American College of Gastroenterology Public Workshop
Eosinophilic Esophagitis (EoE):

What are the clinical endpoints for treatment and drug studies?

[Introduction] Good afternoon, thank you for coming. My name is Costa Cofalis. I'm the Chair of the ACG FDA Related Matters Committee. I'm pleased to welcome you all to this workshop placed by the ACG in conjunction with the FDA, on Eosinophilic Esophagitis and outcomes. I'm pleased at this time to introduce the two co- moderators for today's workshop, Dr. Robert Fiorentino. He is a medical team leader at the Division of Gastroenterology and In borne Airs Products and FDA Center for Drug Evaluation and Research. He has been at the FDA since 2004 and has previously worked as a clinical reviewer in The Center For Devices and Radiological Health as well as in The Centre for Biologics Evaluation and Research. He is also board certified in Internal Medicine. From the ACG, our co moderator is Dr. Joel Richter, who currently is Professor of Medicine and Director of the Digestive Disease Center at the University of South Florida in Tampa. It's my pleasure to introduce Dr Richter.

[Dr. Richter] Costas, thank you. So, what we're going to do is we'll have about forty-five minutes of presentations. What we're really wrestling with in these presentations is what should be the end point of therapy? Particularly from FDA standpoint because of the drugs that they're developing but we know most everybody in this room is probably clinicians so I know you're asking that question. Is dysphasia enough to relieve? Or do you want to normalize the esophagus so you don't have to dilate them or do you want to try to get rid of the centafil? So we'll have presentations towards this. Bob will finish up at the end, bringing up some information about an exciting conference they had at the FDA and we're hoping we'll have at least thirty minutes or more of time for questions and answers from the audience.

[Natural History of EoE – Dr. Richter] I'm going to start out talking a little bit about the natural history of the disease. The problem is, this is actually the definition of natural history taken from a couple of dictionaries. "The course of the disease untreated". Another aspect is the natural history of the disease describes the expected course followed by the given disease over time, its characteristic pattern and its time intensity gradient. Having said that once you see a patient, particularly now that we know they have EoE, it's hard to define the natural history but we'll have a little information that will give us an idea what these patients are to expect over time. I've broken this up into what we know about the natural history of EoE in children and adults. It's been known for all long period of time in the pediatric population the children present with a number of presentations. Very early on, they may have failure to thrive and feeding

disorders. In the middle school period of time vomiting, abdominal pain, GERD like symptoms. As they get older into adolescence they may resemble more like what we see in adults with dysphasia and food impaction. This gives you a breakdown of these presentations at The University of Cincinnati Children's Hospital.

I'm going to show you two studies, first is from Jonathan Spergel's group at Chop Hospital in Pennsylvania looking at one to fourteen year follow-up of a group of patients with EoE .You can see there are about three hundred and thirty that were followed for an average of three years and this isn't the natural history because they were treated with the dietary manipulation PPI's and inhaled steroids. Over that period time only eleven patients had complete resolution with no food limitations, so at least in the pediatric population they're always going to have some restrictions of their dietary intake. None evolved into Eosinophilic Gastroenteritis or other Eosinophilic diseases. That's been a fairly consistent finding in the pediatric literature, and it was interesting to note that they had twenty four patients that were lost to follow up..these must've been younger children that were having more urgent GERD abdominal pain and when they presented again for follow up about six years later they were troubled with dysphasia and food impactions. From this, Dr. Spergel hypothesized that maybe you do have a continuum of the disease in the pediatric population, with overtime going from what I like to call an inflammatory disease to a disease that has much more remodeling and much more of a fiber stenotic disease.

The second study is from The University of Cincinnati. It's an interesting study because they went back through the Eosinophilic Esophagitis Database and were able to get a group of patients that they did have follow up for on average of about ten years In this first slide gives you an idea of the patients that they had to control**.** You can see they try to match them for gender and race**.** They had a group of patients with chronic reflux esophagitis with up to ten years follow up or more. Sixteen is the median, and patients with Eosinophilic Esophagitis, they must've been diagnosed when they were quite young because the mean age when they called them back in the survey was twenty two years of age with about fifteen years of follow up. They found that seventy three percent of these patients had symptoms that persisted into adulthood and most of that was from the fiber stenotic disease, particularly food impactions and strictures. Their quality of life was worse than controls but as you'll see from the next slide not any worse than patients with chronic esophagitis which for most gastroenterologists, we don't think is a very morbid disease. Food impactions and dysphasia seem to correlate with the initial peak in eosinophil count and whether or not they had histories of food allergies and atopy. None developed Barretts esophagus, there was one patient had developed a esophageal cancer, but that was a relatively unusual patient that had a lung transplant for reason that I don't know, that had been on suppressant agents. I suspect it was not related to the EoE. This gives you some data from their study. You can see that overall the frequency of dyphasia was fairly similar with their patients with chronic esophagitis versus EoE. However, the EoE patients were more likely to seek medical attention because of dyphasia and though the quality of life of both of these groups

