasing from about 3.4 percent in 1997 to 1999 to 5.1 percent in 2009 to 2011 in ages zero to 17 years of age. Additionally, about 50 percent of

cases of anaphylaxis reported by emergency departments is due to a food allergen. The fatalities are estimated at about 100 per year. Data suggests that those in early adulthood are at higher risk of death from exposure to a food allergen and those that are allergic to that allergen.

There are a few foods that constitute about 90 percent of food allergies in children. Those include peanut, tree nut, milk, egg, soy, wheat and shellfish. Some of these allergies tend to resolve with age. These would be milk, egg, wheat and soy. There are also some allergies that tend to persist over time, and these include peanut, tree nut and shellfish food allergies.

The current standard of care for food allergies follows. Diagnosis is usually made by clinical history and specific IgE. There is no specific therapy available. Clinical management is limited to a strict avoidance diet and treatment of reactions with epinephrine or antihistamines for milder symptoms.

Here we're defining desensitization as the ability to tolerate increased amounts of the food allergen during allergen immunotherapy. Typical protocol designs include a screening period, so subjects might have an entry food challenge, specific IgE and a skin prick test. There's a dose escalation period and a pre-specified

treatment period where subjects are on a maintenance dose. There can also be an exit food challenge at the end of the study protocol to assess the desensitization.

This is a schematic representing what I just talked about. Subjects enter the screening phase and there may be a baseline food challenge, IgE and skin prick testing. Oftentimes there's an initial dose escalation that occurs over one day, and then an incremental dose escalation that happens about every two weeks until subjects reach the maintenance dose. At the end of the protocol, an exit food challenge is done to assess desensitization.

I'm going to talk a little bit about oral immunotherapy. Typical protocols in the published literature include an initial rapid dose escalation just like the scheme I showed you, a bi-weekly dose increase and a maintenance dose. While on this therapy, subjects continue to avoid the food allergen in their diet.

Some studies have reported about 50 percent to 60 percent desensitization. The criteria for desensitization vary across studies. Some studies include an oral food challenge as an entry criterion in addition to specific IgE and skin prick testing. The maintenance phase ranges from four weeks to five years, and maintenance dose ranges from

500 mg to 4,000 mg of food protein.

There has been a high rate of adverse events leading to a 10 percent to 20 percent subject withdrawal. Serious adverse events include anaphylaxis, asthma exacerbations, and oropharyngeal edema. Younger study participants may be at increased risk for serious reactions because they are unable to communicate the early symptoms of reaction such as oral itching, and they also have smaller caliber airways. Eosinophilic esophagitis is a particular concern as well.

In sublingual immunotherapy, food extract is placed and held under the tongue for about two to three minutes, then spit out or swallowed. A few studies have evaluated this form of allergen immunotherapy. Data suggests that sublingual immunotherapy has lower efficacy than oral immunotherapy. Some investigators assert the safety profile may be more favorable for sublingual immunotherapy.

In epicutaneous immunotherapy, the food allergen is placed directly on intact skin through a patch system. One study was published that evaluated epicutaneous immunotherapy for treatment of milk allergy. The safety profile was reported to be reassuring; however, the therapy did not appear to be successful in inducing

desensitization.

For subcutaneous immunotherapy for food allergy, limited data suggest about 50 percent of subjects experienced some degree of desensitization. There was a relatively high rate of adverse events reported including systemic reactions during the build-up phase and one fatality due to inadvertent administration of subcutaneous immunotherapy.

I am now going to talk about demonstration of efficacy. The treatment goals are to induce a state of desensitization and to protect against a serious allergic reaction following accident exposure. This would result in a clinically meaningful reduction in the risk of a serious reaction.

On the subject of food challenge studies to demonstrate efficacy, they are often used to assess the degree of sensitivity at the beginning of the study and efficacy at the end of the study. There are two types used, a double-blind placebo-controlled food challenge and an unblended oral food challenge.

Before treatment is initiated, a double-blind placebo-controlled food challenge is performed to identify the eliciting dose or ED. The ED is the lowest amount of food that elicits objective signs or symptoms. After a

defined period of treatment with allergen immunotherapy, the degree of desensitization is evaluated by the change in ED by a double-blind placebo-controlled food challenge.

I'm going to talk about food challenge studies to demonstrate efficacy and a term called sustained unresponsiveness, which we consider to be the capacity to maintain desensitization to the food allergen. After termination of therapy at various time points after allergen immunotherapy, the eliciting dose can be re-evaluated by a food challenge. The length of time after termination of allergen immunotherapy that defines sustained unresponsiveness has not been established.

Tolerance is currently defined as complete and permanent resolution of clinical response following exposure to any amount of the allergenic food after termination of therapy. The length of time off therapy to claim tolerance has not been established.

This is a busy slide, so bear with me. On the Y axis we have the final eliciting dose over the baseline eliciting dose. The X axis is time. Where you see the desensitization block, this is when subjects are on allergen immunotherapy and they are desensitized. After allergen immunotherapy is withdrawn there may be a period where they are still desensitized, but that hasn't been

well defined yet and this is why you see the question mark in the slide.

Afterwards, there's a period of sustained unresponsiveness. Up in the corner you will see the box for tolerance, and those are people who can tolerate any amount of food protein without a reaction, as I described. Those treatment failures were not able to be desensitized and, therefore, cannot claim sustained unresponsiveness or tolerance.

Given that exposing food-allergic individuals to multiple food challenges during studies can be very risky and can be a recruitment challenge, there are some alternatives that could be considered such as a field trial. This would be a randomized controlled field trial where the primary endpoint would be a reduction of the rate and/or severity of reactions to accidental food exposures in the treated group versus the control group. Limitations of field trials have been noted including large cohorts, long study durations and need to detect statistically significant differences.

In addition, biomarkers may be considered as surrogate endpoints in clinical studies. These may include allergen-specific IgE and IgG4 levels including cytokine production. However, none of these have been well

established to support efficacy.

I'm going to briefly talk about safety. In most food allergen immunotherapy studies subjects incur two sets of risks -- during the use of the investigational product as well as during food challenges. These risks include anaphylaxis, abdominal pain, asthma exacerbations, oropharyngeal edema as well as death. Risks are substantially different for the different routes of administration of immunotherapy. Surveillance, counseling and follow-up must mitigate the risks of reactions, especially in those reactions that occur outside of a clinical setting.

In summary, food allergy is a serious public health issue. Potential risks and benefits vary according to the route of allergen immunotherapy administration. To support labeling, agreement is needed between the applicant and the FDA on the study design, study population and clinical parameters for demonstrating desensitization, sustained unresponsiveness and/or tolerance.

Thank you.

DR. NELSON: Thank you, Dr. Hise. Since we have a few minutes and to prevent the committee from digging in, rolling up their sleeves and discussing at great length the questions that have already been posed to us, I would open

it up to the committee to ask if they have any particular questions for Dr. Hise.

DR. KELSO: I am still confused on the difference between sustained unresponsiveness and tolerance, because those sound like the same thing to me. I guess in some respects you can think of tolerance as cured -- you can eat it or not eat it at any interval for the rest of your life; you are basically cured.

DR. HISE: Yes.

DR. KELSO: But sustained unresponsiveness seems a little less well defined. The kind of implication is that there could still be some -- Even if you have sustained unresponsiveness there still could be some restriction saying that you have to consume the food at some interval or that you cannot consume more than a certain amount of the food. I'm still fuzzy on that.

DR. HISE: It would be more that there is a certain amount of food that you wouldn't be able to consume, but you can't add the food *ad lib* to your diet, if that makes sense, as in those who are tolerant. I don't know if Dr. Slater would like to add anything.

DR. SLATER: I don't think you're confused at all. There are two axes on this thinking about it. One is the axis of time and the other is the axis of eliciting

dose. Our thinking about it was -- and this is based on looking at what other people have said -- that for tolerance, both axes have to be satisfied. It has to be, quote, unquote, “permanent” and we can argue about at what stage we decide relapse won’t happen. That’s another question mark that should be on this slide but it’s not there.

And the other is the axis of the dose. As you said correctly, our sense was that a tolerant individual is the way I am. My only limitation on eating peanut butter is time and space, but it has nothing to do with allergy. So that’s why we were tucking tolerance into the upper right hand corner there, because it satisfied both axes.

Sustained unresponsiveness can fail on either one of those. In other words, it can succeed in having essentially an infinitely high eliciting dose, but it can fail because it disappears after a period of time that we will all agree makes it lack permanence. On the other hand, sustained unresponsiveness can also occur permanently, but it’s not truly unresponsive; it’s hypo-responsive. For individuals who perhaps have a clinically meaningful but not complete response, a tripling or quadrupling of their eliciting dose but they still have a problem when they go above that, even if it’s permanent we

would consider that to be in the sustained unresponsiveness group.

It’s possible to make up another set of words to describe that group, but we were reluctant to invent another term just for the purposes of this meeting. Those are two separate populations.

DR. WEBER: Well, having just heard that you would rather not use another phrase, I was going to suggest that “modified responsiveness” perhaps describes the spectrum better.

DR. PEDEN: This is Dave Peden. One of the other questions that I think we’ll have to wrestle with is whether or not the goal of immunotherapy is that people can eat food with impunity and enjoy it versus are they protected from life-threatening events associated with accidental exposure. And I’m not sure that -- You could have different kinds of indications and while you may not achieve a goal of permanent ability to eat food with impunity, I do think that protection during a certain risk period is like -- in young adults, you know, it might be a worthy goal and worthy of indication.

Now, when you have indications for a specific and not permanent life phase, that’s a problem, but I do think there’s a substantial interest in decreasing risk of death

associated with accidental exposure that is at least as great as being able to eat peanut butter anytime you want to.

DR. PETERSON: Jane Peterson. I have some questions about population and age groups. Sometimes it sounds like from birth to death almost in this, and this sounds like this has different ages in it. At some point, that should be discussed.

DR. HISE: I agree.

DR. APTER: Piggybacking on that comment, most of the information that we have, limited as it is, is in children or young adults, and there's very little exploration of older adults who are also at risk.

DR. DYKEWICZ: Just a semantics suggestion in terms of sustained unresponsiveness or sustained modified responsiveness -- it could actually go either way -- sustained reduced responsiveness is what we're discussing.

DR. FINEGOLD: Ira Finegold. Just one point about degrees of food allergy. I don't think that was addressed. There are some food allergies that are minimal and there are some that can be catastrophic.

DR. KELSO: Another issue that I think we should address that's sort of a corollary to this is the reproducibility of double-blind placebo-controlled food

challenges. If somebody passed their double-blind placebo-controlled food challenge we sort of figured they're good to go, at least for now, given that they may regain their sensitivity in the future or whatever, but that is sort of always taken as one test is sufficient, and it may be.

But given the number of variables that go into what allows a patient to have a reaction to a food on any given occasion, including cofactors such as exercise and illness and NSAIDs and whatnot, and, for example, in the case of hymenoptera sensitivity where even people who are sensitized may only react 60 percent of the time -- so how many sting challenges do you have to do to prove that somebody is really desensitized?

I'm wondering if maybe there's some element of that in food allergy unresponsiveness as well, if passing a single double-blind placebo-controlled food challenge really is sufficient as a statement of the person's current level of tolerance.

DR. NELSON: I had a related question and I'm wondering, Dr. Hise or others, if you came across any literature that looked at the correspondence of what the eliciting dose is during a challenge and what's observed after that patient is released essentially to a trial of life afterwards with recommendations. Does the accidental

exposure dose correspond -- when they have a reaction -- actually correspond to what was observed during those double-blind placebo-controlled trials? I was unable to come across that in the literature.

DR. SSLATER: No. I'm sure some of the investigators that have done these studies have information but I haven't seen it.

DR. NELSON: I'll tell you the reason I asked. We're being asked, it looks like, to make some recommendations with regard to eliciting dose parameters, and I think what underlies that is an assumption that a single eliciting dose determination will be persistent over time, and I'm not sure we have the data to support that assumption.

Other questions or comments? Hearing none, I would prefer, if everybody is amenable, to proceed with the next speaker and then we'll take perhaps a little longer break after that session.

This brings us to our next agenda item, Dr. Thomas Platts-Mills, Division Chief, University of Virginia Division of Asthma, Allergy and Immunology. His talk this morning is entitled "Can we control the atopic march? How do we design and assess relevant intervention studies?" Certainly pertinent to the second question that we'll

address as a group later this afternoon. Welcome, my friend, Dr. Platts-Mills.

Agenda Item: Presentation, Thomas Platts-Mills, MD, University of Virginia

DR. PLATTS-MILLS: Thank you for the invitation, and I want to thank Jay Slater for the invitation and for not clarifying at all what it was I was supposed to be discussing. He also didn't warn me that it would take three hours on the Beltway last night, and for this he owes me.

(Laughter)

I definitely have conflicts in many things that I say. We have received support from Phadia Thermo/Fisher. I have many friends involved in studies related to this, so I think everything I say should be taken with a grain of salt, but that's always true.

The atopic march. Forget what it means. There are three major things when you're thinking about what we need to do about it. The first is when do you start intervening. Do you have to start at three months?

The conclusion of the LEAP Study of Gideon Lack, his evaluation of the data is really that the earlier you start the better, and that you should actually introduce oral protein from three months of age or earlier -- a wide

range of proteins. And how long do you have to go on? Of course, the LEAP Study went on for five years. That's a very tall order.

For the maximum evidence of the role of allergy, Jay hinted that he would like me to address inhalants more than food, and clearly, we've heard a lot about food already. The intervention can be avoidance or exposure -- both things have been tried with various degrees of success -- and then a range of other things which we'll consider.

Then there's the issue of the target population. Do you actually try with a random population with no choice? Do you use at-risk children? That is, children with a close family history of allergy. Or do you actually take children who have already developed an allergic disease? And, again, in LEAP, remember the children had already got significant atopic dermatitis. They were at high risk for sensitization to peanut, and that was the strength of the study but also a major weakness in terms of thinking about the registration of a product.

Is there really an atopic march? How do you evaluate it? You can evaluate atopic march as a sequence of different diseases, so there's eczema, asthma, then rhinitis as judged clinically or as a sequence of sensitization. This is a big study which Adnan Custovic

and John Henderson did. John Henderson represents Alspak, which is in Bristol, and Adnan managed the allergy and asthma study in Manchester. Bristol is a much nicer town than Manchester, but Manchester has a better football team.

The truly important thing about this is to notice that in the first three years of life there's a lot of eczema and wheeze, and most of this wheeze in the first three years of life is non-atopic. Almost all the wheeze that hits hospital as bronchiolitis is viral. Actually, they don't have significantly elevated IgE levels at that age. After age three, it becomes progressively atopic. So, if you want to do something back here, at what age can you reliably say that you're looking at allergic asthma and that the major risk of allergic asthma is there?

Custovic concluded that only a minority of the children actually had a sequential thing. But the important thing to realize is that the march may be seen as a progression from one allergen to another, from one epitope to another. There's very good evidence for epitope spreading. There's very good evidence in some mouse models but also in human data for spreading from one allergen to another, and there is actually some evidence that subcutaneous immunotherapy for grass can prevent the progression to sensitization with dust mite, and dust mite

is much more strongly associated with asthma. So this possibility of preventing -- but that's subcutaneous immunotherapy, which is clearly not going to be done on a population basis.

I want to do a little bit of history because there are an awful lot of people around who believe that the rise in allergic disease occurred parallel -- that is, that rhinitis rose together with asthma and that we just had this monumental rise in allergy starting in about 1960, and that's totally wrong. I want to take you back to John Snow, because this is a religious issue with the English doctors, the most significant doctor of all time. He convinced the world -- convinced London first and then convinced the world -- that actually typhoid and cholera were spread through the water. You would think that was known before. Yes, that was known by many people but not by the people who ran the water supplies of London.

And he famously took the handle off this pump. Actually, I went to try and stand on that spot last summer and it's not there. It has been moved for some commercial reason but they promise it will come back.

I want you to remember that he also administered chloroform to Queen Victoria for the birth of her eighth child. I don't believe anyone in the history of time has

done anything of equivalent bravery. What would happen to you if you killed the queen? Not good!

This is one of his maps, a famous map that shows that if you get your water from Teddington here, you would do much better than if you get it from Battersea. The Battersea water was being filtered through sand and looked crystal clear but carried typhoid and cholera very nicely.

What I want to show you here, this is Chicago. In Chicago in 1892, 7 percent of all deaths were due to typhoid fever. The figure in London was .6 and the figure in Berlin was .5. So they decided to pump the water out of the Chicago River into the Mississippi so that St. Louis could get typhoid. St. Louis sued against it but they lost. They had a smaller town. That's called democracy.

These are all sewage outlets. It's pretty stunning that having sorted this out in 1893 Flint is having trouble with not getting water from the lake now.

So, from 1893, actually the introduction of chlorination of water was complete by 1912, and by 1920, helminths was eradicated on Staten Island, malaria was eradicated on Staten Island. So everything that we think of as hygiene, the really important things, were completed in the United States by 1920, or in the big cities in the North. So, if hygiene is responsible for the rise in

allergy, what happened? The answer is, of course, that hay fever happened.

Was hay fever developing in the United States in 1870? The answer is absolutely yes. The hay fever association was established. Bretton Woods became a major resort for hay fever sufferers for the ragweed season. It was very fashionable indeed, and it was a mark of being a member of the leisure class that you got hay fever. Hay fever was very strongly associated with middle class or upper middle class, not a disease of poverty. The fact that asthma became a disease of poverty in the United States did not start until 1970 and was the first place in the world where anyone suggested that an allergic disease was related to poverty.

This is a map of the ragweed-free areas published in 1890 or 1880. Hay fever was already established. If we go to New York City, we can see this very clearly. In New York City we know the sequence of many changes. The Rockefeller Foundation was responsible for the eradication of helminths in the North, and it was completed by 1920 and they went to the South. Then the South said, oh, you think we're all worm-infested people, and were very angry with the Rockefeller Foundation for coming South and suggesting that the South was full of worms, which it was.

But in New York, Ratner and Silverman, Allergic Disease, rising to 10 percent to 13 percent. At University of Virginia, Oscar Swineford was appointed the professor of allergy and rheumatology in 1935. He was actually recruited back from Vienna where he was doing pathology research to deal with the allergy epidemic. 1935.

In 1946, the City of New York decided that hay fever was such a severe problem that people had to cut down all the ragweed in Manhattan, which made no effect because the ragweed pollen was coming from New Jersey, courtesy of the then Governor of New Jersey. And then asthma rapidly rose from 1960 on.

I would argue that there has been sequential rising. If we want to break this cycle of development we need to know why each of these occurred. I think the rise in hay fever unequivocally involves a major element of hygiene. We have hay fever, tons of evidence it still persists, but many allergists would regard hay fever as much less severe than it was. My colleague, Ira Finegold -- I won't accuse him of having been there in the 1930s but he feels as though he was --

(Laughter)

The hay fever they described in the 1930s was much more severe than what we deal with today. I think the

main reason is that most people today live in houses with air conditioning. When I first came to Hopkins in 1971, we had a house without air conditioning. We discovered how hot it was in Baltimore.

Pediatric asthma starts here, and this peanut allergy here probably, and here we've got alpha-gal, but we've actually got an extraordinary phenomenon here. In this time range, we in Charlottesville have epidemic tick bites giving rise to IgE to alpha-gal with delayed anaphylaxis to red meat. We have a new adult and pediatric clinic for eosinophilic esophagitis, and we have tons of peanut allergy. Why should these three develop at the same time? Why should they increase? They appear to have very different reasons but they all are developing at the same time.

Looking at the asthma issue, can we actually see this phenomenon occurring? That is, going from a pre-1954 situation to a post-1954 situation within a town. The answer is there are several places in the world where you can, but this is a town, Kumasi, in Ghana which was studied by Dr. Addo-Yobo, together with Adnan Custovic, and they looked at schools within the town. I'm just showing you two of the schools. This is affluent urban; they are all Africans. These are employees of the university. They had

clean water, shoes, regular anti-helminths treatment and they lived in houses. That's all you need to do.

There are two things. This is urban poor who have worm infestation. They get tick bites. They have IgE antibodies to mite but they are all low titer and they have no relationship to wheezing.

Here, in the affluent school, there's a very strong association with mite allergy and asthma. The model we see in Auckland, New Zealand, in Sydney, in London, all over the world and, as I'll show you, Costa Rica, IgE to mite very strongly associated with asthma but, more important for the moment, high titer. Wickedly high titer.

This is in Kumasi, and children living on the other side of the town, you don't see it. You can see this phenomenon, and some of the African doctors working in Africa believe you can see this within about three or four years of moving people from one type of living to another.

When we first developed the techniques for measuring IgE to mite we did a study in a pool, in Dorset, where we followed children for 10 years. How do you follow children for 10 years? It's an important issue, how do you keep people in a study. They were promised at birth that they would meet Princess Diana if they stayed in the study until they were ten. No, she wasn't actually part of the

scene when they were born.

What I want to show you is that not only was mite sensitization very strongly associated with asthma, but also the level of mite allergen in their houses at birth. Lots of people tried to replicate this, and sometimes it works, sometimes it doesn't. But what I want to say is that, actually, this town was in a different state than things are in today. That is, most of the children did not sleep in any other houses; they slept in their own house the whole time, so that their own house was a good model. Today, we don't think that's true.

Indeed, the Moss study -- and Custovic again did a very aggressive allergen-avoidance study in the children's houses. It did not prevent sensitization to mite. The implication is that the children can get sensitized from Grannie's house or their friend's house or transient exposure, which is exactly what we think is happening with cat. Children living in a house without a cat can get adequate exposure in the rest of the community from passively transferred cat or visiting houses with a cat and they become sensitized. Then, the house itself is no longer a reliable model of what's happening, and avoidance studies in the house are going to be very difficult. That I think is the situation.

Is dust mite dramatically different from other things? This came up in a study that was reported last year in an attempt to use dust mite oral immunotherapy to break the cycle. I just want to point out that dust mite fecal particles contain Der p 1, which is a potent enzyme, and endotoxin, Der p 2, unmethylated DNA from mites and from bacteria, and chitin. To suggest one of these agents is THE agent that causes dust mite sensitization is nonsense. The fecal particle contains all of these things and is an unbelievably good immunogen. It may be better than others, but, as we know, as Peter Gurgin keeps saying, all the FDA has to do is to approve all immunotherapy for cockroach and asthma will be abolished within five years. Isn't that what you said, Peter?

You have got to let the audience know that you know they are there.

So, what are we looking at when we talk about IgE production? We all think that germinal centers are very good at generating antibody responses, but we also know that IgE B cells undergo apoptosis very easily. It's not clear. There are very few IgE B cells in the circulation; it's very difficult to identify IgE B cells. So the general view is that IgE production requires a switch subsequent, and some of that goes through G4, but there are

other ways of making IgE where there is no sign of G4.

Here we have a different alternative; that is, you can go from an IgM B cell via perhaps G1 to an IgE B cell and produce high levels of IgE. Indeed, we have dramatic differences in different diseases today. Eosinophilic esophagitis is characterized by very low levels of IgE to milk, all the milk proteins, and very high levels of IgG4.

By contrast, the tick-related disease where we see IgE levels comparable with those we see with mite and peanut -- that is, very high levels; levels over 100 are common -- we cannot detect IgG4 to galactose-alpha-1 3-galactose, the sugar, so is it that the IgE responses to sugar are separate? But we do not understand the rules for production of Ig to sugars.

Alpha gal, as far as I know, the only method of avoiding it is to avoid ticks which would be easier if we didn’t have a herd of deer on my lawn.

I want you to realize that there are different methods of producing IgE, so that simply saying we’ll give IL-10 and produce G4 may or may not interfere with this. If you had a cytokine regime that could achieve this kind of thing, it might interfere with one IgE response and not interfere with an IgE response that was going through the

skin -- in our hands, IgE to peanut. The G4 levels in patients who have been strictly avoiding peanut are very low, and the moment you give oral immunotherapy it goes higher. So with oral immunotherapy you can monitor by IgG4 levels. How good it is at predicting anaphylaxis is less clear.