was worse than the normal, as you can see a quality life was essentially the same in the EoE children or in this case young adults verses the patients with chronic esophagitis. This is a particularly interesting slide, looking on the X axis . The total eosinophil count, when they were initially diagnosed to the probability of developing dyphasia and actually some of this has also been replicated in the adult population. Eosinophil feels more like you over time you'll get remodeling-fiber stenotics disease.

Now let's turn to the adult disease because this would suggest the data in these two pediatric studies would suggest that a lot of these children are presenting as adults with EoE's but I think most of us that deal with these patients only about twenty or thirty percent of time can I get a history for my adult patients, that it really went back into childhood so maybe it's two separate diseases or some of them are part of a continuum. This is probably the only true natural history study that we have. This is Alex Straumann's first report in 2003, 30 adults that he followed for about seven and a half years. Supposedly he was treating only with PRN dilations dyphasia symptoms were stable or improved in most of them but seven worsened and you can see that some of these patients required single dilations and occasionally repeat dilations. This was important because this was a small group of patients in Switzerland in a community that he was able to follow these patients fairly easily, fourteen of them had no impact on their quality of life. Fifteen of them did have to do minor dietary changes and there was one gentleman who was a salesman who would travel to actually throughout Europe selling various things, frequently having to go out to various dinners with his customers and as result of his EoE he had to change his profession. Symptoms were most severe in those with blood eosinophilia, or pronounced endoscopic changes. Here again, no malignancies were reported in the seven and a half year of follow up.

This is a slide that looks at two things. It looks at the eosinophil count, shown in the dotted line and though it decreases over time does not seem to go away and then they felt like using whatever questionnaire they were assessing the dysphasia with that it possibly got better a little bit over time. Since being at University of South Florida the past year, Dr. Wirth has recognized this disease since the mid nineteen eighties. His pathologists weren't helping him because they were calling it 'reflux esophogitis' or 'reflux esophagitis' with a lot of eosiniphils. Wirth called this 'congenital esophagil stenosis' and all these patients he had were only treated with PPI in dilations with the goal to get them to seventeen or eighteen millimeters. We went back to look at a series that had follow-up release five years or more and initially on a they required frequent dilations to kind of open them up and then afterwards it was about every other year but the important thing for this presentation we had on average thirteen years were to follow up and we had one patient with twenty four years worth of follow up. Eosinophil counts did not change did not change it all over this period time, they kind of went all over the place. The important things were the patients didn't develop complications, there were five patients had Barrett's Esophagus,

primarily irregular Z-line. None went on to develop dysphasia, none of the patients had esophageal cancer or required esophageal surgery.

So again, I think in the adult population we have two studies now with follow-up on average up to fifteen years showing that the overall their quality of life seems to be good and the fear of developing Barretts Esophagus and a malignancy is really not there with at least up to twenty five years of follow up. Alex wrote a general article in 'The Clinics of North America' a couple years ago and this is kind of a summary of comments and I have a lot of respect for this because working worry was diagnosed in this early. Being in an area where the patients weren't moving in and out, he really does get to know the disease. He thinks is a chronic disease and the patients have had their symptoms for on average about four years before they present for management. It's restricted to the esophagus. He asked the question, is some of this a natural evolution from a childhood disease to the adult disease? Or are there subsets and some present in the adult population with only an inflammatory subset or some present with the fiber stenotic subset. He believes their quality of life is impaired person but most compensate very easily, no increased risk of cancer and he has about two hundred adults with over seventeen years of follow-up so there's no EoE. So this is what we know about 'the natural history' somewhat manipulated you know in the populations but overall it's not a disease that is particularly associated with cancer. It's not a disease associated with developing Barretts Esophagus and I do think that becomes important as we're talking about the long-term therapies and the risk and benefits to the patients and it's a little bit of lead in and everybody could've pulled out the various articles or various cases that they have for their scenario but I just showed this case and it has a little biased towards dilation. It just shows question of what the patient want versus what we want and what the eosinophils are telling us.