There is mouse data suggesting that the only important IgE production goes through germinal centers and has this switch. We don't believe that's true. In fact, the New England Journal paper from NIH shows that BCL-6 impairs germinal center formation but allows normal IgE in patients. I don't think it's clear that this IgE is normal affinity, but so be it.

To get back to the story, what is hygiene and when did it happen? The essence of hygiene is some simple changes in how we live -- complete separation of untreated sewage from drinking water and food, control of helminth infection by eradication of sources of worm exposure, shoes, regular anti-helminth treatment, houses worth living in. The houses worth living in we will come to in a minute.

Absolutely, those things which will cause the shift to modern asthma in Ghana and in Costa Rica in other parts of Africa were completed in the United States

northern cities in 1920. But not everything was completed.

Potential interventions -- Oral allergens we have been over. Dust mite I'll show you. Sublingual drops or tablets; transdermal patches. I'm told this is supposed to be epicutaneous -- it is on the skin. There is some very interesting stuff about the difference of putting allergen on the skin and abrading the skin and then putting it through.

Abrading is what we did to develop patches of eczema with dust mite on the skin, but putting it on undamaged skin -- wait a minute. Undamaged skin. You mean never damaged by detergents, and that is a tremendously important issue now in the whole of trying to understand what the LEAP study is about. I hate to be sexist, but most of the children are being washed by their mothers. They can't get the fathers to do it. And they're being washed every day. I was never washed!

(Laughter)

I can remember my other shouting at me, Tom, you're filthy. Go and have a bath. There was no shower; we had a bath, and the bath water was brown. That's what the bath water color was supposed to be. Today, no child dares go to high school without having a shower.

But now we have mothers who are washing babies

twice a day. If you put detergent on the skin and then you put allergen on top of the skin that has been washed with detergent twice a day, that's not undamaged. That has been abused. And the scale of this -- I find it difficult to express what happens. You're taking fat out of the skin the whole time.

In the 1960s the cardiologists worried that the amount of detergent being put on the skin was taking valuable lipids out of the body and was influencing the changes in lipid that were related to cardiovascular diseases. That had nothing to do with our world; that was already there. It's much more now.

So there is no such thing as undamaged skin. Undamaged skin is greased and is treated, as we did in Charlottesville, Virginia. 100 years ago, you had a bath before the winter and after the winter, whether you needed it or not.

(Laughter)

Maybe this is the really important message, that we're living in a situation where, in the time -- I went to Hopkins. Hopkins was totally focused on hay fever. By the time I got back to England in 1974 asthma had broken out and was expanding rapidly, and the first data showing the increase and the relationship to dust mite was coming.

Asthma went up like crazy. We didn't really see the food allergy until the 1990s and now it dominates our practice.

We are living in a life that's changing all the time. There used to be families of five children. There are no middle class families of five children anymore. We have four, but it was an accident. It's an extraordinary situation that things are actually changing much faster than we are willing to admit.

Let's get to something really productive. Can we reverse hygiene? Can you actually reverse hygiene? There's a plan to give people a vial full of lactobacilli that come from dog poop and you persuade the mother to sprinkle it on the carpet every day. That doesn't seem to go over very well, but the alternative is to get a dog that's allowed outside every day which achieves exactly the same effect.

So these lovely studies from Christine Johnson's group in Detroit where -- one of the lactobacilli is called lactobacillus jonsonii, and we all think it was named for her. But Nick Lucas, who is here, who is doing the mouse studies with bacterial extracts, is showing that getting the right bacterium in -- and it's a real question for the whole of the probiotic world; that is, are there really specific bacteria that if you could get them into the biome

as a specific intervention you could reverse the problems of hygiene with a very specific intervention? But that certainly isn't straight yet.

This is Ben Bjorksten, who was one of the first people to focus on intestinal microflora and said they were different in relation to allergy, and that that was one of the things that was changing. If I was asked what simple thing you could do today, I would say absolutely get a dog in the house and make sure that it's allowed outside free so that it can go and find the poop of another dog to roll in. That's the productive thing.

Cat is different. Having a cat in the house can induce tolerance, and that tolerance is dominated by IgG4. I would happily give a lecture about IgG4 but that would be to the wrong audience.

In New Zealand, 50 percent of the houses or more have a cat in them, and children raised in a house with a cat are less likely to be allergic to cat. But it's very blurred because the prevalence of cat allergen throughout the community is so high.

What I want to show you here is that of 55 children with asthma living in a home with a cat, 34 were sensitized to mite but not cat. That is, they can go tolerant to cat but not be tolerant to mite, and that issue

is very important. Can you induce tolerance to one allergen that will have a diffuse effect over the whole community, all allergens, an interrupted march, or do you have to do it for each allergen one at a time?

The preliminary data in the LEAP study suggests that it's allergen-specific, what happened with the oral desensitization. One would love to see a non-allergen specific. And I said before, immunotherapy with grass pollen appears to reduce the response to mite, subsequent mite, but that's subcutaneous.

This is Wellington where my grandmother put up a plaque as a doctor in 1902.

I mentioned before that asthma started to rise in 1954, and these are four bits of data. This is England where the rise was first seen, and this is Australia, New Zealand, a little bit of Canada, Wales -- rises in hospital admissions. This is Charleston, South Carolina, MUSC. Here are the African-Americans, who at this point are all planning to vote for Hillary. Of course, this was a couple of years ago.

This rise starts here, 1960. What happened in 1960? At this point, before the Charleston study, we were thinking dust mite is it. The only rises in asthma had occurred that were really seen were in Japan, Taiwan, New

Zealand, Sydney, Australia, the UK. America didn't have any epidemiologists; they didn't know what was going on.

Here, this was the big break-through. In 1990, it became clear that the same rise had been occurring in Finland and in Sweden. These are Army recruits. But look how ridiculously low these prevalences are. They were down below .1 percent of recruits. All Finnish young men had to go in the Army, and it went from .1 or .2 up to 1.8 percent, whereas, in New Zealand it went from 2 percent to 20 percent. Very different. This is clearly not mite. In Finland, mite is not an important allergen; this is cat and dog. So the rise is not a function of one allergen and can't be attributed to increased exposure alone. It has got to be something different. This matters if we want to try and intervene. So what happened in 1954?

I started bleating about television in 1996, and Fernando Martinez said, oh, it's just Tom's latest monomania. I like that! What happened in 1954? It was the Howdy Doody Show and the Mickey Mouse Club, and there are people -- I bet Ira can remember the first day that someone said I'm going in to watch television. In the last 10 years, no one has ever gone in to watch television because they never came out in the first place.

My wife was raised in New York and she remembers

absolutely three hours a day you would change your shoes and go out and play and the last thing you heard was don't be late for supper. This is an extraordinary change in lifestyle that occurred and was driven by television.

I love this advertisement -- nothing to break the spell. This was in the 1950s. The television shows were trying to put children into a trance, and they do. If any of you can remember children without a cell phone -- I know it's a bit old, but if you touched them when they were watching a television program they'd startle. No one with a cell phone startles. When they were in that trance, their breathing pattern changed and they don't take sighs, and sighs are important in asthma.

You say wait a minute. What has this got to do with it? Allergic people normally get hay fever and rhinitis, but when you put them sitting without breathing for hours a day, wheezing develops. We may have to intervene in both, or you may fail to change it because you don't get back to some healthy situation.

Here's a beautiful study from Europe really arguing -- This is Peter Burney who has done some lovely studies with the European Community Respiratory Health Survey. This is one in which they argue very strongly that physical exercise decreases bronchial hyper-reactivity, and

also the studies at Hopkins where they showed quite clearly that deep breathing decreases the resistance of the lungs and is really an important way of controlling asthma.

Finally, I would just like to go over the situation -- How are we doing on time? I'm obviously on good time because I'm actually before the time I was supposed to start.

(Laughter)

Michael was an MD PhD student at Charlottesville when he was a young boy. He wasn't actually much use. He was very nice; he was just as nice then as he is now.

(Laughter)

Here is Costa Rica and here's Ecuador. Costa Rica is a weird place, as you all know. They had four gentlemen who got together, a priest, an army person, someone else and a communist, and they all got together and said we don't need an army. They decided not to have an army. They decided to put some money into healthcare instead. Wow -- radical!

Anyway, they did that and they actually have clean water. In San Jose you can drink the water out of the faucet. It's the only place in Central American where you can do that. And they have houses and they have shoes and they have health service. Ecuador, here in Esmerelda's

Province, the northern tip of Ecuador, they have towns which have gone modern and villages which are really brilliantly pre-hygiene.

Let's just look at Costa Rica. These are children being admitted to an emergency room to be treated for asthma. These are the children with asthma, and these are the sensitization in IgE antibodies, and dust mite completely dominants what happens. We're not sure why cat is so little here and the cockroach -- there's a lot of cockroach sensitization but very little high titer. I apologize for not having mouse up there because there are communities such as Baltimore where mouse is the most important. And, surprisingly, mold was not very important. We've looked at many other molds; we can't find it. Dog and cat we don't see much.

So you can see with mite what we showed is that, exactly as we found in Charlottesville, if you have a recent rhinovirus infection and you have IgE mite high titer, you have a very high risk of asthma. So this whole business of rhinovirus and the relationship of rhinovirus to acute episodes of asthma, which is an extraordinarily important aspect of bad attacks of asthma in children over the age of three -- here is exactly the same in Costa Rica. That is, it is a fully western model; that's all you have

to do. But they don't have the food allergy. They appear to have very little food allergy. Maybe they're going to get it next week, but we don't see it yet. You really ought to be able to tell why that's happening.

This is one of the villages in Ecuador -- it's actually rather lovely. This is a chicken. There's a duck here somewhere. There's a saddle here, so there's a horse in the family, and this is your friendly neighborhood pig with a large litter. Pigs carry many things but particularly they carry one of the fine denizens of the jungle, this fellow. This is a child's stool after two days of anti-helminth treatment and this is Ascaris. That's a genuine stool sample from a 7-year old child in Ecuador.

When you're looking at the village in Ecuador, is it the helminths that prevent the development to allergic disease, or is it contamination? That house gets its water from a river, and the latrine flows into the river downstream of them, but they collect their water downstream from the next village up so real diversity of bacterial exposure is present.

Interestingly, the bacterial content of the stool, or the microbiomics, is completely different in the Ecuador villages than we see in Tanzania, where my son has

been doing research. Should we be intervening with worms, or are worms irrelevant? Is it all bacterial? That we need to know.

Obviously, people have tried worm studies, but as far as I know they have all failed. Not all failed, but they are not convincing. You can't colonize some children with worms and get them to stop the development of allergy. At the moment, it looks more likely that it's bacterial.

Here, in Esmeraldas Province, this is actually a random population with very few of the children from the town, but if they have high levels of Ig to mite, then it's related to asthma. Overall, mite allergy is common but not related -- looks like the situation in the poor places in Africa. Alpha gal, which is the tick-related thing, is not related to asthma at all. And here, Ascaris is the strongest association overall. A large proportion of the children are positive, and a very strong association with wheezing. But Ascaris wheezing is different from acute asthma that we see with dust mite.

I want to mention one subject which I think is relevant. If we're thinking of stopping the march, we need to know what else could have led to the march, could have led to this increase. A lot of people have insisted that this should be included. Many people do not realize just

how much alum is being given, and there are actually two issues here in relation to vaccination policy that I think pertussis -- pertussis used to be cellular pertussis and it caused a lot of reactions, and the FDA for very good reasons decided they don't want any cellular vaccines given. They're not going to go back to cellular vaccine.

But a lot of things happened at the time when it changed from cellular pertussis to acellular. I understand that within about five years there will be a recombinant form of pertussis vaccine which may change the situation so that you can have a vaccine that's achieving the effects of the cellular vaccine without the risks. But that is to be seen.

So there was this change which occurred in the early 1990s. Many people have pointed this out including Rob Albers, Pat Holt and I think Hugh mentioned it. But then there's this one, hepatitis B at birth, where actually the situation is really bizarre. That is, every middle class family I ask the parents and they say no, my pediatrician said we should delay that. So it has actually not been given to middle class. None of my children's children received it at birth. They delayed it for some reason. So it's being given to people in hospital who are bullied into having it. We've heard descriptions of people

being bullied grossly.

If you ask the FDA for details about the side effects of alum at birth, as far as we can see there are none. There is very little data at all. My message about this is that anyone who says that all vaccination is wonderful and we should never, never argue about any form of vaccination is being ridiculous. There is no form of medicine -- protein pump inhibitors are coming under real question now. So I want this as part of the equation.

Finally, a study was published last year from the Isle of Wight which illustrates a bunch of questions about the intervention. This is at-risk children on the Isle of Wight who were given oral immunotherapy with dust mite, quite a high dose, for one year, and they followed their sensitization as judged by skin tests and here you will see surprising results A significant reduction in sensitization to any common allergen but not an effect on dust mite, as if dust mite could actually have a poly-specific effect without protecting against itself, which simply adds to the complication.

But I would say that you can’t tell much at one year; it’s much too early, and it poses the whole question what is the intervention, who are the target population, and how long do you have to carry on.

Approaches to intervention are: Avoidance of allergens -- for dust mite, it's very difficult. For cat, it's not relevant because children living in a house with a cat actually have less sensitization. Oral feeding of allergens, yes. Peanut, no. Dust mite has not worked yet. Altering the microbiome -- Dog in the house during the first year, bacterial, worms, living on a farm. All the new products you can think of -- probiotics, CPG, lots of different things, IL-10, monoclonal antibodies. But you're left with the issue of how do you judge it, when do you start and how long do you continue. But I think, for the moment, we are going to be happiest about a filthy dog.

Thank you.

(Applause)

DR. NELSON: Thank you, Dr. Platts-Mills. I'm sure you will entertain a few questions after entertaining us for the last 45 minutes. This is not a bashful group but I'm going to take the speaker's prerogative and ask mine first.

You made a strong argument that it's an imposing challenge to clinical investigators and the FDA to decipher the signal of when, indeed, an atopic march is, in fact, interrupted with immunotherapy because so much four-letter word happens, or stuff happens. You mentioned things such

as allergen specificity, sedentary lifestyle, watching TV, location-dependent allergen exposure -- people do move during long clinical trials -- the vaccination status and perhaps alum exposure.

It’s hard to capture everything going on in a volunteer’s lifetime as they participate in a clinical trial. What truly surfaces as some of the higher-risk things that should be captured across clinical studies so that we can be sure that the observed achieved endpoint is indeed due to the intervention of the immunotherapy and not other stuff that’s going on in that individual’s life?

DR. PLATTS-MILLS: In terms of what do you need to know about their life -- oh, wow, it’s horrendous. I think you clearly need to know about dog and cat ownership. I think you need to know whether they actually live at home.

In our experience, African-American families in the South are very stable by town and remarkably unstable by house. That is, they often spend time living with an auntie or some other family, so that they change. But they’re remarkably stable by town. Whereas, white families are remarkably unstable by town and much more stable by house, in the short run.

Diet -- you’ve got to be interested. The food

allergy stuff now is very clear that the idea of avoiding exposure while peanut is present in the house is a complete no-no. I would say that definitely failed.

You need to know about animals in the house. What can you say about physical activity? The Alsbach study had very good data showing that more than two hours a day spent watching television was strongly associated with asthma at age 6, so you can't ignore that

But I really think we're living at a time when the electronics are changing childhood behavior so rapidly that the children are either on a computer or they're texting. We have never done breathing studies on those situations in comparison to people watching a program that they like where they will sit still and, as I say, go into a trance. If every time it stops you start texting a friend, you won't go into a trance.

In terms of monitoring exposure, something I may not have said clearly enough is IgE antibodies we can measure with great accuracy. We can measure them to specific proteins. We can argue about whether you need to know about Rh1, Rh2, Rh6, Rh8, all those things. That has come a long way. And the challenge for any surrogates is to compete with IgE, and that's going to be very difficult I think.

DR. KELSO: I would like to take a minute to challenge the notion of the atopic march. If what we're doing is to try to intervene to prevent a child with one atopic condition from developing others, I think it's important to know how often that happens naturally and in what order.

There was a study published in 2009 where they looked at an unselected birth cohort of 24,000 children and followed them for the first 18 years of life, and 36 percent of them had developed eczema at some time in their lives, 22 percent had developed asthma, and 11 percent had developed rhinitis. In the index condition, the first atopic disease that any given patient developed, 60 percent developed eczema as their first disease, but 28 percent developed asthma and 10 percent developed rhinitis. And of the patients who developed any of those three things, 65 percent of them didn't march. They didn't go on and get any other atopic disease.

Of those whose index condition was eczema, only 5 percent went on to also have both allergic rhinitis and asthma. And similar numbers -- if your index condition was asthma, only 4 percent went on to have both eczema and allergic rhinitis. And if your index condition was allergic rhinitis, only 5 percent went on to also have both

eczema and asthma.

I just think in terms of context, it's important to realize that most children who develop one atopic condition will not march; they won't develop other atopic conditions, and of those who do, they can sort of develop them in any order and at any time.

A lot of that can be corrected for, as can I think the concerns you raised about other factors that may be involved in somebody's life that may affect the outcome other than the intervention. Of course, much of that is covered with randomization. So it's important to look for identifiable variables that may have affected the outcome, but, of course, the beauty of randomization in research trials is that it controls not only for suspected variables but all the unknown variables as well.

DR. PLATTS-MILLS: Absolutely. I don't know which study that is --

DR. KELSO: It's a UK birth cohort, so that will make it a little closer to your heart.

DR. PLATTS-MILLS: It's not Alsbach?

DR. PETERSON: No. Punikar and Shake are the authors -- clinical and experimental allergy.

DR. PLATTS-MILLS: Yes. What's interesting is you call those atopic conditions, but of course, wheezing

in early childhood is generally not. In under age 3 it is generally not atopic. And a lot of eczema doesn't have an atopic basis in the early stages, and it will become atopic if it continues, or most of it becomes atopic, as judged by IgE production. So you can solve some of those issues that you're talking about.

But your point is very well taken. If you want to deal with that kind of diversity and fully randomize, you're going to have to have a very large cohort before you can see anything.

I think that's the important thing about the LEAP study. They correctly identified a situation where you could answer a question. The fact that it's not generalizable to the whole population -- but if 36 percent of the population have eczema, then the LEAP study becomes highly relevant and relevant to a lot of peanut -- I hope everybody understands what the LEAP study is. The LEAP study is the peanut oral immunotherapy done by Gideon Lack and George DuToit in London where they followed children who had eczema, who were at risk of sensitization to peanut but not reacting to peanut at that stage, and followed them for five years and showed that it dramatically decreased IgE production to peanut and dramatically decreased reactions.

It is a model, but of course it's an extraordinarily difficult study to do, and in many other situations it would be very difficult to identify an equivalently at-risk population. If you want the data to be relevant to a population, then that's a different question.

DR. PETERSON: I had a question about the populations. Thinking of the Isle of Wight, which is a confined area, is there any way to use that to look at just everybody and doing something?

The other part of this is, at one point I think in Denmark, they had been collecting information on kids at birth. Everybody got a number and got something, and they could follow them, and people knew they were being followed and looked at. The anthropologists were coming up with all kinds of data they didn't need, but useful data that was tangential that they would never have found out otherwise.

Is there anything in finding a population like that to follow?

DR. PLATTS-MILLS: Data of that kind is available. Of course, the most dramatic example is Iceland where they know where everybody came from. Isle of Wight is not like that. There's way too much movement on and off the island.

Just as an historical point, the reason the study was done there is because David Hyde was there and it's called the Hyde Center. The person who was there before him was called Dr. Giles, who was actually Carl Prausnitz who invented the PK test in 1921. His father was German and his mother was English, Mrs. Giles. He moved to the island because for some reason it seemed unwise to stay in Germany.

But I think the possibility -- they can do this in New Zealand. You can really follow the Dunedin cohort which is now at 27 years. There's Malcolm Sears. They can really follow the population and not lose them all. We followed a community in northern Sweden and followed them for 12 years and you can pretty well tell where all the children are. But the Isle of Wight, not. In most places, not.

DR. PEDEN: On one of your slides you commented on, I think it was one of the Costa Rican studies where rhinovirus infection caused wheezing in kids who were mite sensitized. So the question is, does the rhinovirus in mite-sensitized people worsen something about mite responsiveness or the mite biology, or does the increased IgE or the immune response to mite reflect a diminished antiviral host offense, and what you're really seeing is

diminished host offense against that? And one of the phenotypes we're looking at is actually not pro-allergy; it's anti-Th1, and it's kind of analogous to why are asthmatics at higher risk for pneumococcal disease.

DR. PLATTS-MILLS: Judith Whitford just reached a stage at which you can actually look at mite-specific T cells and rhinovirus-specific T cells using tetramers to identify the T cells during the period of a challenge. I don't know the answer. I think you put it very well; that is, is the rhinovirus enhancing the mite response or is it a marker of a changed or different response to the rhinovirus. It's very difficult to do.

We have the rhinovirus challenge model in Charlottesville but it's extraordinarily difficult to do.

DR. NELSON: I have one more question and a comment on Dr. Kelso's statement about the atopic march. Thank you for bringing that issue up. It is an important one.

I won't speak for Dr. Slater and the FDA, but I think that probably played into why they phrased their second question to us very specifically on the prevention of asthma as opposed to the atopic march, because of some of the grayness in that area. I'm sure we'll get into those details later as we enter our discussions this

afternoon.

I wanted to ask you, Dr. Platts-Mills, you alluded in your talk to allergen specificity, in particular those asthmatic children in cat houses who are not sensitized to cat but are sensitized to dust. We know that immunotherapy, through a number of studies, is able to prevent new sensitizations, not an allergen-specific response but an observation that goes with treatment, and leads into this question of whether early intervention with immunotherapy can actually prevent later atopic disorders or, in this case, the development of asthma down the road.

From your observation of the literature, does a decrease in new sensitizations actually lead to a decrease in the burden of existing disease or, in fact, a decrease in the risk for development of additional atopic disorders?

DR. PLATTS-MILLS: The tradition is actually in Bill Franklin's initial controlled trial of grass pollen. In the first controlled trial of grass pollen immunotherapy, he said that it prevented the development of asthma. And there have been several studies of that kind saying that grass pollen -- that is, immunization against a seasonal allergen -- can decrease the risk of asthma. I wouldn't say it's universally accepted, but it's definitely being achieved.

In the situation in New Zealand, 50 percent of the houses have a cat, but asthmatics living in a house with a cat who become allergic to mite may, nonetheless, be tolerant to cat. In most models, that is strongly associated with IgG4 production, the form of tolerance.

The alternative is that in Sweden, in the Swedish cohort -- this is way up north, close to the Arctic Circle, and there are no mites whatever, so you can study the effect of cat. There, ownership of a cat, which decreases the risk of sensitization to cat, also decreases the risk -- if you are non-allergic to cat and you live in a house with a cat, you will not be allergic to anything else. But there's no mite.

And that would argue -- The comparison with the New Zealand data is that there may be something magic about the mite. That is, the mite may be able to overrule it, just in the sense that a tick bite on the skin -- our experience with tick bites on the skin giving rise to IgE to alpha gal says there is absolutely no difference between atopic and non-atopic people. That is, their pre-existing state does not tell you what's going to happen in the skin if you inject the allergen through the skin. That raises this whole issue of the real difference between different routes.

DR. NELSON: Additional questions from the panel?

With that, I want to thank Dr. Hise and Dr. Platts-Mills for outstanding presentations and setting the stage for our discussions this afternoon. We will stand in recess until 11:00 and we'll start off with Dr. Chang.

(Brief recess)

Agenda Item: Clinical Considerations for Aeroallergen Immunotherapy, Tina Chang, M.D., DVRPA

DR. NELSON: Welcome back to Part 2 of this morning's session. We're going to begin with a talk by Dr. Tina Chang, medical officer from the Division of Vaccines and Related Product Applications. She's going to discuss the clinical considerations for aeroallergen immunotherapy.

DR. CHANG: Thank you. The title of my talk is The Prevention of Respiratory Allergic Disease with Allergen Immunotherapy.

The outline of my talk will begin with a background, then discuss regulatory considerations, then the clinical development specifically in regards to the demonstration of efficacy and safety, then end with a brief summary.

First I'd like to start with a background. As we've talked about the allergic march, or atopic march, it's referred to as the clinical progression of allergic

diseases or sensitizations that begins early in life. As shown in this diagram, the first sign of the allergic march or atopic march is eczema or atopic dermatitis with later development of food allergy, rhinitis, and/or asthma. Investigators are exploring the administration of allergen immunotherapy early in life to interrupt the progression of the allergic march and to prevent asthma.

This diagram was taken from the LEAP study, also known as the Learning Early about Peanut study, that showed early oral introduction of peanuts decreases risk of developing peanut allergy in infants at increased risk of peanut allergy. The LEAP study was a randomized, open-label, controlled study including 640 infants 4 to 11 months old, believed to be at increased risk of peanut allergy based on a history of severe eczema and/or existing egg allergy. The infants were randomized to either avoid peanuts or consume 6 grams of peanut protein until 5 years of age.

In this table, the LEAP study is compared to two examples of published studies that suggest allergen immunotherapy may decrease the risk of developing asthma. The first is an example using subcutaneous immunotherapy, and the second is an example using sublingual immunotherapy. The first is the Prevent Allergy Study by

Moller and colleagues, which is a randomized, open-label, controlled study that included 208 children 6 to 14 years old with a history of seasonal allergic rhinoconjunctivitis to grass and/or birch pollen and a positive skin prick test to grass and/or birch only. These children were treated with a three-year course of subcutaneous immunotherapy with grass or birch pollen extracts and were assessed for asthma at the end of treatment with additional follow-ups at 5 and 10 years.

The second study by Novembre and colleagues was also a randomized, open-label, controlled study. They included 113 children 5 to 14 years old, also with a history of seasonal allergic rhinoconjunctivitis to grass pollen and a positive skin prick test to grass only. These children were treated four months out of the year with sublingual immunotherapy with grass pollen extracts for three years and then assessed for asthma at the completion of treatment. Potential routes of administration include subcutaneous, sublingual and oral.

I forgot to mention that these studies have now sparked interest in developing allergen immunotherapy products with an indication for the prevention of the development of asthma; specifically, with treatments starting at a much earlier age. As you can see here, the

LEAP study started treatment at 4 to 11 months old, and the other two examples started at a much later age.

Next I would like to talk about the regulatory considerations for such products. The CFR states that all indications must be supported by substantial evidence of effectiveness. It's our expectation that the demonstration of effectiveness is based on adequate and well-controlled studies. Some characteristics of adequate and well-controlled studies quoted from the CFR and pertinent to this discussion are included here, although there are others. The methods of selection of subjects provide adequate assurance that they have the disease or condition being studied or evidence of susceptibility and exposure to the condition against which prophylaxis is directed, and the methods of assessments of subject's response are well defined and reliable.

According to these regulatory standards, I'd like to talk now about the clinical development, specifically in demonstrating efficacy of these products.

In evaluating the effectiveness of allergen immunotherapy products for the prevention of the development of asthma, the agency has identified several challenges: selecting the trial population and control group, choosing criteria for asthma diagnosis and

endpoints, and defining the timing of the assessment of asthma endpoints.

I would like to focus on the first bullet, selecting the trial population and control group. In order to develop a product to prevent the development of asthma, subjects at increased risk for developing asthma need to be studied. As I mentioned before, the interest is to start treatment early for prevention of asthma since the population of interest is infants and children less than 5 years of age.

Reliably identifying infants and young children at increased risk for developing asthma is challenging partially due to the fact that asthma is a heterogeneous disorder with variable expression influenced by many factors, host and environmental, as the ones listed here. Some of these risk factors may be influenced by allergen immunotherapy and some may not. Some risk factors that may be influenced by allergen immunotherapy and selected for inclusion criteria include family history of atopy or asthma, atopic dermatitis, food allergy, allergic rhinoconjunctivitis and allergic sensitization.

Next I'd like to talk about choosing criteria for asthma diagnosis and endpoints. The National Asthma Education and Prevention Program Expert Panel Report 3, or

EPR-3, and the Global Initiative for Asthma, also known as GINA, guidelines recommend the use of the medical history of wheeze, shortness of breath, chest tightness, cough, a thorough physical examination, and spirometry that documents airflow limitation for the diagnosis of asthma in adults.

For children less than 5 years of age there are special considerations. Pulmonary function testing is difficult to perform. Although many children as young as age 5 may be able to perform spirometry, the majority of children less than 5 years of age are unable to perform acceptable and reproducible spirometry. Also, not all children who wheeze develop asthma.

As mentioned earlier in prior talks, wheezing is fairly common in young children. Although asthma could be a cause of wheezing, there are other causes such as viral upper respiratory tract infections, gastroesophageal reflux disease, obstructive sleep apnea, and almost any respiratory disorder that leads to airway narrowing or obstruction can be associated with wheezing.

The EPR-3 and GINA guidelines address these considerations and recommend that when diagnosing asthma in children less than 5 years of age, we use a combination of the pattern of symptoms, presence of risk factors for

asthma, the physical exam and a therapeutic response to a two to three-month trial of as-needed, short-acting beta 2-adrenergic agonist and inhaled corticosteroids.

Although there are no objective tests that help us diagnose asthma with certainty in children less than 5 years of age, there are additional tools that we can use such as tests for atopy, like skin prick testing, or allergen-specific IgE testing, use of risk profile tools as the ones listed here, the measurement of the fraction of exhaled nitric oxide or FeNO, and imaging to exclude structural abnormalities.

One potential tool that I'd like to talk about is the fraction of exhaled nitric oxide. Normal reference values have been published for children aged 1 to 5 years, and the fraction of exhaled nitric oxide has been shown to be elevated in eosinophilic airway inflammation, and an elevated fraction of exhaled nitric oxide in preschool children with recurrent cough and wheeze is associated with subsequent diagnosis of asthma in school-aged children.

The last thing I'd like to talk about is defining the timing of the assessment of asthma endpoints. The timing depends on age at asthma diagnosis and should consider the number of years subjects need to be on treatment to assess the prevention of asthma and, if

applicable, consider the number of years subjects need to be off treatment.

Two potential approaches to study designs and endpoints based on age include continuing clinical efficacy studies until children are able to perform pulmonary function testing, such as 5 years of age or older, or assessing children less than 5 years of age based on clinical symptoms and other laboratory tests or diagnostic tools.

I would like to end with safety considerations. Safety monitoring in infants and young children presents unique and challenging issues. Adverse events depend on the route of administration. In an effort to improve tolerability both in patients and with parents, oral and sublingual immunotherapy are more likely to be accepted than conventional subcutaneous immunotherapy. Common adverse reactions such as pruritus, mouth edema, throat irritation and oral pharyngeal pain following oral and sublingual immunotherapy may be difficult to reliably detect and treat. Simply, infants and young children really can’t communicate what they are feeling.

Risk of severe or fatal laryngopharyngeal swelling is greater due to their narrow airways, and it’s also important to monitor for eosinophilic esophagitis.

Eosinophilic esophagitis is a reported adverse event that has been described with sublingual immunotherapy products. Monitoring for EOE may be difficult in this population because symptoms of EOE in infants and young children may be subtle and the disease may be unrecognized for years. Also, the definitive diagnosis involves invasive methods such as endoscopy and esophageal biopsy.

In summary, the clinical development of allergen immunotherapy products to prevent the development of asthma presents challenges including selection of the study population, criteria and timing of assessment of asthma endpoints, and safety monitoring in infants and young children.

To support labeling, agreement is needed between the applicant and the FDA on the study design, study population and clinical parameters for demonstrating prevention of the development of asthma.

DR. NELSON: Thank you, Dr. Chang. I will open it up to the panel for questions at this time.

DR. KELSO: Not so much a question as a comment in regard to the diagnosis of asthma in young children and the majority under age 5, or a large percentage, being unable to perform spirometry. Impulse oscillometry is another technique for evaluating lung function that is

completely passive. Although I don't have any experience with it, there's a fairly substantial body of literature suggesting that it is quite an accurate assessment of lung function and is something that can be done in infants and young children.

DR. NELSON: I had written down the same thing to discuss later.

I think it's very important that you ended with respect to safety -- safety of the volunteers in our clinical studies and the safety of those intended to take any approved products at the end of the rainbow, if you will. It's a distinct challenge identifying what those safety parameters are in clinical design and is part of the endpoints that we should capture.

I wonder if you would like to speculate any further -- or anyone on the panel, for that matter -- with respect to whether or not we as a panel today should be stratifying risk according to specific ages; *i.e.*, subdividing the young age group, considering that different age groups do indeed have different risks.

DR. CHANG: I think that would be appropriate, considering that different age groups do have different risks for different adverse events. I guess that's one of the questions that we would like the rest of the panel to

answer.

DR. NELSON: Dr. Slater?

DR. SLATER: I agree. I think, because for the most part we have the least experience with allergen immunotherapy in the very young children, I would probably want to direct the discussion to the very young children, which of course is the hardest group to discuss. I think the concept of stratifying is a fine idea, but I want to make sure that in the discussion we really focus on infants and young children.

DR. WEBER: I'm not really aware of efficacy studies in very small children. I know that frequently, immunotherapy is put off as a consideration just more for social reasons than for the aspect of lesser effectiveness. For example, we're talking about small children here, so is immunotherapy appropriate for someone who is three, four, five? Probably one or two, although I wonder about how often you come across the indications for such. But again, I am not personally aware if there's much published in the literature on that.

DR. NELSON: I would agree, but perhaps there are some lessons learned, although probably not intentional, in the way of studies that can be generalized -- the use of hymenoptera or venom immunotherapy in the very young,

particularly in that risk population, for either the winged hymenoptera or, in particular in the South, for fire ant. There may be some lessons learned that we can draw upon for allergen treatment in this age group.

I believe Dr. Finegold is next.

DR. FINEGOLD: A number of years ago, I was looking at the question of what age is immunotherapy acceptable. At that time, there was a very strong guideline that said 5 years of age and above. I said, well, how did we get to that?

When I looked further, one of the lynchpins of that argument was based on one of Bosque's colleague's studies of rush immunotherapy in small children. What they found was that children less than 5 years of age had an increased incidence of reactions. I can clearly remember him coming to an Academy meeting or a college meeting and standing up there saying this shows that you shouldn't do immunotherapy in children less than age 5. But, when I looked at that study, what I found was that there was no dose adjustment for the small children. The dose adjustment was from, say, 3 years to 12 it was a half dose, and above 12 was a full dose for the rush treatment.

But my point was that children less than 5 years of age really are very small, as a rule, and don't weigh

very much compared to children, say, age 12, but their dose was the same. For example, with anti-IgE we have dose adjustments, but for immunotherapy we don't. Bottom line is that I think in these studies, safety may be to have weight-adjusted dosage for immunotherapy, and there's not a whole lot about that.

DR. APTER: These studies, of course, are going to be very difficult to perform in terms of safety and efficacy, and then even to think beyond that, because what we really will want to know eventually is effectiveness if they're used in the real world. You can see that if you were administering immunotherapy to young children, the parents of course would be involved in making decisions, too, about safety. We know that adherence isn't great in immunotherapy in adults and SLIT, and you can imagine that it would be further complicated in children.

What I'm wondering is if we should go back and take a very good look at the birth cohorts we have in the studies of patients with databases of young children that we already have to look for the answers to some of these questions first.

DR. KELSO: I guess, too, again, where we're talking about intervening and what population might be studied to help answer the question if the immunotherapy

intervention can prevent the development of allergic respiratory disease, even though, as the data I gave you suggests, most children don't march or don't march neatly through this progression Clearly, children who have one of the genetically atopic diseases are at increased risk to develop at least one of the others. So, if nothing else, you could stack the deck by taking patients who already have one allergic disease, as has been done in some of these studies, children who already have allergic rhinitis but do not yet have asthma, to see how many of them go on and have asthma.

If you're talking about that group of patients, you're not talking about infants and toddlers, typically. By the time you have an established diagnosis of allergic rhinitis, you're usually a little older child. If that's the group we're talking about, some of these issues about very young infants may not be applicable.

On the other hand, there was just a study published in the December JACI of taking children who had no sensitization to allergens and no atopic disease but were born into an atopic family -- so stacking the deck that way -- and giving them house dust mite oral immunotherapy from birth, and their endpoints were looking at sensitization to house dust mite and sensitization to

other allergens. Curiously, giving these at-risk children house dust mite oral immunotherapy didn't make them any less likely to become sensitized to house dust mite over the first year of life but did make them less likely to become sensitized to other aeroallergens.

So, if that doesn't complicate the picture -- I mean, we really have to be careful about what we're constructing. There really are a lot of variables here in terms of the patients in whom we would be intervening, at what age we would be intervening and what our endpoint is, whether we've prevented something or not.

DR. NELSON: Dr. Chang, I did have one additional question. You alluded to the use of additional tools perhaps in study design and, in particular, mentioned several indices for asthma that can be used. What is the FDA experience for using these indexes or indices in the process of product approval? I know that they're used in a variety of studies that tend to contribute toward product approval, but I'm wondering if there has been specific addressing of the use of these indices in the product approval pathway.

DR. CHANG: I don't believe we have had any experience yet with these. Dr. Slater?

DR. SLATER: Right. In our experience in the

Office of Vaccines, the SLIT approvals were on the basis of composite scores. And, of course, we didn't have any of the issues of how do you measure this in very young children. I think the comments have pointed to some of the difficulties.

I guess the reason that we feel driven to ask the questions of the committee regarding very young children is from the suggestions that were made both in Dr. Chang's presentation and in Dr. Platts-Mills' presentation that the biology of interrupting allergic responses in this way and preventing the development of allergic disease is such that the window may be early in life.

It's certainly possible that the data, as it evolves, is going to show this to be incorrect and that would make our lives a great deal easier, but certainly the evidence that we have so far, limited as it is, suggests that we ought to be anticipating that sponsors are going to be looking at infants and young children and we need to be prepared for how we're going to deal with that.

DR. PEDEN: In terms of early life prevention of disease, the one corollary I wonder about -- and I'm embarrassed; I don't know what the endpoints were other than acquisition of the infectious disease or vaccines against infectious diseases. There, that's not a host of -

- other than antibody titer or maybe immune response, other than counting the people that got pneumococcus and others that didn't. I think when we're talking about prevention of an allergic disease, ultimately, the biomarker is the prevention of the allergic disease. You either have asthma or you don't, or you have eczema or you don't, or you have less severe asthma or you don't.

You're looking for lessons learned. I think one of the lessons learned is when there's a new methyl group plugged onto a protein so that you can see polysaccharides better, what are the things that the FDA has been comfortable with in making those approvals and then moving forward? Because this is really immune-modulation of a host response to a foreign antigen.

DR. WEBER: My comment is on a different tack. If we're trying to intervene as early as possible, the first step is to identify the at-risk population, and it's easy to say that children of atopic parents -- that's an obvious at-risk population. But since atopy in general and allergies appear to have been increasing, if you go back to data for the last 100 years, that would suggest that either atopic people are very prolific and produce many more children or that there's a group that have not been identified as having a family history or whatever of being

atopic who are becoming atopic.

The question is what should we do to try to identify these really young children. Should we be doing cord blood IgE on all infants, just like we look for things like PKU and those kinds of things? I just raise that as a thought.

DR. KELSO: Just to point out, too, that one of the things that was mentioned and kind of addresses that in terms of what population do we pick was the asthma predictive index.

And just a remark -- the positive predictive value of the asthma predictive index. So kids who have all these features that should make them prone to go on and develop asthma, it's actually quite low. Most kids with a positive asthma predictive index will, in fact, not go on and develop asthma, although its negative predictive value is excellent. If you don't have any of those things, you are almost certainly not going to develop asthma.

Whatever tool we pick to identify our population, we have to realize what the chance is of those patients developing the condition we're trying to prevent because that plays into all kinds of things, not the least of which is how large a population do you have to study in order to demonstrate an effect.

DR. NELSON: Any additional comments?

Dr. Chang, I want to thank you for an illustrating talk and congratulate you on switching uniforms. Tina was an Army allergist as her roots. Hopefully you're still bleeding green even in your new capacity, but we thank you for your service to your nation, nonetheless.

I want to thank all of our speakers this morning. A note for the Committee -- Dr. Platts-Mills I believe is leaving during the lunch hour. We do have a few minutes before the scheduled break and I just want to ask if there are any last alibis or questions for really any of our three speakers this morning before we break for lunch and a really hardline, defined time for the public comment period.

DR. GILL: Since Dr. Platts-Mills won't be here this afternoon, and we were also excited by your talk and I've been thinking ever since. I'm wondering as we think about biomarkers and the struggle of trying to balance -- at least in my mind as I hear what has just been presented -- if we put safety at the top and we're talking about a really high-risk population that we may be asking how can we test a question that may take 9 to 14 years to answer -- do you develop asthma -- and you give potentially dangerous

therapy that we can't always detect a response to because they're too young, it really becomes a struggle in my mind to put that together with what you so nicely presented, Dr. Platts-Mills. Maybe we should be talking about identifying high-risk infants and saying get a dog or bring some dog feces in and roll around in it. It's to kind of put that together.

Thinking about biomarkers or identifying populations, I wonder about other things that we haven't talked about, things in the airway. We talked about IgE, specific IgE, different allergens, exposure to those in different populations, how the mites seem to rule or overpower the cat, et cetera.

Overlaying on all of that, what about markers that might be in the airway? Maybe you as an expert could guide us. IgE in an airway, other things we should be looking at, or response to the nice question about cord blood IgE, as we try to overlay these things together and make rational recommendations. What are your thoughts?

DR. PLATTS-MILLS: Just starting with the cord blood IgE, obviously there was a lot of enthusiasm for cord blood IgE, but it's very important to remember that 99.98 percent of the IgE that goes across the placenta is destroyed because it's not protected by fc gamma rn in the

placenta. The transfer across the placenta of IgG is dependent on protecting the IgF with fc gamma rn. So the IgE in the cord blood is very unlikely.

In one of the studies we did with Diane Gold, the cord blood IgE correlated rather with the maternal IgE. And we know that the baby can produce IgE. There are plenty of infections of a fetus that will produce IgE, so it can happen, but I don't think that's a reliable measurement.

The issue of what you can tell in the lung, this is what we dealt with in the original pool study. At the age of 5, we were very disappointed with the results. We were supposed to be studying viruses and it was too early to study viruses; the PCR wasn't available, the cultures didn't work. But at age 10, suddenly the whole story was much clearer. That's a real challenge. The question is could you have told from IgE measurements.

Well, the IgE measurements have gone quite dramatically more sensitive; that is, we can measure .1 of IgE. So, could you do it with component assays? When you try and measure IgE in secretions you've got awful problems guaranteeing that you have collected correctly. We have measured IgE in secretions on the Costa Rica cohort, and you can measure IgE but it actually correlates again with

serum. It's not that that means it's produced in the serum; it's just that if you have significant IgE production going on in the nose, then you'll find it in the serum, and the serum is easier to measure.

I don't know where -- IgG4 is a dramatic marker of eosinophilic esophagitis. I think there's a possibility that one could actually have a G4 marker for eosinophilic esophagitis for bost 4, bost 5 and bost 8 but not bost 6. So there are real issues where you could do it.

Someone raised the issue of for eosinophilic esophagitis in young children where they don't have symptoms, and to me that's an absolute no-no. How do you define an allergic disease when we know that in the population there are lots of people who make IgE antibody but don't develop the disease? Ultimately, you can study sensitization just on the basis of IgE antibody or skin tests but you can't find a disease without symptoms. The young children with EOE are really difficult. Very few of them have a symptom that you can actually ascribe to the esophagus.

The lungs -- you can't wash out the lungs. You can't get sputum from the lungs. It's an illusion. Many people think that asthmatics cough up sputum but actually it's a small minority of asthmatics who cough up sputum and

that’s an important marker in adults. It’s not going to help you in a young cohort at all.

I’m sorry to be unhelpful. I think that because of the quality of IgE measurements and the sensitivity of IgE measurements and the ability to look -- let’s just make this clear. I talked about bost 4, bost 4 and bost 6. Well, you can’t do that with skin tests; it has got to be done with serum assays. So the fact that peanut sensitization to rh 8 -- that is, the B1 analog -- does not associate with anaphylactic reactions to peanut at all -- that can only be told on serum samples, and it’s interesting and useful in studying the cohort.

I’m afraid at the moment IgE assays have got to rule. T cell studies -- Who has ever kept a T cell study going for 10 years in a lab that you can really say that the assay is after 10 years, and you’re going to freeze samples for five years? No.

Interestingly, in the LEAP study, a Dr. Santos did a beautiful paper about basophile histamine release as a marker of whether they were going to get anaphylaxis. There was a beautiful footnote to the paper which said these assays were only done when Dr. Santos was in the lab. And you thought, wow. I think basophile histamine release with CD 63 is really a possibility but it clearly isn’t

ready for prime time yet.

What other marker do you want?

DR. GILL: Something from the upper airway, from the nose? No. Something easy to get.

DR. PLATTS-MILLS: You used the term allergic rhinoconjunctivitis. Of course, conjunctivitis is a very important symptom of seasonal hay fever, and 90 percent of the children diagnosed with rhinitis do not have seasonal conjunctivitis; they have just rhinitis. Very vague, indeed.

I think the study that John Kelso mentioned earlier from Dr. Aziz Shake in England, that's a general practice survey, and one of his studies shows quite clearly that there is no association between a diagnosis of rhinitis in general practice and the development of asthma. That's because the diagnosis of rhinitis has nothing to do with allergy. They don't do allergy skin tests, and the symptoms are not clearly related to a seasonable exposure or an accidental exposure. And dust mite, in my experience, does not cause conjunctivitis in houses. The cat occasionally but rare. Cockroach, I think not rhinitis.

The cockroach, in our experience, is not associated with rhinitis in the asthmatics, and it was

originally very difficult to persuade the asthmatics that they were really allergic to cockroach, as it is difficult to persuade people about dust mites. Who believes in dust mites? I think it's heresy to suggest that there's an animal with legs that is too small to see. Galen would not have approved.

That's Galen who published in 400. And in 1400, if you denied what Galen said you could be burned for heresy. That was 1,000 years later.

DR. DYKEWICZ: FeNO has been mentioned as a possible marker of interest. FeNO does associate with for eosinophilic airway inflammation. Apparently, there is some evidence that it may be associated also with for eosinophilic esophagitis, loosely.

I also think in considering FeNO, though, we have to step back for a minute and look at the heterogeneity of asthma. In broad stroke terms, Dr. Platts-Mills and others have already mentioned that if you look at younger children you're looking at generally non-allergic asthma; whereas, when you go to somewhat older age groups, maybe the 5-plus range, you start getting into allergic asthma.

But, based on at least adult studies, the Severe Asthma Research Program, there can be a great degree of heterogeneity of inflammation of the airway. You can have

cases where there might be allergic asthma without a whole lot of for eosinophilic inflammation. You certainly can have for eosinophilic inflammation without IgE.

So I think we have to be mindful as we're looking forward at an intervention that's directed more specifically at IgE, that we consider that FeNO is actually measuring something sort of connected but not always connected. I think it is a marker of interest, but I don't think it's going to be a totally sufficient surrogate marker for assessment about asthma -- not just the presence of asthma but asthma inflammation.

DR. PLATTS-MILLS: Yes, the Severe Asthma Research Program raises actually a very different issue; that is, that it's a tertiary care clinic in a country where six million people are taking corticosteroids with LABA. Therefore, we always refer to it as a LABA combination failure; that is, the patients we now see in the adult clinic have already been treated with high-dose inhaled steroids and long-acting beta-2 agonists, which excludes all the ordinary inhalant allergy patients, so it's a very odd group and it's dominated by vocal cord dysfunction, AERD and fungal infection of the lungs.

I think if you're in a population where there is a lot of treatment, you change your observations

dramatically. I think it was one of the things that made the Costa Rica study so beautiful, that there really isn't much inhaled steroid being used in the community.

DR. DYKEWICZ: I certainly agree with your comments but I think, conceptually, the importance here from SARP that can be extrapolated is the concern that there is heterogeneity of disease, heterogeneity of inflammation, and there would be heterogeneity of connection, if you will, between IgE and eosinophils.

DR. WEBER: I thought I would take a moment and point out that we have kind of gone astray over the years as far as what our definition of atopy is. Atopy was first defined as that constellation of generally hereditary diseases such as asthma, allergic rhinitis and atopic eczema. It didn't say anything about IgE. Now, of course, this was before the days of 1967 when IgE was actually characterized.

But we now, with time, equate atopy with IgE positivity. That is not the case. For example, even with eosinophilia, years ago there was a paper out of England -- I think it was Goff -- that pointed out that eosinophilia in asthmatics was higher in those who had negative skin tests as opposed to those who had allergic asthma. I have just seen a deep intake of air from Dr. Platts-Mills, so he

may have a comment to make also.

DR. PLUNKETT: You have often talked about the Thanksgiving effect. The subject goes away to college, had a cat in the house, comes back and all of a sudden has problems with the cat but did not have problems with the cat before he left for those couple of months away from the home.

Do I understand you to say that that kind of a tolerance -- I guess more of a desensitization -- is due to IgG4?

DR. PLATTS-MILLS: The Thanksgiving effect is a student who has been living in a house with a cat or a dog, usually a cat, and goes to college for three months. This is a very American phenomenon. In Europe, it's unusual that people go away from their own home town and most of it is at home, so you don't see it in Sweden at all.

But the Bostonian children who go away and come back, and the allergists used to keep their clinics open on the day after Thanksgiving because so many children were having problems. Some children find they go back to a house that they could tolerate perfectly well before.

The important question about it is were they skin-test positive before they went, and we don't know that. That is, are they skin-test positive, already making

IgE antibody, or did they have IgE antibody before they went away and they have simply become more allergic? What we know happens when being not in a house with a cat is that the IgG antibody levels fall much faster than IgE antibody levels, so the ratio changes.

But I believe it's more likely that there are T cell changes going on, so they react. Some of them become tolerant again quite fast, within about a week. It's a beautiful phenomenon, but without knowing whether they were skin-test positive beforehand it's very difficult to look at the science.

We estimate that you need to study 200 kids, really have skin-testing samples before they go to college. My wife was doing admissions at University of Virginia and they had the question, do you have a cat at home, so it was a criterion for admission to University.

(Laughter)

DR. KELSO: Just to echo or amplify Dick's point about our definition of atopy, which of course is important if we're defining a population that we're going to study and have some intervention with. The imperfect association between the definition of atopy, which means you have one of the four genetically atopic diseases -- asthma, hay fever, eczema, food allergy -- versus the definition of

atopy that said you made IgE antibody to something. There clearly is an imperfect overlap between those two definitions and it becomes important when we're deciding who we're studying and intervening with, particularly since the intervention that we're anticipating has to do with the introduction of allergen into patients.

So we need to clarify what population, or what sort of atopy we are talking about.

DR. PLATTS-MILLS: It was Coker who gave the original description of atopy, and in 1915 or just before that he was the first editor of the Journal of Immunology and he remained editor for quite a long time. There were wonderful allergy papers in the Journal of Immunology before it lost its real sense. Remember, the PK test had not been defined when he described atopy, so it wasn't clear what super-sensitivity was at all.

The only other thing I need to correct is that IgE was described in Denver at CARI in 1966, not 1967.

DR. WEBER: And I certainly should have known that.

(Laughter)

DR. NELSON: We have come to the end of our morning session. I want to thank all of our speakers, Dr. Platts-Mills, Dr. Hise, Dr. Chang and Dr. Slater for

kicking us off with the FDA perspective. We will break for lunch. A public comment period or open public hearing will occur right at 1:00 p.m. Stay tuned. I think it will be a great afternoon.

We stand in recess.

(Luncheon recess.)

A F T E R N O O N S E S S I O N

Agenda Item: Open Public Hearing

DR. NELSON: This afternoon's agenda. We're scheduled for an open public hearing. I have an introductory statement that's a mandatory read.

It goes as follows: both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from

speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances, and for many topics, there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair and thank you for your cooperation.

So again, this is a little atypical in that we don't have our product before us for consideration, but I think the statement of your financial affiliation is still very appropriate in advance of your comments, so we'd very much appreciate that.

I believe we have a series of seven speakers that are due to come, and they've been assigned a number and our AV crew is going to help us out by bringing our first speaker. They will come to the microphone behind the red tape there, where we ask you to announce your name, your affiliation, and proceed with your statement. The first speaker, please.

Kimberly Hunter Turner

MS. TURNER: Hi. Good afternoon. Thank you for allowing me this opportunity to speak today. My name is Kimberly Hunter Turner and I'm director of government affairs for Allergy and Asthma Network.

The network is a leading patient education advocacy organization dedicated to ending needless death and suffering due to asthma, allergies, and related conditions through research, education, advocacy, and research. We currently reach over two million people each quarter through our programs and resources. I am honored to represent the patient's voice here today, especially because I have an 11-year-old daughter with life-threatening food allergies.

The numbers are astounding. Greater than 50 million Americans live with allergies. More than 20 million Americans have been diagnosed with life-threatening allergies and are at risk for anaphylaxis. Approximately 15 million Americans live with food allergies and the prevalence continues to rise for reasons unknown. In fact, estimates are at least two children in every elementary school classroom now is diagnosed with a food allergy. The economic burden of these conditions is mind-blowing and estimated to be greater than twenty million dollars

annually.

Finally, and perhaps more saddening, is the fact that one in two people die every day here in the United States due to life-threatening allergies. While we have made great strides over the past decade in recognizing these conditions, unfortunately we still have no cure, nor do we fully understand why the prevalence of disease is growing at such an alarming rate. Currently, children like my own are limited to avoidance of a potentially dangerous allergen and must always live on life guard and on guard with their epinephrine autoinjector close at hand. In fact, studies have clearly demonstrated even the most diligent of patients and families experience one to two accidental exposures each year.

The truth is an unmet need exists in this space for innovative treatments. Our community needs answers to the countless unsolved mysteries surrounding life-threatening allergies. Questions like: Why is there such a dramatic increase of prevalence of life-threatening allergies? Are there innovative tools or methods to better diagnose and assess true risk? What innovative treatments can be developed, approved, and brought to market to reduce the risk of reaction? What preventative measures work most effectively to reduce the risk of accidental exposure, and

how frequently are patients truly at risk for anaphylaxis? Is there an adequate supply of community-based allergy specialists who are willing and able to conduct oral food challenges -- the current gold standard for food allergic patients?

In closing, we at the Allergy and Asthma Network commend the community for shedding light on these important issues. Furthermore, we ask FDA and other federal agencies to allocate the necessary resources to address these unanswered questions. No mother, father, or child should live in fear of food. Our network hopes and prays that there will come a day when we were able to say there was once this thing called life-threatening allergies.

Thank you.

DR. NELSON: Thank you so much for your comments today and your advocacy. We'll proceed to our next speaker.

Cary Sennett, M.D., Ph.D.

DR. SENNETT: Good afternoon. My name is Cary Sennett and I am president and CEO of the Asthma and Allergy Foundation of America –- AFFA. I thank you for the opportunity to bring AFFA's perspective and the perspective of the more than 60 million Americans with asthma and allergic disease to the committee's deliberations.

I would like to briefly introduce AFFA and the patient's perspective on allergic disease for the committee. I will then focus my remarks on what we believe are the issues that the committee must consider. Finally, I will close with what I hope is a clear offer to provide help to the committee as its work moves forward.

AFFA is a not-for-profit organization working to improve the lives of people with asthma and allergic disease. We believe that the patient's voice is a critical input as we strive to create a health care system that is centered on the needs and values of patients and hope to bring the patient's voice to conversations like the one we are having today.

What is it like to have food allergy or allergic rhinitis or asthma? Food allergy means a life of constant, unremitting vigilance, living with the reality that your next meal or your child's next meal could be her last, living with the reality that a bully at school or even a friend at a birthday party could threaten your child with something as simple as a peanut butter and jelly sandwich.

The symptoms of allergic rhinitis and asthma limit life profoundly. Remember the misery of the worst cold you've ever had? What if it lasted for three months? What if it happened twice a year? This is the reality for

millions of allergy sufferers who may be, as the committee clearly appreciates, at risk to march on to develop asthma, which not only limits the quality of life, the CDC estimates that asthma kills nearly ten Americans every day.

So what do patients want? They want treatments that are safe and effective, although I should point out that a study that we did with collaborators at the University of Pittsburgh and Michigan published in the Analysts of Allergy and Immunology in 2012 suggest that families participating in food allergy or oral immunotherapy were surprisingly willing to begin that therapy without evidence that OIT was safe and effective. I think this speaks to the sense of desperation that is prevalent in the food allergy community and the importance of the work that the committee is considering.

We believe that the risk of life-threatening anaphylaxis related to food allergy requires the safety of food allergy immunotherapy products be assessed in a double blinded and highly controlled environment. We believe that the evaluation of effectiveness should include metrics that reflect the issues that are important to patients -- symptom control, quality of life, and functional status, and that endpoints need to be meaningful not only to statisticians, but to patients.

Finally, we believe that effectiveness has to mean it works in the real world. This is especially true for therapies directed toward aeroallergens or patients with allergic rhinitis. From a patient's perspective, the important questions are: Is this therapy better than what I have now? And will this therapy will make me feel better in the environment in which I live, work, and play?

I want to take just a moment to make sure that I remind the committee and the FDA that important as your work and new therapies are, there remain significant opportunities to improve the lives of people with asthma and allergic disease, by finding ways to make the therapies that we have more available and more effective for those who will benefit from them. This may be a topic for another day and another meeting, but it is so important I wanted to call it out in my brief remarks this afternoon.

Finally, we appreciate the opportunity to share our thoughts today, but I want to close by making it clear that AFFA is willing and maybe able to assist the committee and the FDA to move the work of evaluating allergenic products forward. In particular, AFFA has the ability to bring the voices of families with food allergy and increasingly individuals with other allergic diseases to evaluation work through the online communities that we

support, and we have the opportunity to assist the committee and the FDA to build expertise in the patient community through work that the Patient Centered Outcomes Research Institute, PCORI, is supporting.

Finally, we are ready to partner with the committee, the FDA, and any number of others who recognize as we do the opportunity not only to advance the basic and clinical science related to immunotherapy, but to advance our collective efforts to implement the science that we have more consistently and more effectively.

Thank you.

DR. NELSON: Thank you, Mr. Sennett. Again, thank you for your advocacy and very enlightening comments.

Speaker number 3.

Margaret Brannigan, M.D.

DR. BRANNIGAN: Hi, my name is Dr. Margaret Dayhoff-Brannigan, and I am the patient advocacy project manager at the National Center for Health Research. Our research center scrutinizes scientific and medical data and provides objective health information to patients, providers, and policymakers. We do not accept funding from pharmaceutical companies, and I therefore have no conflicts of interest.

Thank you for the opportunity to speak here

today.

I completed my PhD in biochemistry and molecular biology at the Johns Hopkins School of Public Health. In addition, my three-year-old has life-threatening food allergies and was recently started on inhaled steroids to treat asthma-like symptoms.

My husband and I do not have food allergies. So we were shocked when blood tests for our then one-year-old came back with an extremely high level peanut allergy. The pediatrician called us personally with the results and to tell us to go to an allergist immediately for an EpiPen. After making an appointment, I proceeded to scour the internet for available research on food allergies. Unfortunately, I met the same frustrations that many in the food allergy community find. There were no good answers.

Many small trials are being conducted to treat peanut allergies, and they have very promising results, but they do not have long-term results. Peanut allergies tend to be lifelong. So it is important to know if the treatment works for more than just a few months. It's also critical to know if patients develop allergies to other foods they are not being treated for.

None of these trials discuss what happens to the children that fail to develop tolerance to peanuts after

treatment. These children need to be followed to see if their sensitivity to peanuts is now more severe or if they have other immune problems.

Due to the nature of these treatments, parents may be tempted to try these remedies at home. Many people who saw these cures in reports on the news asked me if I had tried feeding my small child amounts of peanuts to cure his allergy. It must be clear to everyone, not only allergy sufferers, that these treatments are only to be tried with careful medical supervision. It's critical that the appropriate studies be performed to get better understanding of these treatments.

Ideally, clinical trials would include the following: large sample sizes that are representative of the ethnic makeup of allergy sufferers and be double-blind placebo controlled. Subgroup analysis should be conducted to make sure the treatments are safe and effective for each group.

They need to be conducted on children representing a range of ages. Metabolism rates vary significantly in children depending on age. So doses for two-year-olds would be very different from those of ten-year-olds. Subgroup analysis are again needed, this time for different age groups.

A long period of follow-up evaluations, including data for the allergen being tested, as well as development of other potentially relevant immune responses, such as other food allergies, seasonal allergies, or asthma. There should also be follow-up studies on patients that fail treatment to determine if the allergic condition worsened as a result of the sensitizing event from the treatment.

Follow-up should include patients who withdraw from the trial voluntarily due to their inability to tolerate the treatment. It's important that these treatment options be tested under careful supervision of trained medical professionals due to the risk of adverse events. All of these treatments carry significant risks which need to be better understood.

There have also been promising new studies on the prevention of allergy, especially the LEAP study. The study shows that early peanut exposure in children at risk may prevent allergy. Unfortunately, these trials only look at children up to 5 years of age. So it is still unknown if these children will go on to develop allergies later in life or if they will develop serious allergies to other foods such as shellfish or tree nuts.

Unfortunately, updating the standards to encourage parents to feed at risk children peanut products

early in life presents a certain amount of risk. There is already reports of children having severe reactions, despite negative skin prick tests. We must be cautious about the application of these new standards and we must continue to study the long-term ability to prevent allergy and other allergic disease.

In addition, these promising studies need to be supplemented with treatment options for children and adults who are already allergic and for children for whom prevention does not work. Allergies can be a life and death situation. Approximately 100 people die each year from anaphylaxis due to food allergies.

Treatment options for food allergies could save lives, significantly improve quality of life for many families, and reduce the number of severe reactions from occurring. The increase in food allergy prevalence is an important public health problem. We must require that clinical trials study all of the necessary variables to help family make informed treatment choices. I really hope that the treatment options continue to look promising. Better clinical trial data will help families make important decisions about the risks and benefits of treatment.

As a researcher, public advocate, and a mother, I

thank you for your consideration of these important research design issues. Thank you.

DR. NELSON: Thank you so much for those practical recommendations, and thoughtful ones.

Our next speaker?

Scott Richio

MR. RICHIO: I am Scott Richio. This is my daughter, Maya. By way of disclosure, I am the senior vice president for education and advocacy at the Food Allergy Research and Education Organization, but I am not here today in an official capacity. Our CEO, Dr. James Baker, will be providing organizational perspective. I am here today as a father to share the parent's perspective and most importantly to support my daughter in sharing her perspective.

So if she leaves me a minute or so at the end of this, I have some closing thoughts. Maya?

MS. RICHIO: Hello, my name is Maya Richio. I'm 11 years old, and I have a life-threatening allergy to peanuts. I had my first reaction and trip to the emergency room before I was 2 years old. I had my first serious reaction from both eating something my parents and I did not know at the time had peanuts in it or from touching something that had been played with by kids who had eaten

peanut butter or something of the sort. Wherever I go, I have to take my EpiPens or Auvi-Qs with me. I have a set at school. My mother carries a pair with her, and I have mine wherever I go. I have mine today with me.

I like to fly and go places, but there's only a couple of airlines that allow me. Lots of them still serve peanuts or snacks with nuts in them to cause a reaction for me, or they won't let us board early to wipe down our seats and trays to make sure that there is no peanut crumbs from the last person who sat there. So we drive more than we fly. That means we still have to check at restaurants that we can eat at.

More than 5 years ago, I was accepted into a clinical trial to help me hopefully not react to small amounts of peanuts. To start out the trial, I had to go to a hospital in North Carolina and had to have a food challenge so they could see if I was fully allergic to peanuts and how much peanut I could take before reacting. They mixed small amounts of peanut into pudding to see how much I could take.

I started to react after the very first batch, the smallest dose. I still can't eat pudding to this day.

I know I will have another food challenge, hopefully in the near future, and to see if the drops I

have been taking every day under my tongue have been helping me not react to peanut. I will still forever need to carry my EpiPen or Auvi-Q with me to be safe. It would be extraordinary if I would not have to worry about wiping down my seats, going on field trips at school, and eating at the same table with people who have eaten peanuts or nuts or anything like that.

Please help me and people with food allergies just like me. Food allergies have changed my life, my family's life, and everyone's around me. We need more treatments to help us be safe, to get those treatments approved, and to know we will be safer. We need food challenges to be a part of these trials and to know that we will no longer have to live in fear.

Thank you.

MR. RICHIO: And she left me two full wonderful minutes. So thank you.

So as a parent, my wife and I have to balance the sometimes overwhelming urgency to minimize the risk of Maya having an accidental exposure to peanuts with the heartbreaking emotions when she isn't able to do something or go somewhere that the other kids can. We want Maya to be able to do more than just survive. We want her to live and to be able to thrive.

In order to give Maya the best chance of being safer as soon as possible, five years ago we enrolled her in that clinical trial at Duke University. We knew the trial would start and end with a food challenge, and though we knew there was risk in the food challenge, as a family we judged that the potential benefit Maya could receive from being desensitized to peanut would far outweigh the risk from the challenge. We also judged that the real-world information we would receive from that challenge telling us exactly how Maya would respond to ingesting varying amounts of peanut would be critical for helping us better understand whether the trial therapy had resulted in helping Maya truly be safer.

If Maya achieves desensitization to even a very small amount of peanut, enough so that she would be safe if she ate something that happened to have trace amounts of peanut due to cross contact or manufacturing on shared equipment, this in itself would be a life changer for all of us. While a larger absolute amount would be delightful, it's important that the agency recognizes how significant achieving just that lower level threshold of desensitization that would significantly increase Maya's safety on a daily basis, an oral food challenge that can tell us exactly what amount of peanut it will take for Maya

to react truly is the gold standard for us and protection against even a small absolute amount of peanut is a tremendously and clinically significant measure of effectiveness for us and should be the endpoint upon which these treatments can be approved.

Is it scary to watch your child undergo an oral challenge? Yes. Is there risk in an oral food challenge? Yes. But let me assure the agency and the members of this panel, the alternative, which is not being sure if your child will have a reaction, not knowing if your child is at risk from the smallest amount of that peanut, that is far, far more scary and a far bigger risk. I ask you all to help us be sure. Help us get the information we need. Help us be safer.

Thank you for your consideration and your efforts.

DR. NELSON: Dad, thank you for your comments, and I think it's appropriate that we all give Maya a round of applause for her contributions today.

(Applause.)

Thank you both for putting things in perspective. Sometimes it's easy to get lost in endpoints, study design, but your true on the ground story of what it's like to live with food allergy is very important for us as we enter into

these discussions. Thank you again.

Our next speaker, please.

James Baker, M.D.

DR. BAKER: My name is James Baker. I have been an allergist for 35 years. I was on the board of allergy. I was head of allergy at University of Michigan for 20 years. In addition, I have also had a background in pharmaceutical development. I started three biotech companies, and I served as the global head of vaccines at Merck, and for disclosure's sake, I still have stock with Merck.

However, I am here today as the chief executive officer of Food Allergy Research and Education, FARE. FARE is the largest national organization solely dedicated to supporting the life, health, and hopes of the 15 million Americans and 6 million children who have food allergies. As measures of its extensive influence, FARE's website had 3 million unique contacts last year and provided information and documents to 35,000 individuals with new onset food allergy.

We provide extensive advocacy work supporting the ability of people with food allergies to go to work, go to school, and fly safely. In addition, we funded $80 million in research, $7 million in just the past year, and we were

the organization that funded along with NIAID the LEAP study, which has a lot of talk today.

Importantly, we have now put together a network of 24 sites across the country that we vetted that have both the clinical capability and the research capability to do registration trials so that we will have a network that's large enough to actually do largescale phase 3 trials to approve therapeutics.

I would like to make three important points surrounding the development and regulatory process for new therapeutics to treat food allergies. First, food allergies are an incredible important and underserved problem. Despite the rapid increase of these in the past 20 years, there is no specific therapy whatsoever for individuals with food allergy, and these people are left to try to treat themselves with epinephrine to save themselves from reactions.

As a resident physician 40 years ago, I was first exposed to another epidemic, HIV, and if you had told me then that HIV would be a totally treatable disease and food allergy would not, I would have been shocked. But that's the situation we are currently in.

In part, this is a reflection of the lack of investment in food allergy research and therapeutics, and

despite the fact that every 3 minutes a food allergic reaction sends someone to the emergency room and the estimated cost of dealing with this problem is now $25 billion with a B, we have yet to see the industry commit. So we at FARE are strenuously working to encourage the development of therapeutics.

Secondly, there's a unanimous feeling of people with food allergy. Their initial desire for therapy is to be safe from life-threatening reactions. They know that food allergy is a complex problem and the type of cure that induces tolerance will be hard to come by, but initially we would like to focus on the ability of people not to have a life-threatening reaction if they are accidentally exposed to food.

Finally, we understand that the development of food allergy therapeutics is not simple. Food reactions tend to be variable depending on the type and the amount of food ingested; as well, it's a situation of the individuals such as exercise or other concomitant drugs. It is also difficult to diagnose allergic food reactions, because these markers of anaphylaxis that are seen with other triggers such as bee stings, are not consistently present in food allergy.

In addition, there are currently no surrogate

diagnostic tests that have the predictive value to allow use in therapeutic development. Therefore, we strongly support the use of double blinded placebo controlled oral food challenges as a measure of outcome for the initial therapeutics to treat food allergy.

We believe that trials that look at real world circumstances will be very difficult to do since those reactions will not be observed and given the variability in food allergic reactions themselves. We encourage the FDA to work with companies who are developing therapeutics to better define the outcomes from these challenges as relates to potentially approvable therapeutics.

In conclusion, FARE is willing and happy to support their extensive knowledge and expertise to help define consistent and well-documented regulatory practices for the approval of new therapeutics for food allergy. We encourage the FDA to work hard on this. It is a matter of great concern and life-threatening issue for the 15 million Americans with food allergy.

Thank you very much.

DR. NELSON: Thank you, Dr. Baker. Appreciate your advocacy and great comments.

Our next speaker, please.

Hendrik Nolte, M.D.

DR. NOLTE: Good afternoon. I am Hendrik Nolte, section head of respiratory at Merck Research Laboratories in New Jersey, and we develop immunotherapy sublingual products for treatment of allergic rhinitis. On behalf of Merck, I thank the FDA and the committee to be allowed to speak during the public hearing here.

I will be brief, and I will speak to a few important points for consideration by the committee with respect to the target population and the indication for allergy immunotherapy in early childhood. Allergy immunotherapy may be effective for the prevention of asthma in children whom have evidence of an Ig-sensitization to specific allergens and are at risk of developing asthma such as a family history of atopic disease.

There are now studies which indicate that early oral exposure to high allergen loads may induce tolerance development, and it appears increasingly likely that very early treatment, as early as six months of age for several years, may be beneficial. Because the diagnosis of asthma can be difficult in young children, Merck believes it's important for the committee to clarify whether the goal of intervention is limited to the prevention of asthma defined by lung function impairment or alternatively with a goal such as prevention of asthma-related symptoms and

healthcare utilizations such as medication use in children could be supported.

We believe it is important that regardless of the definition that cases should be adjudicated by experts against agreed upon criteria. Our current experience which spans the research and clinical development of asthma medications over many years is that objective lung function changes in young asthmatics is a poorly sensitive measure of asthma and may be variable over a longer period of time. This was confirmed in the just completed Grazax asthma prevention trial including children between 5 and 12 years of age.

In contrast, asthma-related symptoms and medication use may be reliably measured in young children by caregivers. Although we acknowledge that asthma-related symptoms and medication use may suffer from some lack of specificity, in our experience the sensitivity and the specificity of the asthma diagnosis and response to interventions can be improved through the use of validated instruments and adjudication by blinded clinical experts.

We don't recommend including challenge procedures or FeNO, because it will be difficult to incorporate into large trials where standardization of methodology is maybe critical.

With respect to the duration of study and time of analysis, especially in very young children, asthma is typically characterized by intermittent and progressive signs and symptoms. Accordingly, the primary endpoint of an asthma prevention study should be assessed over an extended period of time, such as the last one or two years of the clinical trial, to allow as many subjects as possible to reach a stable disease pattern to confirm the diagnosis.

Importantly, the current experience indicate that most subjects would not meet the case definition until adjudicated at age 5 to 7 years, and many asthma subjects may not show impaired lung function reversibility at this age group.

With respect to sample size and clinical relevant effect, we believe it's important to acknowledge that in contrast to regular vaccine trials conducted in otherwise healthy individuals, allergy immunotherapy asthma prevention trials will by design select a high risk population. As a result, the benefit risk evaluation of an asthma prevention trial will not be the same as a vaccine study. In previous studies of immunotherapy for the treatment of allergic rhinitis, FDA has typically applied criteria for success based on vaccine studies such as an

upper bound of the 95 percent confidence interval of the treatment difference relative to placebo being at least 10 percent.

If applied to an immunotherapy prevention study and assuming an adjudicated asthma diagnosis rate of 45 and 30 percent for placebo and active respectively and a dropout rate around 20 percent, it would require a trial size of 1,000 subjects. In our experience, such a large study with such an extended follow-up period will be quite challenging to recruit, and we would encourage the committee to consider whether application of success criteria from vaccine studies such as the 10 percent confidence boundary is appropriate in the context of asthma prevention studies.

Finally, with respect to the safety database, we recommend the committee discuss what the expected size of the safety database for an indication for prevention of asthma for use in children should be. Merck proposes that 500 subjects exposed to active drug are sufficient, and this is based on three years of exposure and the expectation that no surprising or unanticipated adverse events will be considered. We believe this is a reasonable assumption based on the prior experience we have.

We thank the FDA and the advisory committee for

the opportunity to provide these comments and look forward to identifying an appropriate path forward for immunotherapy based asthma prevention studies. Thank you.

DR. NELSON: Thank you, Dr. Nolte, and especially for providing the insight from the perspective of industry and the challenges in conducting studies and bringing products forward for consideration.

Our next speaker, please.

SPEAKER: I think the next speaker was a mistake. So there is no speaker number 7.

MR. NELSON: Very good. Any last alibis? At this time, the open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as long as the public comments. So again, thank you to all the speakers. I thought your insight is tremendously helpful as we enter into these discussions and by chance, the perspective that you all brought to the table does indeed cover everything we need to look for.

Agenda Item: Committee Discussion

DR. NELSON: Dr. Slater, do you want to reintroduce the questions to our committee? Is that a fair

way to start this?

DR. SLATER: Yes, thank you very much. So as I said, we are going to take the questions one at a time, although in your slide sets you have all the questions in front of you. We will talk about the treatment of food allergy first, and question one is as follows.

Regarding food challenge studies to assess effectiveness of immunotherapy in allergic individuals, please discuss objective criteria for determining the eliciting dose, particularly in children less than 5 years of age, clinically meaningful parameters, including amplitude of response and duration of time off therapy, that could be used to demonstrate the effectiveness of immunotherapy for desensitization and sustained unresponsiveness. That is, the maintenance of desensitization of therapy, as well as safety considerations for the food challenge.

DR. NELSON: Thanks so much. Not an easy one, and I see a lot of heads shaking around the table. These are tough tasks. I will now open it up for the panel to discuss these points, and I'm happy to guide the discussion if necessary.

Anybody with initial recommendations or comments for any aspect of this question? All right, well, let's

begin with eliciting dose, right at the very top, and particularly for children less than 5 years of age. I have to tell you from a personal perspective in preparation for this meeting, I struggled. I am a purist in the way of therapy and look for full tolerance when we introduce a medication for treatment as a clinician, and I think you heard expertly today from our audience and Maya in particular that that may be an unreachable goal for food allergy as the ultimate goal for treatment with these products. So evaluating changes in all these eliciting dose is indeed a viable way of evaluating the effectiveness of an intervention of this type.

So with that in mind, I think it's important again to readdress how we define what the eliciting dose is and in fact its stability or predictive nature for what that individual is likely to encounter and be able to tolerate in the real world.

So I'll open it up for discussion about the eliciting dose and how best that should be achieved or identified by our clinical investigators. Dr. Finegold?

DR. FINEGOLD: I was impressed by the young lady's remark that the first test dose for her challenge made her ill, and concerning safety I said, well, why not do a microarray before a challenge and find out what the in

vitro numbers are, and with experience we could determine that if you have a very high specific IgE of the right or wrong kind, that the dose would start 100 or 1,000 times lower than somebody who has either mild elevations.

DR. KELSO: I guess, just in response to that, it is my understanding that while there is an excellent correlation between the level of specific IgE antibody to a food and the likelihood of having some sort of reaction, there is exceedingly poor correlation between the level of specific antibody to a food and the severity of that reaction. So while I understand the thought that maybe you could alter your dosing based on specific IgE antibody, if I am understanding you correctly, I don't know that a child with a lower food IgE specific antibody is necessarily less likely to have a severe reaction to a challenge at any given dose.

DR. PEDEN: I would echo that, that conceptual biomarkers, whether it's basophil degranulation assays or other assays would generally tell us about allergic populations or food allergic populations versus not. Precise correlations may be difficult. So you may want to have this discussion in terms of gaps in knowledge and are there things that we could actually identify that would become metrics that could be used, and then there is the

more pragmatic, you know, so what is the safety? Part of the safety is the dose, and part of the safety is the environment in which the dose is given. So I think part of this discussion needs to be around what are the -- what should be the minimal clinical capabilities and pragmatic approaches so that you start out in the clinical trial, and if someone is unexpectedly sensitive and has full-blown anaphylaxis with an initial dose, they have the highest likelihood of being recovered. That is the person running to the challenge room perspective that you have to have.

But I agree, and I said, I alluded to I think earlier, I think an appropriate goal for this intervention, at least one indication -- you can have multiple -- but one indication is to diminish the risk of life-threatening allergy, not to eliminate it, not to allow you to eat anything you want, but to substantially as a risk reduction measure -- and so I think if we could be confident that you started out with a challenge dose, and you could increase the dose of tolerated food substantially after a given period of treatment, that would be, I think, an important public health goal to have.

DR. PETERSON: I am kind of stopped at what age do we start and, yes, the challenge dose, but the challenge dose of what? How do you know she was allergic to peanuts?

I mean, where did that start, and how could somebody know ahead of time? That's kind of -- I don't know how to say that. But how do you -- without testing them, without doing something first to infants or -- how can you figure that out? I know parents are used to giving their kids one item at a time to see how they do separately. So maybe there's something in that. But I'm kind of stuck on how to get started.

DR. KELSO: Now that I look at this I think we are trying to answer the wrong question. What we are asked, I think, we are not trying to pick what an effective or an eliciting dose would be. What we are being asked for is how would you know if a child responded to some dose of something during a challenge, because it asks for -- it says in allergic individuals.

So we are already presuming that these are children who have been determined to be food allergic by some combination of history and testing and whatnot, who are now undergoing a therapy for food allergy, and if I'm reading this correctly, what we are being asked for is when you are doing a challenge to determine whether -- what the eliciting dose is for a food. What should you be looking for that counts as a positive challenge? Is that what we are --

DR. NELSON: That is a fair statement of the question, and as we entertain the next couple of speakers, something perhaps that the two of you could address is what is the particular type of study that should be undertaken? I think we have all assumed based on the presentations today that a randomized double blind placebo controlled trial is the approach for administration and identifying the eliciting dose. That's not a slam-dunk. I think that is open.

I think clinically we all know that most don't perform double blind placebo controlled challenges. They in fact do an open challenge with incremental dosing. So it is a valid question to open up to the committee. Is that sufficient, given that we have already identified that the enrollees in these trials already have established food allergy and we are trying to achieve -- so again, let's step back and look from a 10,000-foot view about the clinical trial design, and then we will get into some of the details about what is the specific criteria that defines -- i.e., what is an eliciting dose? What reaction is the minimum definition that would satisfy a definition for eliciting dose?

DR. PETERSON: Could I just ask what age would that child be that's already identified as having food

allergies?

DR. NELSON: That's one of the things that we are -- I think it's all comers. They would like us to focus on those less than 5 years of age, and we do certainly have a large cohort in that arena.

Dr. Plunkett?

DR. PLUNKETT: I just wanted to, just to make as a consideration, when we are talking about what the dose is, we have to think about what are we actually measuring? What is the potency or whatever? So by just saying peanut, that is kind of a general statement that can cover all kinds of things, peanut contains many different kinds of oils; you can make powders. You can have peanut that might not be so potent. So should we be considering the dose of a particular protein for instance that is eliciting the response? So when we are discussing what that dose is, I think we should think about that.

DR. PEDEN: Part of John's answer was what I was going to say, which is that these are people -- this is not a prevention study, per se. These are people who are already identified.

So part of this is deciding what is the clinical syndrome. So anaphylactic food allergy risk or allergic emergencies, airway, respiratory tract, maybe vomiting with

a food, you know, we could get into a gray area if we start talking about eczema and whether or not the relationship between food, atopic -- let me rephrase. IgE desensitization impact on eczema, and I am not sure I would necessarily lump that into the anaphylactic emergencies that I think are most concerning to people.

The problem you get into is it's not just people less than 5. A 2-year-old is going to articulate early symptoms like by screaming or passing out versus a 4-year-old who may actually be able to say something is wrong. So some of this is we are not going to absolutely define in this roundtable. I think we should actually have developmental psychologists or people who actually understand what kids can say and actually thoughtfully look at the literature for what can you expect out of a 2-year-old. Many of us do pediatric allergies. So we perceive that we know that. I think when I talk with people who are psychologists, what I perceive and what they perceive to be my truth is not the same.

So I think we actually need to have objective metrics as to, one, what can you glean from a 2-year-old? Then it comes down to what are the physical exam criteria? So and actually paying attention to what's pulse, blood pressure, is there a general sense of scoring of malaise?

There will be any number of these scales that any number of investigators have come up with, but I think as a clinical trial is designed, I think the questions -- there ought to be the onus on the investigator to say how are you going to tell -- what is your criterion versus when a 2-year-old is beginning to have symptoms and then the medical, the lucky medical officer gets to review that protocol, you know, with guidance from the literature and then decide if that's an adequate response or if there are some other things to be considered.

There may be other biometrics that will evolve in terms of monitors and other things that might actually make some of this easier to do.

DR. APTER: Given the danger in doing these experiments, I think that we should start with the information we already have. So for example, we know that children present to the emergency room for presumed food allergy. We know that there are certain experiences where children have been exposed to those foods. So we need to collect that information. The responses they have had, the doses they have been given, of the particular agents so that they could use those as starting places.

DR. NELSON: I think that in thinking about what population should be studied for this, that we should

specifically not exclude children who have had truly life-threatening reactions to the food. I mean, there might be some temptation to say, well, you're going to study kids with peanut allergy, except those who almost died, but the ones who almost died are the ones who are most in need of the therapy, as we have heard from some of our patient organizations. What patients appear to be most concerned about is that their child is going to die.

So that is kind of a corollary to what we are talking about, but I don't think we should exclude patients because despite what I said about the poor relationship between IgE levels and severity, probably the best predictor of the severity of a subsequent reaction is the severity of a prior reaction. So by having children in the study who have had truly life-threatening reactions, I think that is important so that we are able to answer the effectiveness of the treatment in those children, and then just to back up perhaps one more.

This is objective criteria, and I don't know if that specifically meant objective like you saw a hive or if that's what they are really talking about, because that also raises the question of in a child who is allergic to peanut, for example, and is undergoing a challenge who is old enough to announce that they have an itchy throat but

there's nothing to see, does that mean you keep going? If you have to get some objective criteria to say that the challenge was positive, does that in fact mean that you won't accept any subjective criteria as evidence of positive challenge?

DR. PEDEN: I would submit that there are survey data and there are people who are experts in surveys that can take data points that seem subjective, but you can score them, and that's still much more objective than the general sense that someone said they are itchy. So you can grade it out with either a line art or some other scale. I mean, I think there are ways that you could do that, but I also think it, as I've said before, needs to be age appropriate. There are going to be some -- and maybe even beginning with an assessment of what an individual -- some 4-year-olds are very articulate. Some 57-year-olds are not.

So I think that part of that has to be the clinical trialist's judgment guided by starting, you know, by entrance and stopping rules as to what you are going to -- you know, are you comfortable that this person can adequately report things, and I think that's -- and there's a whole survey science behind that that I'm not expert in.

DR. APTER: I just want to add to that that we

have the electronic health record now, so we have a source of these events that catch a broad population and can go to a broad population of patients which is also important to study.

DR. NELSON: So I would like to focus on just -- I was going exactly where you talked about, which is the start and stop criteria for some of these challenges. Done very differently throughout clinics in the U.S. based partly on the risk acceptance of the patient undergoing the procedure, as well as the risk tolerance of the physician performing the procedure, and I know we are not going to be able to come to a complete consensus on the exact way we need to conduct food trials going forward, but I wonder if the committee in general would take a moment and focus on the spectrum from which we need to make this determination.

It could be the first symptom or objective sign that it occurs. It could be the requirement for a systemic manifestation, something beyond what we see in the way of contact, i.e. oral symptoms. One might not that definition, but disseminated hives would be a systemic reaction. Or it could be similar to the reaction that brought the patient in for diagnosis. So there are different ways that -- or a full blown anaphylaxis with two organ systems involved.

So I wonder if the committee in general would talk about where is an average endpoint that would serve as a good defining of eliciting dose that can be cross lateral to cross different studies as we perform these with different products.

Dr. Weber, start us off.

DR. WEBER: So that was the point I was just going to bring up. What do we consider a point at which you stop the challenge or proceed, and certainly more astute observers may be able to pick up very subtle things like the beginning of flushing of the earlobes or a little more crankiness in a small child, and which usually then in retrospect, after you proceed on to another dose, you get a much more dramatic reaction and you say, oh yeah, that was suggestive.

But is that enough in a well-designed study to actually be a stop point? Would you consider a combination of a little bit of subjective and maybe very modest objective signs to be adequate for saying, okay, we have a reaction? This is it. Or for the goal of more definitive response, do you need more than that? And I just offer that as a question, because I don't know what the answer is.

DR. NELSON: Others on this point. How do we

standardize this across studies?

DR. PEDEN: I will just borrow the very, very general approach I used with airway challenge, which is analogous, not the precise. We use, we typically for our phase 1 studies that we do in otherwise healthy people after we have exposed them to a pollutant, so we have to be very careful, because we are not going to help them at all. They are helping us learn stuff, period.

It's a combination of one would have to define a suite of either clinical observations or symptoms, and that depends on the age and what they can say. You can assign a severity to each of those. You have a general score that guides you. You force yourself to score them out each time, and then there are some very objective things that you do like did someone have, you know, urticaria more than X number of lesions in a particular period of time? Did they rapidly subside, or did they persist?

And I think that's the other part is once you begin to have a symptom, you're going to need to have a time for refractoriness. If somebody's symptoms go away on their own, then maybe they can go to the next dose. If somebody percolates and they're not going south but they are still like in purgatory, you probably should not go on beyond that. So there's like a midrange.

So I think we can borrow from the graded dose inhaled allergen challenge paradigm, not specifics, and then we get into the issue of, you know, how do you know when a 2-year-old is itchy or just annoyed? But if they start out not annoyed.

The other practical issue is the time -- you know, take a kid who hasn't eaten. You are going to do a graded dose challenge, and after a while, they are going to start having symptoms, as it were, because they're just hungry. So you are going to have to account for that.

But for me, it would be a combination of physician observations, either by querying and then objective physical examination metrics that would move forward, and then you would score those as a guide, and then there are a couple of absolutes. I mean, someone who becomes overtly hypotensive, loses consciousness, I'm probably not going to proceed at that point.

But I think that there are -- I think you could do that, and I would err on the side of caution, start out with what may be an arbitrarily selected low dose that X number of people will still react to, and then dose grade up to a dose that is -- that you think represents the amount of allergen, and we can discuss -- you can discuss, because I don't know this exactly -- which specific metric,

whether it's an allergen level or a certain weight amount of a dry material or whatever, to a target dose and say, okay, at this stage we can say when this is your eliciting dose, and if you max out then maybe your eliciting dose is pretty low or your tolerance is pretty high. Tolerance is probably not the right word to use.

But that general paradigm is how I would begin to tackle this and then get into the specifics of each metric I would use.

DR. KELSO: You kind of raised the issue about how many organ systems and whatnot. I guess I would be in favor of picking sort of a middle ground in that, for example, if a child developed any objective skin, respiratory, GI, or cardiovascular symptom, that that should be sufficient, and by symptoms I mean that are conceivably mast cell mediated, so that a child who developed an obvious urticarial lesion, even one, then clearly that was because they ate the food, and I think that's a positive challenge.

I guess you could go on and see what else happened to them, but that seems like a reasonable stopping point or a child who developed objective wheezing or for children who are having lung function had a decline in lung function by a certain percentage or who threw up even once.

So even though that's one organ system, in the setting of doing this challenge, the overwhelming odds are that that child who threw up threw up because they are having a reaction to the food, and that's an objective sign, and that would be a reason to say that was their eliciting dose and stop.

The other point I guess is that as part of study design, looking for any of these objective signs along the way requires that there be a thorough baseline examination to have been a complete skin examination to know what the child's skin looked like before you started and to know, again, for those who are old enough to do lung function, what their lung function was before you started it, et cetera.

DR. NELSON: I agree wholeheartedly, including an oropharyngeal exam, which is often overlooked. So it sounds like we are looking at thresholds for identifying that eliciting dose, Dr. Slater, and I think we have heard that the first appearance of any objective signs might be a reasonable criteria. I think one that has been maybe not explicitly stated but certainly implied is self-declared by the patient and family. We don't want to go on anymore. This is exactly what happens when we have our reaction. Would be one.

Then I think the other one is maybe persistent or non-transient and more than minimal symptoms that may not be objectively identified is a reasonable starting point as opposed to requiring a higher threshold of a more severe systemic reaction, seems to be the tenor of the conversation. Would the group agree with that?

DR. APTER: I think these studies can be titrations and the information we glean from one set about what is the minimal reaction can change as our experience increases. So it's moving target that should be moving.

DR. DYKEWICZ: I think we may also be looking at even within a couple year timeframe age range different thresholds for calling an end to the challenge. We discussed from a safety perspective that we might have some increased risk in doing these challenges with very small children who, for instance, have smaller airway caliber. You don't have potentially the safety margins of physical size with larger children.

So my sense in terms of trying to protect the children that would be entering into these trials, mindful that some of the most severely allergic ones are the ones that need to have the treatment, my sense still is that we have to have, particularly with the lower age ranges, a pretty low threshold perhaps for stopping the challenge

from a safety perspective.

DR. PEDEN: The other question I had is just a comment, but the epidemiology must be able to guide us as to what's the lowest -- what's the age range when a life-threatening reaction versus someone gets hives but nothing else when they have like some milk or something. So we could maybe target the earliest, the lower age at which you would want to do a trial to represent the age at which the life-threatening reactions seem to be a much bigger threshold.

So if that happens at age 3, then I'm not sure you would do trials below age 3. If there's a lot of anaphylaxis that occurs in 6-month-olds, which I don't think there is, that's a different issue. But I think that so you could less than 5, developmentally there's a lot of room in the less than 5 between 3 and 5 and 4 and 5 versus 18 months and 5, and I'm not sure -- and so I would be guided in part by where the epidemiology tells us the life-threatening sentinel events tend to occur in those people.

DR. NELSON: Let's move the conversation forward a little bit. So we have identified criteria for eliciting dose. We get some for participants in clinical trials. What is a meaningful response to an intervention when that eliciting dose is retested after the intervention? How

much of a response is good enough to indicate meaningful effectiveness for a product that might come before the FDA?

I'll open it up for comments.

DR. WEBER: If we were talking about some pharmaceutical intervention, we would want to have repeated values so that we could determine a mean and a standard deviation or whatever. However, I would think the reality of the situation with small children and their parents is that they are not going to put up with the concept of repeated challenges to really determine what that variability is from one exposure to another.

So I'm not sure exactly how we get around that, and that would apply for both obviously just initial challenge to demonstrate the validity of the reaction as well as after an intervention. I think it's going to be very difficult to do repeated challenges. I think it's going to be -- it wouldn't be difficult for us to do it. It would be very difficult to get the parents to approve that that would happen.

DR. PEDEN: Although we just heard that there are families that actually are pretty okay with this. I mean, the people who are scared about this, I'm not sure if you did a graded dose and then you got an eliciting dose and then they went on therapy X, whatever it is, probably not

worms, and then at a period of time they had a challenge and they did that, and then at some other period of time, maybe X months later or a month later, they did it again to be more confident that you could actually tolerate that dose, because we also have to deal with false reassurance. A one-time improvement versus -- this gets back to what is sustained and responsiveness, and you may wish to determine how that is, even with anti-infectious vaccine studies, we have learned that once is oftentimes not enough, and of course we have the advantage of believing we can follow titers for that.

So I don't know that families who -- it might be different for airborne allergen hay fever allergens, but for food allergy, where you think your kid is going to die, I think being tested in the controlled setting is a much more palatable thing for many families, including those in study, than some of the other things we talk about.

DR. NELSON: I will insert that in a randomized design, it does present perhaps an ethical dilemma for those on placebo to undergo multiple challenges without a classical intervention, at least in the absence of a crossover design. Just food for thought, no pun intended.

Dr. Apter?

DR. APTER: I think people mentioned

organizations like PCORI, the Patient Centered Outcomes Research Institute and the importance of including patients, and we heard from advocacy groups today in these trials is going to be very, very important probably to have wide-ranging patient advocates, parents, and children -- well, some children -- participating in the formation of these studies in the setting of the criteria.

DR. KELSO: I think to answer this question about -- I think what this question is asking sort of gets back to that graph of sustained unresponsiveness, tolerance, et cetera. You know, what counts as a success. So you can say that whatever intervention you had, quote unquote, worked, and I think, again as we have heard from families, one, the idea of tolerance meaning cure, you can eat the food or not eat the food at any interval forever, I think that's too high a bar.

I think there would, as we have heard from the families and the advocacy groups, be value in some treatment, some intervention, that allowed you to not have to worry that if you ate a certain amount of the food, that would constitute an accidental exposure, that you would have a serious reaction, even if -- I think studies should be designed to answer these ongoing questions in terms of time off therapy and do you still respond 6 months later,

et cetera, but it may be enough to have a therapy that allowed you -- even if it allowed you to eat three peanuts every day and not have a reaction, even if the qualification was you have to eat three peanuts every single day for the rest of your life, and what that protects you from is only that amount of peanut protein, that that sounds like that is valuable enough to enough people that that could constitute a success.

Then just in that regard, just yet another caveat or wrinkle in this, in a lot of these studies where there have been successes to oral immunotherapy and patients are in fact happily eating their three peanuts every day to maintain their desensitization, then a month later they get a cold, they take some Motrin, they have a stomach flu, they go for a run, some cofactor comes into the picture, and now all of a sudden they have a reaction.

So even the sustained unresponsiveness in many cases is somewhat tenuous, and I think once people achieve whatever is considered a success, even if it's that lower bar of a certain amount of food and that you have to keep eating it to maintain your desensitization that we should have some mechanism to follow those patients over time to find out whether they continued to be able to tolerate that dose with, once they have other life exposures.

DR. PETERSON: I was thinking that I don't know if -- I think worry-free. People want to be able to eat and not worry if they accidentally have a peanut in something, batter in the cookie was made after a peanut thing. So I think, yeah, one, to be worry-free, and then also to know what to do if they start in -- so if their reaction after they have been okay for a while, they start to have symptoms, that they have something -- they know what to do. They can do something quickly, be it an EpiPen or whatever.

And then they can go back and start their whole regime over again. I think that would create a whole different sense of wellbeing than to say you can't have it ever.

DR. NELSON: I asked to have this slide reproduced. One, I like it because it's a great overview of some of the questions before us. I was intrigued by the axis label on the vertical axis which shows a ratio of the eliciting dose, final versus that over baseline as a potential endpoint. So I bring forward for the committee to talk more about what is a successful intervention with respect to the eliciting dose. Certainly raising it as the goal, but how much? Should it be raised to an absolute threshold? One of the things we do in clinical management

of patients is challenge them to a normal meal dose. So a question before us is should we be looking for an absolute threshold that will probably have to be determined by the allergen itself, or is a surrogate such as a ratio of eliciting dose change over time before and after the intervention sufficient?

Dr. Peden?

DR. PEDEN: I think part of it for any given allergen, if there was a treatment and I was explaining it to a family, the real question would be if you did this, the protection this would provide you would be roughly equivalent to if your child inadvertently encountered X amount. So we have to figure out what X amount would be, a peanut, an equivalent of a peanut, a mouthful of peanut butter, eating at -- because I think that's kind of what I hear our patients talk about, what I heard today. It's the inadvertent unintentional exposure that happens.

So I don't know how you define what that is. I guess that's -- you're telling us that's our job to define what that is, but I think to me the threshold, whatever ratio, whatever measure it was, what I think people want to know is can my kid go out in the real world with reasonably careful avoidance, without kid in a bubble avoidance, and not worry about falling off the end of the world. I think

that is what they are worried about.

The other thing in this age range I forgot to point out earlier, there is going to be natural tolerance that occurs for many foods as well, and we are going to have to account for that, maybe not so much for peanut, but certainly for milk and egg there's going to be, in this age range, there's going to be a lot of kids that reacted at 3 and if you didn't do squat they would quit reacting by age 5. So either a placebo group is going to be somewhat important, or we may from a public health perspective -- you may want to focus on things that, you know, the allergens that stay with you forever and do that first, and then think about the more labile ones.

DR. KELSO: So I think in answer to your question, I think you need both. So we do need to know that there was a tenfold increase in the eliciting dose, but that's not by itself a measure of success, if that tenfold increase in eliciting dose doesn't get you to some clinically meaningful minimal amount of the food that you might encounter in an accidental exposure. I mean, if you used to be able to tolerate 1 nanogram and now you can tolerate 10 nanograms, that's a tenfold increase, and it means nothing because you need to be able to tolerate more than that. So the delta I think is important, but we also,

as I think Dave's kind of alluding to, need to decide whether it's a peanut or some -- there is some minimal amount that you have to also get above that absolute bar. Otherwise we wouldn't consider it successful.

DR. DYKEWICZ: One other thought would be if we are looking at the threshold of evocative dose, final versus baseline, there would be also the consideration that if there has been some integral change in the severity of the reaction that occurred at the same dose in an individual, that still might be significant. I mean, if somebody had with the initial dose at the beginning of the trial hypotension and bronchospasm, and then they go through the trial and at the end they still might have a reaction at that same dose, but they have some flushing or a few urticarial lesions, I think that would be another criterion by which you could judge that there was some benefit from the intervention.

DR. GILL: Not to take us backwards, but as I think more about that eliciting dose baseline and what objective measures and we all kind of scratch our heads about that, I think about something that Dr. Peden said, and I think we should really talk about going young, into younger children, and the developmental aspects of that.

Maybe one area, safety focused and also to help

us learn what a true eliciting dose is in a young age group, to really focus some effort on would be maybe do a big -- look at that first and then try to learn from that, all right, an 18-month-old when he shakes his head and starts walking around head-shaking, that really conveys itching in the throat or some sort of reaction.

How young are you when it's appropriate that persistent crying should be read as a reaction, and you can go on and on about different things like that, but I think if you learn where that number is, it may be that the dose is lower than we think, and if we are off there, it may make it more difficult going forward. So I just think some real effort and thought in developmental specialists, pediatricians, behavioral specialists, to help look at these may really help going forward before you even think about how much change is needed.

DR. NELSON: Other comments? Okay, let's move to a different aspect, and in particular let's focus a little bit on safety, because I want to make sure we don't wrap up this discussion of food allergy with respect to safety itself in food allergy. So what are your concerns and comments regarding this young age group and things that clinical trialists should be looking for in the way of safety and assuring that volunteers and families engaged in

these studies are cared for appropriately?

DR. WEBER: We might as well start with the worst case scenario. So the episode of the 16-year-old with peanut allergy involved in the peanut immunotherapy study at National Jewish in 1986. The patient had been treated with placebo and was, due to an error in the pharmacy, given a dose of peanut, and despite the fact that there were medical people right there at the time he ingested the dose, he still died.

Now, so I guess the first step of safety is to be damned sure that what you are challenging someone with is really what you think it is and that they are probably, just as there are safeguards in giving immunotherapy where someone looks at the vial and the dose and all that and has someone else, should be someone else to verify that that is correct, that these types of safeguards absolutely have to be in place.

DR. KELSO: I think by the very nature of these kind of studies that we are talking about with the challenge being a dose escalation challenge, whether it's the baseline challenge or a follow-up food challenge, there is some built in safety to that, because instead of just feeding the kid a peanut butter sandwich to see if he still reacts to peanut butter, that's not what we are talking

about. We are talking about at any one of these challenges, I assume, or think we should be, having this be a dose escalation where you really are starting with some amount that is either unlikely to provoke any clinical symptoms or at the very least unlikely to provoke a serious clinical symptom.

So there is some safety aspect just in the way the study is done, because you're starting with a small amount, and you have the opportunity to declare it over or positive before you would get to an amount that would cause a more serious reaction.

The other thing that is in our favor and kind of goes in the way of safety here is that the majority of these reactions are likely to be urticarial or emesis. So the child of any age who would have their sole manifestation of their positive challenge be sudden respiratory or cardiovascular collapse, while not impossible, is pretty rare event. Again, particularly with the dose kind of escalation that we are talking about.

DR. THOMPSON: And I think with this age child there's a huge component of educating the parents or the caregivers or whoever else is around there. You don't want adults that are afraid. The kid themselves might not want to eat, but you don't want the parents to say, oh, Johnny

can't have this, I'm sorry, and jumpy all the time, because the kid will certainly pick that up.

So there is some education or something to be done with at least the family.

DR. NELSON: I am hearing three main aspects with regards to safety. One is the adequacy and ability to treat immediate reactions certainly needs to be in place, that the risk would be somewhat mitigated by the way in which these challenges are conducted, and we have a long history with that, which provides some safeguards, but the unexpected does occur, which we just heard. So the expertise for emergent resuscitation is an absolute need.

We also heard about educating the parent. So the possibility of delayed reactions hasn't been a big part of this discussion, but it does occur. So having adequate access to educational methods to make sure that parents are able to recognize and bring children who are in clinical studies to emergent management, making sure that there's no reticence to use autoinjectable epinephrine when needed, et cetera, is also a key part of these clinical studies.

I also want to take a little bit of time, because this has come up during some of the other product reviews at our past meetings, to talk about the more delayed adverse events and in particular the possibility of

development or exacerbation of eosinophilic esophagitis. We don't have a lot of data with regards to this age group that we are talking about, but there certainly is an implied risk, certainly not proven, that this type of therapy may contribute to the evolution of this disease or perhaps contribute to its worsening for those patients who have it and haven't quite manifest in the way of symptoms yet.

So it is a practical consideration as to whether or not we engage or acquire clinical trialists to consider, one, long-term management or evaluation for the development of this for those enrolled in these trials, or actively evaluate for the presence or emergence of the disease during the conduct of a 3- to 5-year trial in the way of endoscopic biopsies, et cetera? So I wonder if the committee would take a moment to discuss eosinophilic esophagitis, the risk, and maybe appropriate monitoring activities for those considering clinical trials in this area.

DR. KELSO: I guess the first would be to get a baseline. I know that there are anecdotal reports of children who were in oral immunotherapy trials who went on to develop eosinophilic esophagitis. As far as I know, that's what our dataset is. So we don't know if those

children already had it or were on their way to it before they got into the trial or really whether the trial had anything to do with it or not. I mean, because it's biologically plausible that doing this could induce eosinophilic esophagitis, the temptation is to say that that's a risk, but eosinophilic esophagitis predominantly occurs in people with other genetically atopic diseases, including food allergies.

So I guess before we answer that question about how aggressive we should be for looking for it, it would be a good idea to know, to thoroughly review the data that's already available. Do we really think that children who are undergoing oral immunotherapy are at increased risk compared to other atopic children to develop this condition?

DR. PEDEN: To me, just being dirt stupid about it, either they are having difficulty swallowing or you have to look. I mean, you're talking about instrumenting people if you are going to really demonstrate that they have eosinophilic esophagitis, or at least esophagitis, and you have to biopsy to know if it's eosinophilic or not. Aside from that, surveilling difficulty swallowing or the food catching, that sort of thing, I am not aware of any other easily obtained pragmatically approachable way to

screen for eosinophilic esophagitis other than until the swallowable camera that you can do and a swallowable camera that can be swallowed by a 3-year-old and not aspirate it and get your free bronchoscopy, I don't know how you are going to do it other than that. So that's just putting your cards on the table. That's what you are talking about, and what's the risk of that really happening, versus the risk of having an invasive procedure as part of that?

I would also say that another safety parameter -- there is technology. So the kid, if you have a study team, particularly if it's a multisite study, you have a coordinator that was someone on call, if a family wasn't sure, they had their mobile device of choice, were given one as part of this study, and you could actually look at what the kid looked like, and you could actually in real time not just talk to a scared parent over the phone, but actually look at some things.

Depending upon your sense of worry about the safety part, that would be another way you could mitigate that. You look and say, yeah, give the epinephrine, call 9-1-1, and call me back when the paramedics are there. I think those are -- because right now we give instructions like that, but there's not -- I am not sure how many studies really do that.

DR. KELSO: I guess unless review of this baseline data I'm talking about reveals a higher risk than we think there is, for example I would not want to suggest that to do these studies that every child had to have serial endoscopy to find out whether or not they developed eosinophilia in their esophagus. I think that is clearly too much. There is a risk. If doing endoscopy was benign and not expensive and time consuming and potentially dangerous then maybe we would do that, but there is risk to doing endoscopy, because the children have to be sedated, et cetera.

So some middle ground might be to be aware of the potential, have some predefined set of criteria, difficulty swallowing, the food sticking obviously, but some set of criteria that would surpass some level which would then prompt endoscopy to see whether or not the condition had developed.

DR. WEBER: Those who know more may have to correct me if my sense of the folklore is not correct, but I believe that in children with eosinophilic esophagitis, the symptoms may be a little bit different than they are in adults where in adults you very much get the sense of food hanging up in that sense, but whereas children may actually just complain of some belly pain, and considering that some

belly pain may also be a manifestation perhaps of food allergy, it makes it very difficult to beforehand make this diagnosis, and it might not be as easy to have that suspicion than we would hope.

DR. NELSON: So Dr. Slater, I think what we are hearing is that there's not enough evidence to convince the committee on hand; I can't speak for the rest of the food allergy world obviously, that there's enough of an established risk for either treatment with a trial with oral immunotherapy or sublingual immunotherapy for that matter to require it as a component of all pivotal studies that would come forward. I think there is certainly interest in establishing whether or not there is risk there, probably through separate studies.

I think there are opportunities, however, to engage those volunteers for these clinical studies, for longer term follow-up. I certainly wouldn't mandate a clinical trialist or a sponsor to follow individuals over a decade of time to look for the development of the disease, but to perhaps hand these patients off to a registry that could look for the emergence of symptoms or other clinical encounters suggestive of the development of trial-related complications or to add to the information with respect to development of additional atopic disease, which will be in

our next session.

So I think there are opportunities for partnerships between those conducting immediate clinical trials and those conducting longer term registry based epidemiologic research, and I'm sure the committee will correct me if I have summarized it differently.

Dr. Slater?

DR. SLATER: First of all, thank you very much. This was a very hard question, and I suspect members of the committee may have wondered whether anything useful was coming out of it. I can assure you that you have made a lot of very useful observations on many different fronts, not the least of which identifying the difficulty with identifying age-appropriate symptoms and signs, the problem essentially then in preverbal infants, there are only signs, and converting those symptoms into signs is often very difficult to do. The observation that the intensity of the reaction is another factor that's not actually covered in the graph that we showed, these are all very important observations that were made by many of you.

I would like, if we could, before we leave this question, to dial us back to the question of sustained unresponsiveness and what the committee members' thinking is regarding a claim of sustained unresponsiveness that

might be entertained by somebody coming to us, whether there is a time below which you wouldn't even think of entertaining the claim, whether there is -- you have already discussed the issue of the ED final over ED initial, to some degree, but I think -- do you have any thoughts about time of sustained unresponsiveness? In other words, the time interval after the discontinuation of therapy that we preserve some benefit in terms of ED final over ED base?

DR. NELSON: Great framing of the question.

DR. WEBER: Unanswerable.

DR. KELSO: It is, although I think we can all agree there would be some interval that would be too short. Like a week's not enough. A year is too long. So I am going to throw out 3 months and then another 3 months after that. So 3 months after off of therapy to do their challenge and see if they still react and then do it again 3 months after that. If you went to two 3-month intervals after doing something like this and didn't react, that's clearly sustained unresponsiveness.

DR. DYKEWICZ: And then to follow up with that, though, since we are talking about sustained, whether after some more frequent interval of challenges, 3 or 6 months after stopping the desensitization, I think, for instance,

potentially an annual or a biannual long-term follow-up would be important to address the question about the sustained hypo-responsiveness.

DR. PEDEN: So the question is really how to do that and upon whom is the onus of doing that? So if you are making, say, you want to make a kind of sustained unresponsive -- I actually would argue that whoever is going to make that claim should say for at least X period of time and then the onus should be on them to demonstrate that for X period of time after you gave your last dose, you were able to give a challenge that was nonresponsive, and I think that would be part of the indication they would ask for approval for.

For at least a year after you underwent therapy, there is nonresponsiveness, and then physicians could take that for what it's worth. Yes, it's conceivable that a year and two weeks afterwards it would all fall apart, but I think to a certain extent there's that. I personally feel -- so when you use the word feel in something like this, it means it's completely and totally unsupported by data.

(Laughter.)

But I feel that anything less than a year is hard to call sustained unresponsiveness, because a lot of the --

I mean, with the idea being that -- because when you use that phrase to a family, I think you are conveying that, yeah, it's probably pretty okay for a while, and your kid can go to college and you don't have to worry about this.

DR. NELSON: Dr. Finegold? I'm going to ask the speakers to make sure you speak directly into the mic. We have had some comments from our web viewers that they are unable to hear some of the conversation.

DR. FINEGOLD: Wouldn't it make a difference on the length of the therapy just to hearken back to Durham's work on grass, which is not necessarily equivalent, where after 3 years they demonstrated 3 years of a kind of sustained unresponsiveness?

DR. PETERSON: Three months, very short time to me, and I would go for a year. I would go through the different seasons, the different parties, the different vacations, the different whatevers they have. I mean, in a way that's challenging the family and the people to look at their life, and what comes up. I mean, at Christmastime you might have XYZ to eat and the kid can't have it or the kid can. So I don't know. In the families I have worked with, I think they would take a year. I don't think they would object.

DR. PEDEN: I know, I am being too verbose, but

that's nothing new. I think you could also have a post-market -- I'm sure I'm using the wrong phraseology, but some registry where people keep track of -- so there's the formal, you've done your study, you've got your approval or not, but you have made your case, and then once these people are on this, you periodically surveil them. That doesn't necessarily mean you do a challenge, but if you find out that 20 percent of people 2 years later are beginning to start having -- free range humans start having real reactions, then that would be informative and you could actually then make a post-marketing warning, or you could actually say, you know, maybe we should revisit this.

But I wouldn't want to hold up an absolute cure to provide some degree of protection for people now, and I think that's one of the -- that's the yin-yang I think that we have to deal with.

DR. KELSO: I think we are talking about two different timeframes here. The 3 months that I pulled out of the air, just is in regard to how long do you have the person go back to strict avoidance of the food before you do that first challenge to decide whether or not whatever treatment you did for however long worked in the sense are you still protected, even though you are not getting the treatment anymore, because if they did treatment for

however long, the child doesn't eat the food for a week. They come back a week later, they do another challenge, he still doesn't react, and they say that's sustained unresponsiveness, we're out of here; our study is over. That's not good enough.

On the other hand, so just sort of picking what a reasonable time frame would be in that respect, that is where the sort of 3 months I'm thinking about is, that after you have done your trial for some amount of time and then you are telling the child again or the patient to go back to complete abstinence from the food and then doing another challenge, that for that period of time, 3 months, which again I pulled out of thin air, I mean, that sort of seems reasonable in that regard.

But then as a separate question is how long do you have to follow them with reintroduction of the food, or not, for whatever period of time after that I think maybe is a separate question, but for sort of that initial timeframe, that 3 months seems reasonable to me.

DR. DYKEWICZ: But that does also bring up the question about whether you at the end of the desensitization trial would say complete avoidance or whether eat ad lib in the field of nature, and I think I would be more inclined to say, okay, once you have gone

through the desensitization trial, you are open to having small amounts of peanuts. I'm not sure how I would be more specific, but I do think the concept of complete absolute avoidance versus some tolerance of exposure is an important one.

DR. NELSON: I think you are hearing that for a product to be clinically effective, sustained responsiveness is not required. You can still have an effective product without sustained unresponsiveness.

I am going to argue for a little bit longer than a year, personally, to be perfectly honest. I think a year is a reasonable start and certainly a checkpoint that all studies should follow. I'm going to argue for 2, and I'll tell you why. I'm going to base it on the parallels of the immune response to classic subcutaneous immunotherapy.

We know that almost everyone receiving subcutaneous immunotherapy is going to be immune from recurrence of their disease during their first year after based on the immunologic response and successful treatment. So I understand that food allergy is different, but if we are talking about a product claim of some sustained unresponsiveness, i.e., we have cured you at least for a short or definable period of time, I don't think it's unreasonable to set 48 months as a limit for that and not

confuse the issue of this residual from the initial desensitization with treatment of a product. Let's go a little bit longer and make sure that we really have changed the reactivity of the individual.

Dr. Finegold?

DR. FINEGOLD: But to some extent it may depend on the product. For argument's sake, if it's something that's anti-IgE, after 3 months, that effect will be lost.

DR. NELSON: Fair statement.

Dr. Weber?

DR. WEBER: If we want to say that our intervention is disease modifying if we use the experience with the oral immunotherapy things, when the agents failed between -- or lost efficacy between the second and third year, that eliminated the ability to say it was disease modifying. So I think that 2- to 3-year period I think is -- if we want to maintain some sort of semblance of consistency, now, true, food allergy is food allergy and inhalant allergy is inhalant allergy.

DR. NELSON: So, Dr. Slater, I want to make sure that we have sort of rolled on 2 and 3 which are in this slide. Are you intending to us to go to those? Is that coming behind this?

DR. SLATER: Right, and thank you very much about

question one and thank you for that added on discussion. I appreciated it.

Treatment of food allergy question number 2. Please discuss approaches other than food challenge studies to demonstrate the effectiveness of immunotherapy products intended for use in food allergic individuals.

DR. NELSON: So this brings into the question of uses of biomarkers, field studies, et cetera.

DR. WEBER: I think we already know that looking at blood levels of IgE, if they are below -- let's say if they are above a certain point, you know that you have an 85 percent chance of an adverse reaction or a reaction, but you don't know the severity of it. I think based on that experience, I think it's difficult to come up with at least Ig response of IgE as a suitable biomarker of success.

DR. KELSO: While it might be useful for the people who are conducting these studies to measure IgE, IgG for IL, whatever they are going to measure, that might be useful from a research standpoint, but there's no substitute for an oral challenge. If the question is asking is there something else we can do other than an oral challenge to find out whether or not the treatment was effective, I think the answer to that question is no. You have to eat the food to find out whether something happens.

There really isn't a substitute for that.

DR. APTER: But following IgE levels to specific foods over time in patients who are allergic might give information that might be predictive later on.

DR. NELSON: So I think that inclusion of these as secondary endpoints, certainly not field studies as a substitute for controlled trials with food challenges, is certainly a message to take away, but also the fact that there is some value in looking at biomarkers and potential markers of immune response that over time may evolve into surrogates for hard conduct of serial food challenges. Certainly to do the initial challenge and perhaps towards the end of the study, but if there is a way that we can limit the number of those food challenges and perhaps rely a little bit more on some of these other surrogate markers would be of value, but right now I don't think we have the confidence in any of them to replace that of a straight up food challenge.

Other comments?

DR. GILL: Along that line, remembering what Dr. Platts-Mills reminded us about the LEAP study may consider as a biomarker certainly not to replace a food challenge, but the basophil reactivity or other assays like that that have been done in food challenge studies and learned from

those values, but certainly won't replace the food challenge.

DR. NELSON: Since this question is up, I'll open this up following Dr. Baker's presentation during the public hearing portion. So on a very well-established network of centers that are well-greased in conducting these types of clinical trials, is that a sufficient approach to rely on heavily, or is there any recommendations with regards to inclusions of populations that need to be involved in these centers to make sure that we get an adequate picture for how these products work for all potential beneficiaries down the road?

Dr. Apter?

DR. APTER: Certainly we need to know in populations that mirror the populations of the United States, the results and how these trials work. It needs to be inclusive.

DR. THOMPSON: It might also be a place to recruit patients, and you have some people already very interested in participating and knowing results and maybe families that are there. I think it would be a good idea.

DR. NELSON: So I think one of the takeaways is that using established platforms for conduct of clinical trials will add to the reliability of these studies. We

certainly need to make sure that there are no limitations to access to those clinical trials. I too have been particularly impressed by patients interested in participating. I continue to get calls from patients. Hey, what's going on with food allergies so that I can get involved and perhaps have a chance at improving my individual tolerance.

So what I'm not sure of and perhaps offline I'll talk with Dr. Baker and the others who run these networks how accessible it is for patients throughout the country to become engaged in some of these clinical trials. So that would be a piece of advice to Dr. Baker and those involved in setting up these networks.

Dr. Peden?

DR. PEDEN: Well, one of the really expensive networks the countries set up recently are the CTSAs, and I think that -- and so, I think that's a network that could conceivably be deployed, particularly to be sure that underrepresented groups or those that do not traditionally engage in research are at least approached for the opportunity to do this, because unlike a lot of the studies, I think many people perceive and there's the hope that some of the studies may fairly rapidly bear some protective fruit.

DR. NELSON: Okay, your final question, Dr. Slater, on this topic? Number 3, next slide.

DR. SLATER: Taking into account the route of administration of immunotherapy in food allergic subjects and the age of study subjects, please discuss specific safety monitoring for signs and symptoms of allergic reactions.

DR. NELSON: I will open it to the group. We have already had a little bit of discussion in this area. So I think it does bear discussing out front in front of everybody. We have made some assumptions that OIT is the exclusive route that we should be looking at. Would others like to comment on sublingual and the epicutaneous routes that were also discussed in some of the initial presentations? That scared Dr. Peden away.

DR. PEDEN: Right. You brought it on.

(Laughter.)

So it's actually intriguing, although there are people in my institution that are interested in this. So that will be my little bit of disclosure. But I do wonder if sublingual immunotherapy, particularly for younger patients, could conceivably be a gateway to oral immunotherapy. I think the data are murky as to whether sublingual immunotherapy will have the same immunogenicity,

but I think if you can achieve some degree of decreased reactiveness that may make it easier or safer for a young child to then undergo oral immunotherapy, that's more of a research question than a regulatory mandate, but I do wonder about that. Without data, I have the impression that SLIT is less problematic than oral immunotherapy, but it's just something to think about.

DR. APTER: I am not a pediatrician, but how do you get the immunotherapy under the tongue of a 3-month-old?

DR. PEDEN: Martial arts maneuvers.

(Laughter.)

I mean, you can at least give a lower dose that's sublingualesque and you can target it under the tongue; it's not the same as having a large dose that you are going to get and you are trying to get a systemic dose up.

DR. PETERSON: My comment is could you just differentiate between what would be an adverse effect, like that this really -- the drug is doing something to the kid versus just that they got it in the wrong place and they're squishing it around in their mouth and they start to itch and whatever?

DR. PEDEN: Part of it, I think, would be the dose that you gave initially and where you attempted to

target it, with a dropper or a bulb or something under, somewhere close to under the tongue. Oral itching would be one thing. I would be less bollixed up about oral itching. Wheezing, stridor, vomiting I would be a lot more concerned about.

PARTICIPANT: And then the esophagus will be -- well, under the tongue would be okay.

DR. KELSO: There is some data, existing data, about the relative safety of these approaches, just in the trials that have been done, how many children had systemic reactions to the therapy itself, and it does seem to me that it's higher with oral and less with sublingual, maybe just because they are using lower doses. I mean, I don't know how much data we have on the skin aspect of it.

But as far as what you are going to call an objective trial response, that also is in some route, as has been alluded to, is affected by the route. And this came up when we were talking about the immunotherapy for aeroallergen oral immunotherapy, the sublingual tablets for aeroallergens. So really in sublingual, as you are suggesting, if your mouth is itchy, well, you've been holding this stuff under your tongue for three minutes or whatever it is you're doing, and maybe that happens to 100 percent of people who put something they are allergic to

under their tongue. That somehow has to be counted differently than a child who had a patch put on and is now complaining that their tongue itches. You know, because that's not where you put the food.

Then similarly with the skin ones, you're going to have some criteria for local reactions, just like you do with sublingual, to put those in perspective. A child whose arm itches under their peanut patch, that's not a systemic reaction or whatever. So I think in terms of what they -- how they react to a challenge is completely independent of what form of immunotherapy they underwent. Those questions should be answered about how much you can tolerate and for how long, irrespective of the form of immunotherapy. But as far as what you're counting as a reaction to the treatment itself is in fact going to in some sense be dependent on the route, taking into account local reactions.

DR. FINEGOLD: I am assuming -- maybe I shouldn't assume -- that as part of these studies these patients will receive an anaphylaxis action plan or something of that nature that's quite specific and detailed as part of this study.

DR. WEBER: Going one step further, is it desirable or necessary for some of these, especially the

oral challenges, to have IV access?

DR. NELSON: So you did go exactly where I was going to go. So I know Dr. Slater was probably disappointed we started, because I think the original intent was to get into the nitty gritty of what you just discussed. What specific safety monitoring elements, for example in oral immunotherapy food challenges, should we be looking for? Some of the things to look at is IV access required? Do you really need to do vital signs every X number of minutes? Is there any value in doing that in a 6- or 12-month-old? What is the duration of observation after the last dose that we should require these participants to be evaluated for before releasing them home for the day? And what is the requirement for monitoring them at home? Is a simple survey conducted or diary conducted by the parents themselves sufficient, or are there specific instruments that should be involved?

So I will open it up for those comments about the specifics of conducting that challenge in the setting of oral food challenges in a clinical study.

Dr. Kelso?

DR. KELSO: I don't think they all need an IV in, and so but there should be criteria in place for when you would put in an IV somewhere along the way. It's hard to

picture that they would all need an IV to start with. That seems overly cautious to me.

What was the other? Oh, the monitoring. So I don't think -- I think it is reasonable to have vital signs at some interval and spirometry or oscillometry or whatever if you are going to be following lung function at some interval, and importantly to have baseline measurements, to have them to compare to, because that in some respect helps you to tell if you're really having a reaction or not, particularly in alteration in vital signs, which gets back to -- again, with these very young children -- the specifics about things as mundane as what size blood pressure cuff do you use in a 6-month-old, because it makes a huge difference in the blood pressure that you get.

DR. PEDEN: The technology is actually not super expensive. You don't have to -- you could do continuous monitoring. You could put a Dinamap on them. You could do consistent blood pressure monitoring. There's other technologies to measure blood pressure. You could have an ECG patch on. That's going to be a 12-lead. So you could know if someone is becoming tachycardic or not. You could know if someone is becoming hypotensive or not. It's continuously monitored. You don't have to know about every time you do it it's automatically recorded. You can have a

pulse ox on so you can know if some of those things are beginning to change. You could even have an accelerometer on the chest so you could know respiratory rate and I-to-E ratio if you wished to do that, without having to do something.

So I would subscribe that with relatively modest investment the equipment exists to be able to do that kind of monitoring that you don't need to have every 15 minutes. I mean, you might record what the machine said every 15 minutes, but you could have fairly continuous monitoring. You could actually -- and I would argue trend events would be important. You know, if you were to begin to see that systolic blood pressure was beginning to dip, if you were beginning to see that the pulse was increasing, maybe not in and of itself alarming, but it started out stable and it was slowly going up, that would make me think about what was going on more so than an arbitrary every 15 or 30 minutes you're checking blood pressure.

DR. PLUNKETT: Would that be something you could use as like an endpoint or during the effective -- or the eliciting dose?

DR. PEDEN: So the short answer -- the long answer is you could develop that, but that would require really looking at it and developing your criteria that were

uniformly applied. I think I would still want to use, even though I would see the trends that as an investigator I would look at carefully, I would still want to define or require the definition of a priori stopping rules for the entire study and for any one given individual and have that written down and then have medical office review, vet that, yeah, these seem reasonable to me.

But in terms of just being able to have the data, it's not that hard to actually have that data pretty continuously now.

DR. NELSON: So I think you are hearing that it may not be an absolute requirement, but there is certainly some value in looking into perhaps monitoring in a continuous fashion. We don't have a lot of literature on the evolution of straight up anaphylaxis in this age group, so understanding the physiology of those reactions as they occur in real time has inevitable benefits that extend well beyond the immediacy of the food allergy itself. So I certainly would encourage those designing clinical trials, if they have that capability, to include it as part of their evaluation, but we will fall a little bit short of recommending it for all studies.

Dr. Gill?

DR. GILL: So along those same lines, when you

talk about consistent or constant monitoring, I guess it would be important to think about where you want this to take place. You know, in some big institutions like where I am, a pediatric code team doesn't come to certain places where studies are typically conducted. So I think it might be worth at least discussing thinking about if that's an 18-month-old who has any chance of anaphylaxis, do you want a pediatric code team, versus your adult code team? Very different to intubate an 18-month-old and a 25-year-old.

The type of teams and certifications I think should be considered, because it sounds like we are leaning toward a pediatric focus for the young group.

DR. NELSON: A great recommendation and great follow-up to the discussion of the environment in which these studies are conducted. So that expertise, the real safety comes from the expertise of those conducting the trial being able to recognize the early signs, knowing when to stop, but also how to manage those symptoms and objective signs when they occur, hopefully fairly rarely. But I would agree. If we are talking about not putting in IVs, et cetera, certainly the ability to put in intraosseous lines in this age group is going to be an important skill set that not a lot of adult individuals are facile with, or adult practitioners are facile with. So I

would agree that there should be some minimal competency with respect to age appropriate management of severe anaphylaxis wherever these clinical studies are conducted. Great point.

Others on this topic? Again, the duration that we should observe these individuals before allowing them to leave the clinic?

DR. KELSO: Two hours. I think we have quite a large body of evidence for that, although there will be people who have later reactions. The majority of reactions that are going to occur actually at least begin occurring within 30 minutes. So even an hour later is starting to be a little unusual to start having a reaction, and if you went 2 hours and nothing had started to happen, the chance that something is going to happen after that is vanishingly small, and adding to that safety buffer is the observation that it's even more uncommon to have a late onset and severe reaction.

So there appears to be a correlation between severity of reaction and time from exposure to onset of symptoms, where the more severe reactions are also the ones that are more likely to begin earlier. So granted, lots of exceptions to that all the way around. But 2 hours seems plenty.

DR. NELSON: So it sounds like the prevailing theme is noninvasive monitoring and appropriate management of reactions as they occur as a general approach to designing safety in the conduct of the development of these trials.

All right, are we okay with food allergy with one hour left allotted to us?

DR. SLATER: We're great. I just want to dial back one very briefly. About I guess 5-and-a-half hours ago Dr. Hise briefly mentioned and discussed field trials for allergen, for food allergen immunotherapy. So the committee members didn't discuss that at all. Nobody brought that up as an alternative to challenge. So I guess one way to phrase it might be if you were sitting in our shoes and somebody came to you and proposed a field trial for the reasons that we outlined, perhaps the improved likelihood of recruiting, not facing the issues associated with food challenges in highly allergic children, how would the committee members respond to being approached for a field trial for food allergy immunotherapy?

DR. KELSO: I don't know what you mean by field trial.

DR. SLATER: It would be a trial analogous to a real-world situation where somebody would come in with

demonstrated food allergy, and that could be demonstrated on the basis of an initial challenge study, and then the initiation of therapy, but then rather than use as your endpoint a follow-up food challenge, you would actually follow them for real world accidental exposures. In other words, you would recommend that they continue to avoid, because obviously you have both placebo and treatment groups, and you would be comparing the reactions in the field in the two groups.

DR. KELSO: I don't like that.

(Laughter.)

For both safety and sort of scientific reasons. I mean, I get the sort of real-world aspect of it that somehow sounds appealing, but the -- and we did discuss sort of indirectly that we think that after whatever endpoint is reached with the repeat food challenge and whenever you declare success that there was a lot of interest expressed in continual follow-up of those patients in real life, and if that's a field trial, that part of it I guess you could call a field trial to see sort of what happens to them after that, but not to just kind of turn them loose and see what happens with their accidental ingestions, because those accidental ingestions are hopefully few and far between, and the circumstances

surrounding them are also different. Again, I get the appeal of having it be real life, but that just seems too random to include as a study method.

DR. APTER: The duration that you would have to follow those patients would be a long one, but I think it would be -- I actually disagree with you. I think it would be a good observational study and give us a lot of information about what happens to people in the natural course, as long as we could keep track of them and follow them.

DR. PEDEN: If one were to be committed to eventually doing a field study -- so that's my way of saying I'm not sure how I would commit to that -- like any other intervention study, you have a phase I and a phase II and a phase III. So the phase II, I think you only go forward to consider doing a free range human study if you have solid phase II data that demonstrated that with a food challenge that the drug in the right setting worked, and then the phase III study is to see if in the real -- if in a more representative situation you put people on therapy, and then you looked at those.

The consenting would have to be really clear to families and assent to the kids, depending on how old these people are, what you are and are not confirming. Of

course, it's a little bit of a false piece of gold that we think that the tolerance of the second food challenge, what that really means is that they tolerated the second food challenge.

DR. APTER: I wouldn't completely think about it as phase I, phase II, phase III. I think when we get information about the course of food allergy by following them over time, it would just take a long time and a lot of people.

DR. PEDEN: I guess my point is I would not as an investigator, I wouldn't feel comfortable enrolling somebody into a phase III study of an agent that had not been shown in a smaller number of people that they at least were able to tolerate the second challenge that mimics, that was at a dose that we thought was reflective of a real-life exposure. Even if it was a very modest number, versus here's something we think will work and let's see if it works. I would rather this is something that worked in -- it's like many other drug study. You have a smaller number of proof of concept studies to be sure the drug does what you think it will do first before you go on, particularly if it is a nonpermanent tolerizing study.

DR. NELSON: It sounds like there's significant level of discomfort with someone coming to the table with

three pivotal trials exclusively of the field study design, whereas a mix may be very appropriate and actually may get at some of the meaningful endpoints and meaningful things that we are looking for.

To me, I think it would be very challenging to conduct such a study that has sufficient rigor to assure compliance and that the adequacy of capturing those events or experiences when there was an accidental exposure and what resulted may be difficult, but there is certainly value in applying what we are seeing in the way of a food challenge to what real life is.

So I would encourage investigators to look at that particular study design as an option but certainly not the exclusive means of bringing a product to the table for consideration. That's just my personal viewpoint.

Others?

(No response.)

So as we transition I guess to our next topic, let me take, allow the individuals to stand in place and stretch. We have been going for about an hour and a half. Great discussion thus far.

(Brief recess.)

DR. NELSON: We are in the home stretch at today's session and as our last panel makes his way to our

seats, we'll go ahead and get started with our next question. I will state again it sounds like we're getting a little bit better with regards to broadcasting to the web, but they're still having difficult hearing, so please make sure you're up and close to those microphones when you make your comments.

Dr. Slater, the next question.

DR. SLATER: On the prevention of the development of asthma, question one: studies to demonstrate effective of allergy immunotherapy to prevent the development of asthma will likely enroll a population and increased risk for the development of asthma, including children 6 months of age and older. Please discuss factors to consider in the identification of subjects at increased risk of developing asthma, the diagnosis of asthma in infants and young children, factors to consider regarding the timing of the assessment of asthma endpoints such as age, time on therapy, time off therapy, or others.

DR. NELSON: Another softball. I'll open it up to the committee for initial comments. Let's start with the first one, which is identifying high risk subjects that may be targeted for enrollment.

DR. KELSO: Clearly one of those criteria could be the child already having another atopic disease or --

and parents, one or both parents, having other atopic diseases. Both of those are clearly risk factors for the development of asthma, and then even though it has the imperfections that I described earlier, the asthma predictive index does also increase the likelihood that you are going to develop asthma, so we already have some mechanisms to identify those children.

DR. APTER: You could add siblings with atopic diseases, also.

DR. WEBER: Although we know that wheezing in early age can result from a virus, et cetera, certainly that would be somewhat of a flag to follow those children later in life to see if they persisted in wheezing.

DR. NELSON: Is that any initial wheezing illness or specific to RSV?

DR. WEBER: I think rhinovirus is just as likely even in small children. Was that supposed to be a yes? I guess so.

DR. KELSO: I think that complicates things, both on many levels. One is that we're presumably talking about trying to prevent asthma. So we're trying to find children who are at higher risk of developing, but who do not already have it, and so a child who's had wheezing during infancy, it's possible that you would exclude those

children, even knowing that a large percentage of those are, in fact, not going to go on and have what we would call established asthma. So you have to decide whether you're going to include -- specifically include or specifically exclude -- such children to start with, and then either way, it still complicates the issue of if you're seeing if you're preventing asthma but the child wheezes with a cold when they're three, does that mean your prevention didn't work or, once again, was that a viral induced wheezing episode in a child that is going to be a relatively short-lived phenomenon in a child who is not going to go on and have asthma? So the issue of viral induced wheezing in preschool children really does complicate this picture. I don't have a great way around that.

DR. WEBER: I believe that it was the Australian studies which looked at asthma kind of symptoms in young age and then followed them older, and whereas if the wheezing was only induced by viral infection -- what the Brits called wheezy bronchitis -- that many of those children did not have problems with asthma later, whereas if you added other signs of atopy such as eczema and presence of allergic rhinitis, then the likelihood of persistent asthma really went up quite a bit.

DR. DYKEWICZ: I think what the agency has potentially proposed -- Dr. Chang, her slide 16 with the highlighted red factors being family history, atopic dermatitis -- and by the way, family history could be first degree relative, I suppose, sibling or parent -- atopic dermatitis, food allergy, allergic rhinoconjunctivitis, or other allergic sensitization. I guess that's a little bit softer, but I guess the question would be if some in vitro testing was done for specific IgE to foods or allergens, would they be considered increased risk? I think those are reasonable criteria.

DR. NELSON: Others on this topic? Dr. Kelso, you kind of gave us the lead-in to that second question on this, or sub-question, the diagnosis of asthma in infants and young children.

We're trying to prevent the development of asthma. It's important to know what that looks like when it does develop. What are the committee's thought on how to define that observation?

DR. THOMPSON: One of the criteria that the Robert Wood Johnson one was using had to do with coughing at night. How many times in a -- how often the kid coughed over a 12-month period, which was difficult to monitor, because it was on recall and parents were very fuzzy, but

that plus the wheezing plus some other things was one, and that's the one thing I don't see here and I'm kind of interested that maybe it's not been followed up as a criteria.

DR. PEDEN: I think it is exquisitely difficult to define asthma in infants and I'm not sure that that's even -- until we have better molecular tools, I'm not even sure that that's a real achievable goal. We can define infants who may be at higher risk for having atopic or IgE mediated airway inflammation, but I'm not sure that it's really feasible to say an infant, even a kid with eczema, for instance, who -- how much of their cough and sputtering is asthma versus just being a kid, and to me, kind of the goal of this is to prevent the development of what we would call asthma in a three to 5-year-old.

I'm not sure you have to -- I think you need to define the at risk infants, and I think you need to define what the end goal is. I'm not sure you have to define asthma in an 18 month old necessarily if, for instance, the stated hypothesis is that if you're going to start some kind of immunotherapy of some type at age 6 months, that by age 36 months, the likelihood of developing asthma is less now. Even at 36 months, that's hard.

For me, and this is very globular, a big part of

how my antennae for asthma go up is the question what happens to your child when they catch a cold? If they have a runny nose, it's a lot different than if parents are missing work and albuterol inhalers are coming out and the breathing machines are starting to get turned on. To me, part of that pragmatic definition is what happens when you encounter a viral infection, which is, to me, at least, one of the leading, if not the leading, cause of an acute exacerbation of asthma.

DR. KELSO: Given the fact that half of all children have at least one wheezing episode in infancy, I don't think, even though it muddies the water, we can exclude -- depending on what age the children are coming into the study -- all children who have ever had a wheezing episode because I would think what we're trying to prevent here is the child who has asthma at age six, five, or somewhere down into school age. Maybe there's a study that's trying to prevent -- if the study design is you're going to start doing something at birth to try to prevent wheezing in infancy, well, then that's a different story.

But if what we're trying to prevent is asthma in school age children by some intervention in younger children, I think in the study you'd have to include children who have had some wheezing because that's at least

half of all children, many of whom we already know will not go on and have asthma, so I think we'd have to include those.

And then -- but then, where do you -- the idea about well, okay, when did they develop asthma? When did they stop being a wheezy toddler and now we're going to say yep, your child definitely has asthma? That's one of those like, you know it when you see it, but it's pretty hard to put a definition on that. In lots of these studies where they decide, did somebody develop asthma or not, in big epidemiologic studies, you can just ask -- does your child have a doctor's diagnosis of asthma? You know that some of those diagnoses are wrong and that it doesn't pick up all children who really have the disease, but it's considered a reasonable cut.

Or questionnaires -- you know, the ISAAC questionnaire -- that you ask does your child have a wheezing or whistling sound from the chest apart from colds or something like that? I mean, there's certain questions that have already -- there's extensive datasets saying kind of how good those questions are at correlating with compared to some other sort of gold standard definition of asthma. If you're talking about smaller numbers of patients where you could actually monitor them going

forward, then things like this impulse oscillometry in the younger kids and spirometry in the older kids in serial exams become more feasible. I guess it kind of depends on the number of patients that you're trying to follow over what period of time.

DR. DYKEWICZ: The comment that I was going to make is, number one, to second the motion that I would not exclude children that had some wheezy story because you'd be excluding a lot of kids. But also, if this is a placebo controlled trial, I would presume that you're going to be getting wheezy kids in both groups and you'll still see the signal of benefit of the intervention if it's of actual benefit.

DR. GILL: I think, taking everyone's comments and remembering our last speaker, the gentleman from Merck, and a comment that you made, as well -- maybe if we're trying to really assess the impact of an allergen immunotherapy on -- the pie in the sky dream is development of asthma -- years down the road, but if we stop and take what Dr. Chang had on page 11 of your handout, the slides 21 and 22, and maybe measure in some objective way a difference in the group who received the immunotherapy, the group who did not receive the immunotherapy, and we stop and maybe every year look at these things like this. Have

there been responses? Maybe some of them have been on beta-adrenergic agonist, pattern of the symptoms, maybe one group has more viral induced wheezing than the other, and begin to look at this as a sort of a spectrum that becomes asthma or doesn't over many years, so if we could use something like this as a tool to measure difference or look for potential differences in groups before we wait until 5 to 9 years old or whenever, I think we may be able to at least begin to get a feel of whether that's impacting the asthma-like symptoms that were referred to by our speaker in the public hearing.

Does that make sense? Just trying to take some version of this to give us an idea for impacting. It may be the allergic asthma-like phenotype. You kind of go down that spectrum and you become that or you -- maybe oral immunotherapy or immunotherapy impacts that.

DR. PEDEN: In many of the immunobiological studies, omalizumab, mepolizumab as examples, some of the major endpoints really were diminished number of exacerbations and I think ultimately that -- because we can all quibble over someone needed albuterol or not and the cough and wheeze -- but in the asthma outcomes workshop for the exacerbations part, the single most reliable measure that you could find in the literature with all different

study designs was an investigator or a provider-based decision to use corticosteroid for an acute event.

And so maybe simple is better. Maybe you should just count up the number of times that someone with a priori criteria and for what constituted need for corticosteroid, you just have someone on immunotherapy for whatever X number of times, and then at periodic times, you sort out any number of events. Because eventually you'll get better metrics with the key one being how many times did you have an exacerbation and how you define that?

Because there's so much phobia over steroids, you have to really -- that's a higher emotional bar to decide that you're going to put some -- for parent families to accept, often times, that you're going to be put on corticosteroids, so I would submit that might be one in some ways very crude but actually more reliable in pragmatic measures how often some kid needed prednisone to stay out of the ER.

DR. KELSO: Even short of that, I mean, I think you have a good point. I think that's an excellent measure of asthma exacerbation -- of kind of how well you're controlling somebody asthma is how often they have an exacerbation, but if what we're trying to answer is did the kid develop asthma or not, these children are also

presumably being followed with their regular provider and did they get put on an asthma controller medicine is a very good -- now, again, it's not perfect. There are some kids that should have been put on a controller who weren't and some who were put on who shouldn't have, et cetera, but it's another pretty good indication if their provider put them on an asthma controller medication and for how long. That's kind of an indication maybe the kid developed asthma.

DR. NELSON: And in that same vein, you would probably include emergency room visits for an asthma or respiratory-related event.

DR. DYKEWICZ: The question, I think, is somewhat a sensitivity specificity question. If you're going to have the bar that you have to have required oral corticosteroids for asthma, that's very specific, presumably, for asthma. And the other thing -- and let's say you lowered the bar a bit and said if the child had an urgent care visit, not necessarily resulting in corticosteroid administration, but an urgent care visit for wheezing, shortness of breath, that would improve your sensitivity of pickup of asthma, again, with decreased specificity, but I don't think that bar necessarily has to be as high. The child has to require even a controller or

an oral corticosteroid administration. I think even prescription of short-acting beta agonist would be a signal to look at.

DR. PEDEN: I would have agreed with that until I cochaired the asthma exacerbations committee of the asthma outcomes workshop, and I will tell you that it was all those kinds of things. We looked at all of that, inside out, upside down, but with mirrors, and all those other-- there's so many things that go into a decision about whether needs a beta agonist, whether they actually use the beta agonist, whether they know how to use the inhaler.

So that's why I went to -- and it wasn't just me. We had statisticians people look at the literature. It's actually more vexing than you might think. I think all those data should be collected and I think ultimately, with better mathematical models, you could actually do some of these studies. You would probably define a better statistically balanced signal out of all that, but if you're going to go into a study -- if I were paying for this study, I'd want to know what the goal line was. We've got to help define a goal line that would support that this intervention would be approved for decrease of this, and the most costly morbidity related aspect of asthma is an acute exacerbation.

DR. KELSO: This endpoint of does the child have asthma or not is fuzzy enough that it seems reasonable to collect all the things that are on this slide. If this is what we have to do now is to do some gemish of all these things to make some gestalt decision about does the kid have asthma or not, then if we specify upfront that these things and others have to be collected in terms of data along the line and then have some various levels of certainty in terms of asthma.

There's some things that you can describe that everyone would agree that child has asthma, there's no doubt about it, whereas there's other criteria like somebody prescribed them an albuterol inhaler. Well, some of those kids have asthma, some of them don't, but if you have all the data, then you can have not just as yes, no -- either you developed asthma or you didn't. That would be ideal, but given the softness of the diagnosis, we may have to have a more graded scale where there would be some would have almost certain asthma, probable asthma, possible asthma -- some sort of a graded outcome.

DR. NELSON: Today, or at least in the last few minutes, we've been talking about all cause asthma or all cause wheezing illness, if you will. A priori, the thought process here is that we if we administer immunotherapy

against an IgE mediated disease with the intent of preventing another IgE mediated disease, we know that allergen-driven asthma is only a subpopulation of the total asthma gestalt if you will.

Is there value in defining that subset in the school age population as an endpoint for marker of efficacy, or should we stay with all cause asthma?

DR. GILL: If you go to Dr. Chang's next slide, I would definitely agree with subsetting this and looking at the allergen-specific IgE and looking at that subgroup, because perhaps you are going to find you have the greatest impact, just throwing it out there -- this may be not what you find -- the greatest impact in lessening the development of asthma in those who have specific sensitivities.

Of course you would need to look at exposures, as well, but I think that this laid out a really nice baseline foundation for looking at how to define this asthma or allergic asthma or whatever type phenotype and then looking at those measures as you go through, and as we think about going forward with this, it almost sounds like something that would be very amenable to having a run-in period where you try to get your group who doesn't get any immunotherapy and your group who does equalized in what sort of treatment

-- I know that would be sort of a consortium sort of study, but if you really want to assess the impact of this specific therapy on these outcomes, you want to make sure people are doing this the same way, the treatments are similar and -- anyway, it's probably beyond what you are asking, but yes, I would be in favor of looking at subsetting.

DR. KELSO: That gets back to the intake criteria, as in the studies that have been done thus far, if the question is can you take children who have allergic rhinitis but do not have asthma and treat them and prevent the development of asthma, then your intake criteria has already gotten past some of these issues. I mean, you already have a child who has symptoms and specific IgE antibody that are consistent with -- that is a much easier diagnosis to make. The child has allergic rhinitis.

So once you have done that, then you have already kind of narrowed yourself down into that's the group of patients that you are studying, and that seems most appropriate and most likely for success, because you are desensitizing somebody to something they are already sensitized to, that seems like the place to start.

I would not have thought of using it otherwise until I read the study I mentioned this morning where they

started giving house dust mite immunotherapy to all children even ones who -- in fact, none of them were sensitized to dust mites. So that seems less likely to be successful than having -- if we are what we are talking about is kids who already have allergic rhinitis, that's an easier entry point.

DR. APTER: I am not sure in a 3-month-old you can diagnose allergic rhinitis or anything, but I agree with collecting all the endpoints one could at the time of what's considered the diagnosis of asthma, maybe at age 5 or 6, so that one can in the future be able to predict, use some of those biomarkers for prediction.

DR. WEBER: If we are thinking about outdoor inhalant allergy and asthma there, too, that's one issue, but certainly a much younger child can be exposed to an indoor allergen like the family cat who shares the crib, as has been reported, then developing still allergic asthma, but due to a perennial inhalant.

There was another point that that Mike had brought up, and that was all cause asthma versus allergic asthma, and which do you look at, and it brought to mind the concept of priming, which is well-described in allergic rhinitis, whereas exposure to one particular allergen may make you more sensitive to exposure to other allergens

producing some symptoms. The question is whether that exists also in asthma as well as rhinitis.

DR. NELSON: Other comments on this aspect?

DR. KELSO: Depending on how many questions you want to answer, I mean, the breadth of who you take into the study, you can still have children who are at increased risk to develop asthma because they have eczema, for example, which would increase their risk of subsequently developing asthma, but two-thirds of children with eczema aren't allergic to anything. So they have the genetic definition of atopy, but at least thus far don't have the IgE definition of atopy.

Or if your entry criteria is just a family history of atopic disease, then the patient may not have already declared themselves as having any atopic disease. Again, it depends on how far you want to back up in terms of where you're having people come into the study and what it is you are trying to prevent with the treatment.

DR. APTER: But you are probably enriching the population with people who are at risk for atopy and then randomization will balance out those risk factors.

DR. NELSON: So let's move to how long the study needs to occur to identify the development of asthma. How long should these clinical trialists follow the subjects to

be either identify as sufficient impact on the development of the disease or assure that there's no impact?

DR. WEBER: Oh, sure, why not? You betcha. So I just referenced the Providence data on people who had positive skin tests who were then followed and then developed allergic rhinitis after a fixed period of time, and then the longer you looked, the more it happened. So when with the long-term follow-up, which I believe was like over 20 years, then there was a higher proportion that had developed disease.

So you could argue just like the Australian studies that followed kids all the way up into adulthood that that might be the appropriate endpoint. That's hard to do.

DR. KELSO: I think at least 5 years. So you're absolutely right. Whatever you did, and they didn't develop asthma in 5 years, all you have said is they didn't develop asthma in those 5 years. It doesn't mean they are not going to develop it in year 6 or 10 or whatever. But that's still a meaningful intervention even if you just delayed it, but many of those probably were permanently prevented. So it's sort of balancing the logistical aspects and the 5 years seems like a reasonable interim.

DR. NELSON: So that connotes probably an 8-year

minimum involvement by a volunteer, 3-year minimum of treatment. We usually treat 3 to 5, right, plus an additional 5 years of observation for development. Long study.

DR. DYKEWICZ: I unfortunately agree with what we are talking about, because I realize logistically that's going to present hurdles to a sponsor, but I am also mindful of one of the slides that Dr. Tom Platts-Mills had presented to the committee earlier this morning looking at the timeframe of the, shall we say, the allergic march, and again the data is relatively limited, but that was where the initial surveillance of the children was anywhere from 3 to 2 months, 3 months to 2 years of age, but then there was continued surveillance for 3 to 5 years.

He also suggested that if you are looking at the ultimate impact on development of allergic sensitization, you may be looking at age range from 9 to 14 years. So yes, I think we probably are requiring for treatment effect a 5-year follow-up, but maybe in fact a much longer follow-up, not necessarily -- I should say needed for approval of some indication, but if you're really going to look at the ultimate impact on disease modification even longer follow-up.

DR. KELSO: There are a number of studies with

eczema as an example. There's been a lot of studies trying to prevent eczema, altering mother's diet, introduction of probiotics, et cetera, use of hypoallergenic formulas when you wean. The signal for virtually all of those in terms of their claimed successes are more often that they delayed the onset of eczema rather than prevented its development ever, and so -- those also, that kind of happens over the timeframe of 2, 3 years sort of timeframe. So if that's any sort of a guide, that also makes the 5-year thing seem sort of reasonable to know whether you prevented it long enough that it would be worth preventing for that period of time.

DR. PETERSON: I kind of like the 5 years in that that means the kids will be in school for part of that. So you also have a school nurse. You have somebody who can also collect the data or do the observations at the same time. So I don't know. That seems like a better chance of getting the information and the data.

DR. APTER: In schools where they have nurses, unfortunately.

DR. PEDEN: So question. For stinging insect allergy immunotherapy, how long do those studies go on from the time somebody got started until they were deemed -- until the immunotherapy was deemed preventive of subsequent

response to a sting? I am not being coy. I don't know the answer to that question, because in a way, I worry a little. I mean, I like the 5 years in terms of saying you're not an asthmatic. I will still say that if you could demonstrate decreased exacerbation rates of airway disease which you might be -- you know, because you have to get the maintenance immunotherapy. You have to be on it for a while, and then you have to see some efficacy after that.

So I am just pragmatically, I'm not trying to make it easier on anybody, but you also want the study to get done. So you have to -- either the there there has got to be giant, or you need to have some interim, I would argue, some clinically meaningful endpoint that may not be complete and total ablation or prevention of atopy, but still significant improvement in disease morbidity and mortality.

DR. NELSON: With respect to the venom data, it depends what they were using as the endpoint. So at Hopkins with the sting challenge, the endpoint was a lot closer. But the observational trials, they had significant dropout rate, but they would end up following some subjects out to 20 years after treatment.

DR. KELSO: It would be worth hearing from people

along the way. By the 5 years, I don't think that necessarily means they have to start the study and we don't want to hear anything for 8 years from now. Even if during the time of the therapy while the -- at the end of the initial treatment period, when they break the code or whatever, if fewer children developed asthma even during the 3 years that they were on treatment, that would be worthwhile. You would want to know that.

And then to continue to follow them over time, I mean, we heard the CAMP study for example, we have been hearing every few years about what happened to the kids in the CAMP study, and it has revealed new and important information along the way. So I think we could -- there would be sooner endpoints when you would want to know sort of what was, how things were turning out, but in terms of sort of a more permanent success to say that you really meaningfully prevented asthma, the 5 years seems good.

DR. APTER: Just like the food allergy study, asthma of course is a greater burden for low income minority populations. So this sort of study would have to include a large sample of those patients with the highest asthma burden and certainly reflective of the U.S. population.

DR. SLATER: I think we have heard that five

years would be the right number. I think we also heard something else important that Dr. Kelso said that 2 to 3 years would clearly be too short in terms of a meaningful endpoint. I think -- is there agreement on that? Dr. Dykewicz brought up the idea of approval of an indication at an earlier endpoint with some mechanism in place for longer follow-up, and that is a reasonable course of action if we think that the shorter endpoint is likely to be predictive of what you see at your ultimate ideal endpoint. So I guess I would like a little bit of a comment on what would clearly be too short to be a meaningful endpoint after termination of therapy for the prevention of asthma?

DR. KELSO: We have some data. So the prevention of whatever the PAT stands for, and they are very small numbers and they were not blinded, but I don't know what period of time. We have heard about that cohort twice. I don't remember how long they were followed after the first one to say that they had prevented asthma. So we have at least some data over what interval you can measure a difference. So however long they follow -- when the first PAT trial was reported, I don't know how long they have followed them. So we have that.

The other thing, there was a study just published in December -- no, January. It's in this month's JACI,

looking at epidemiologic data of people who either did or did not go on immunotherapy in 2006 and then followed them forward for a bunch of years, and it made a huge difference. I mean, it cut in half the number of patients who developed -- who had a new diagnosis of asthma after that.

So again, that is not a randomized trial, but it is a powerful signal that we are onto something here that, I mean, you probably can intervene. But what I don't think is in the paper but is probably in the dataset is some more answer to this question when did -- over what period of time did they start seeing the delta that you could say that they were in fact were seeing less asthma? If they only looked a year after the immunotherapy was started, did they see a difference 2 years, 3 years? So in their dataset, and they would probably be willing to share it, they probably have some of that information.

DR. NELSON: I would think you would need to age-stratify that data, as well, depending on what their age at enrollment was, because I think there will be differences there.

Others? Dr. Dykewicz and Dr. Gill.

DR. DYKEWICZ: I think the real question is not how short an acceptable interval may be, but how short of

an interval are you likely to be able to demonstrate a delta in a population that doesn't yet have asthma? If a treatment could be demonstrated within 2 or 3 years to whatever, half the prevalence of asthma or the incidence of asthma, okay. I would be mindful that that would be of value in assessing the efficacy of the therapy. I just don't think it's going to be able to be demonstrated within 2 to 3 years.

DR. GILL: I would agree. If the question is the development of asthma, I think you are going to have to be longer. Two or three years isn't going to be long enough, and age stratification is a great point that Dr. Nelson brought up, too. But I think the question Dr. Peden keeps bringing up of the potential impact on asthma exacerbations, maybe that, although a separate question, could be something that an effect could be demonstrated in a shorter time period, but then you would need to start with people who have defined asthma. So it would be probably older children, but still children and still immunotherapy in children. So that may be a separate question but really, really important in potentially a shorter timeline I would think.

DR. FINEGOLD: The abstract on the PAT studies says after 3 years of immunotherapy, we looked at them 2

years later. So then they called it a 5-year study. But it's 3 plus 2.

DR. PLUNKETT: And they also followed up and did a 10-year study. I just wanted to point out, I have a press release here that came from ALK where they did a prevention of asthma trial with the grass tablets in Europe, and just to point out they did a 3-year treatment phase, and they did a follow-up with 2 years, and that's what was just reported just recently in Denmark.

DR. NELSON: Thank you. I would add that there might be opportunities for shorter windows than 5 years, but you would have to carefully define what you are preventing. So just like Dr. Peterson alluded to, I think there are very good opportunities to look at some of the higher sensitivity endpoints and state that, yes, over a defined period you produced less in the way of emergency room visits or exacerbations or a requirement for long-term controllers, but may have to avoid using the term asthma, which is more of a chronic disease and isn't a single point in time diagnosis, but it's actually diagnosed as established over time.

How about we move on to the next question, as we get close to our endpoint?

(Laughter.)

DR. SLATER: I just want to clarify one thing. We were focusing this morning or we were trying to focus on objective measures of asthma in infants and young children. What I am hearing -- I just want to confirm what I am hearing. What I'm hearing is a comfort level for both intake criteria and for endpoints for using patient reported outcomes or, in this case, parent reported outcomes as an endpoint for these kinds of trials, rather than objective measures, which we think would be difficult to implement and may not actually work in the target population.

DR. NELSON: Specifically referring to the absence of the need for pulmonary function testing and bronchial hyperreactivity testing. Is there consensus among the committee with that?

DR. FINEGOLD: Specifically you're talking about medication scores and symptom scores? Is that the kind of idea?

DR. APTER: Whether diagnosed by a doctor or just purely caretaker or patient report?

DR. SLATER: I am leaving that open.

DR. NELSON: I think what you are hearing is that there is some level of hesitancy in relying on it, particularly for intake in this younger age population,

given the difficulty in acquiring that data. Yes, IOS is there as a possibility, but an absolute requirement for intake is probably not realistic.

I certainly think in the way of diagnosing asthma as an outcome in that later age group population, that at least secondary endpoint inclusion of pulmonary function testing should be a requirement, if not at least strongly encouraged. I think we would all agree with that. We shouldn't definitely exclude the ability to demonstrate pulmonary function testing, but to rely on it for intake at the beginning of the study for implementation of immunotherapy is probably a stretch.

Dr. Kelso?

DR. KELSO: And however the spirometry, oscillometry, et cetera, the objective measure of lung function is included along the way, I think we have to leave open the possibility that there are children who unequivocally have asthma who never get caught having abnormal spirometry. So having always had normal spirometry no matter what doesn't mean you don't have asthma.

Now, having a negative methacholine challenge virtually excludes the diagnosis. I don't know if you want to go that far, but I mean, so if we are going to include

spirometry, the fact that it was never abnormal doesn't necessarily mean you didn't have asthma if it looks like it and walks like it and responds to medication, et cetera.

DR. FINEGOLD: The PAT study included methacholine challenges.

DR. SLATER: Okay, prevention of development of asthma, question number 2. Please discuss the assessment of safety in infants and young children receiving aeroallergen immunotherapy to prevent the development of asthma.

DR. PEDEN: You can't know until you do the experiment. It's entirely feasible that a very young infant may not have developed enough IgE to actually have the same kind of dangerous reactions that a 3-year-old with established disease may have. I'm not sure that without some pilot data you can actually really get a realistic, other than just guessing at it.

I would submit that it's very feasible that an infant given immunotherapy may not have any kind of reaction relative to somebody with established disease.

DR. NELSON: So akin to our discussion with food challenges safety, but about an aeroallergen immunotherapy safety assessment? So in the conduct of the trials, what would you require investigators to look for for infants

receiving therapy?

Dr. Kelso?

DR. KELSO: Are we talking about oral or injection?

DR. NELSON: Classic injection or sublingual. It doesn't appear to be defined here. Either one. I'm sure you are interested in input on both.

Dr. Finegold?

DR. FINEGOLD: Wouldn't we say what the current standards are, waiting 30 minutes, and then probably in a research study postulate that they have an epinephrine autoinjector available as part of this study?

DR. APTER: I can't help worrying about traumatizing infants with immunotherapy.

DR. NELSON: That's certainly a consideration. Would you like to convert that into an endpoint? Patient satisfaction slash tolerance of the treatment itself in this age group where we don't have a lot of data? There certainly is a reasonable suggestion.

Other things that investigators or clinicians administering immunotherapy to the very young should look for systematically in clinical studies?

DR. GILL: So you are back to the esophageal -- I mean, you have to certainly apply the same concepts and

discussion that we had about the food allergens, and if you are talking about oral or sublingual, right? So I guess now you are talking about a longer timeframe, perhaps.

So maybe perhaps the same, everyone needs a baseline. Perhaps Dr. Kelso would suggest a baseline look at the esophagus, make sure that you don't come in with eosinophilic esophagitis. I guess if you're starting as an infant, you likely would not be. But a whole complexity of things, depending on the route. But that's one.

DR. NELSON: Very good.

So perhaps, again specific to sublingual immunotherapy, I'll assume that you're referring to. Perhaps the same approach that we talked about with food allergen immunotherapy is sort of a handoff from an initial trial that looked at the conduct of immunotherapy and initial prevention of asthma, perhaps handoff to a registry to look for the later development of some of these other disease states, and again the same would apply doing the side study to look for what the true risks for esophageal -- eosinophilic esophagitis in this age group actually is and then leverage those lessons learned in the development of new trials down the road. Great comment.

Dr. Kelso?

DR. KELSO: If we are talking about giving

allergy shots to very young children, there really is a -- there's not much data there. I mean, in the real life where many people around this table give allergy shots to patients all day long and see systemic reactions not infrequently, we really rely on the patient saying, you know what? I don't feel so good or I'm pretty itchy.

We rely on that, and we absolutely feel like our intervening and getting epinephrine in that person prevented that from turning into a disaster, and so the lack of a child -- I would be more concerned about that with the subcutaneous immunotherapy than I would with the food allergy challenges, just the fact that by the time a 2-year-old who got an allergy shot, the time that you would see that there was something wrong with that child is almost by definition going to be later than when you were able to intervene in a child who is old enough to say I don't feel good, I'm itchy, I can't breathe, something else.

DR. NELSON: So does that translate into a longer observation period following injection?

DR. APTER: I share your concern. I'm not sure the observation period is the thing. Also worried, as I said, about traumatizing a young child.

DR. NELSON: So it does sound like there should

be some assessment of the tolerability of immunotherapy in this age group since we don't have the data, as one of the factors that you are recommending. I would agree with that.

Dr. Finegold?

DR. FINEGOLD: There's sort of old anecdotal stuff prior to probably 1980s of the old-time allergist who gave young children allergy shots all the time, especially in the New York area, without significant problems that we know of. It's all garbagy data in a way, but it was done.

The other thing is there have been studies -- I think one of them came out of Panama -- where they are injecting 2- and 3-year-olds and don't seem to have particular difficulties, but they are not adequately controlled studies.

DR. APTER: We are talking even younger than that.

DR. DYKEWICZ: And the other question that I would have hearing about stories of the immunotherapy that had been given, what was the dose? Was it something that was really akin to what we are talking about is now more established dosing thresholds, and we may sort of be therefore comparing apples to oranges.

DR. FINEGOLD: Actually Roosevelt Hospital, which

I think did a lot of that, used to make their own extracts, and they were high potency stuff, but not standardized.

DR. NELSON: Are you specifically recommending a phase II type dose ranging study for safety before embarking on some of the more pivotal trials as an approach, since we don't have a lot of data with regards to dose in those younger populations?

DR. DYKEWICZ: That would be a good consideration.

DR. KELSO: The subcutaneous versus sublingual may address a couple of issues. If we take what we already know about the comparison of safety of those two forms of therapy, I think everyone would agree that sublingual immunotherapy is much safer. There is a much lower rate of systemic reactions.

Now whether that translates to infants or not, I don't know, but you would think that it would. That also sort of gets into the tolerability issue of dragging your 1-year-old to get an allergy shot every week versus having them come in and have something put under their tongue. So part of -- the route may matter for several reasons.

DR. NELSON: So it sounds like there isn't that much above the standard of care observation in the conduct of these trials. Certainly, being more cautious in

administration, perhaps doing some dose ranging safety studies, but as far as actual administration of immunotherapy in this group, I'm not hearing a lot in the way of above, say, putting IVs in or doing other things that would be necessary for enrollment in a clinical trial.

Is that a fair statement?

I would probably add a little bit above standard of care in that when we are dealing with very young infants who can't talk about some of their symptoms, we are requiring sequential physical exams and noninvasive evaluations of patients that are periodic is not the standard of care for immunotherapy administration in adults but certainly should be considered in this age group. They are not going to tell you they have a hive underneath their shirt, but perhaps systematic evaluation through physical exam should be a requirement.

Dr. Weber?

DR. WEBER: I think also the suggestion that they be observed a little bit longer than the typical half hour, I think, is a very good one. I would expect that an hour observation for an infant would be appropriate.

DR. NELSON: And I would probably recommend a checklist-driven diary or assessment by parents at night to see what happens at home with these children, because

instead of just relying for passive occurrences to systematically provide a diary checklist for them would be beneficial.

Other comments? Dr. Gill?

DR. GILL: This may be off topic, but we are talking about giving sub-q or sublingual over a prolonged period of time, correct? So I think one thing that you may want to also consider, because questions as an infectious disease physician I get are how does X therapy impact my response to vaccines? So you are overlaying this into a time when infants get all of their primary vaccines, and repeatedly.

So any adverse effects, events, related to that or any modulation of immune response on top of something else you are asking the immune system to do, it may be something at least to consider. How are you going to address going forward that you haven't altered your response to vaccination or, you know, that a vaccine, a live viral vaccine one year, and you're going to give varicella and MMR, is that going to alter your response to immunotherapy? I mean, you have an opportunity I think to address those questions, and anyone who comes forward with a study like this in infants I think should be thinking about those thoughtfully so that they can address that,

either with serum responses to vaccines, or just clinical symptomology and showing that they are the same in two groups, et cetera. Just another complexity. Sorry to add one more.

DR. NELSON: Any final comments? Any closing comments from panel members before we disperse? I personally want to thank all the organizers again and our panel members for their expertise. You really came through with some very difficult questions today, and I again thank those providing public testimony. That was very helpful in our deliberations and for all those in attendance here in the room and on the web, thank you for your patience with us throughout the day.

Dr. Slater, I will turn it over for your final comments before we adjourn.

DR. SLATER: I want to thank you, Dr. Nelson. I want to thank each and every one of the panel members. The comments and the discussion met our expectations, actually exceeded our hopes. This was extremely helpful, and I want to thank you for your hard work today. Thank you very much.

DR. NELSON: Thank you all for joining us. Have a great day.

(Meeting adjourned at 4:10 p.m.)