Thirty two year old gentleman, has solid food dysphasia, even to the point that he couldn't eat sushi, no problems with liquids, came to attention after having food impaction (some turkey at Thanksgiving) childhood asthma, allergies to shellfish. Intial endoscopy showed twenty to fifty isn't built for HPF. He was on Fluoticasone ,two hundred and twenty micrograms, Avoiding shellfish VI PPI BID . Dysphasia improved markedly to about twice a week in relatively mild while he was on the medication. His eosiniphil count went down but as you can see didn't see it didn't totally go away. Basically, you know at that point in time we were just saying to him, why don't you just take your medication as you need it? Turns out over the next year in two further food impactions and then I ended up seeing this gentleman and he asked me if I had any better ideas and I said sure I've got a better idea..it might hurt a little bit as we do it. We actually had these endoscopic slides available and you see here the classic furrows probably but he actually had a narrow esophagus there was resistance to the passage of a nine millimeter scope and evidence of fibrous rings. Biopsies you know a lot of the eosiniphils and then I treated him just with careful dilation a little bit of discomfort with the dilatation's. He's right now just on PPI just in the morning he's been symptom free for the last two years but the quandary is he feels great

he's not having any problems but you still have eosiniphils and the esophagus which should be the endpoint that we push to. Here's set up this is actually a patient that I had to in Philadelphia and here's how his esophagus looks at this point in time so I'll use that is kind of a controversy bringing out some of the dichotomy between these various endpoints and let me introduce Ikuo Hirano. Everyone knows the excellent work Ikuo's been doing in this area. Ikuo is a professor of medicine at Northwestern Medical School and he will talk to us about symptoms and the issue about symptom relief in these patients.

Symptom Endpoint-What The Patient Wants! (?)
Dr. Ikuo Hirano

[Dr. Hirano] Thank you Joel and I want to thank the ACG and the FDA for organizing this workshops and Dr. Richter for inviting to participate. I've been given the task of discussing symptom endpoints and Eosinophilic Esophagitis. I was given the title 'What The Patient Wants?' You'll see a put a little question mark there because I don't think we always know exactly what the patient wants..I'll allude to that when we get to quality of life. So symptom endpoints and EoE. The questions I'll address why symptoms really matter, what symptom assessment tools are currently available for this disease, what we've learned about symptoms occur randomized controlled trials of esophagitis and finally, is there perhaps something better on the horizon in the symptoms assessment for this disease? So I think when we're looking at outcomes we really need to talk about what are the therapies that we have to offer and although this disease only been around for about fifteen or more years in terms the medical literature it's quite gratifying that we have a whole host of medical, dietary and endoscopic therapies to offer to our patients. One of the gratifying things about taking care of these patients is not only can you make a diagnosis but you can offer them very effective therapy.

Now the importance of endpoints of this disease comes for clinical trials, the primary importance of endpoints but they're other advantages. First of all we can standardize standardize our definitions and terminology of not only investigators but also of clinicians. Endpoints help us to better characterize disease phenotypes in the natural history of the disease and finally endpoints can have applications to clinical practice. When we look at endpoints for this particular disease, which ones do you use? You'll see that a whole host of things we haven't looked at in the medical literature. There are symptoms but as Dr Richter already alluded to the symptoms vary-whether you're a kid or adult.

The kids are presenting with nausea, vomiting, abdominal pain, chest pain .The adults are presenting with dysphasia and food impaction, so if you're going to look at symptoms, you're going to have to design different questionnaires for children and adults. Endoscopic findings, Dr. Dellon will be discussing in detail, so I won't go into that. Histopathology will be the subject of an upcoming lecture this afternoon. Histologic biomarkers of this disease have been looked at

including markers of tissue injury and markers of eosinophil degranilation proteins, but these are not quite ready for prime time use. Finally, we have availability of tests that can measure esophageal structure and function. We have the traditional barium swallow or esophogram. We can look at endoscopic stenography to look at thickness.

What is the purpose of our treatments? What are we really trying to do with all our therapies? The real goal I think of therapy is to prevent disease complication. As Dr. Richter already mentioned I think the ideal outcome of any therapy would be a clinically meaningful reduction in symptoms, normalization of our patients quality of life, prevention of esophageal strictures, avoidance of food impaction and elimination of any risk of a softer esophageal perforation, perhaps the most dreaded complication of this particular disease.

So why do symptoms matter? From the title of my talk, symptoms are what drive patients to see us. It concerns most but not all of our patients are primarily worried about this particular symptom. Other potential bio markers of disease activity such as histopathology, endoscopy, esophageal dispensability, gene expression are currently viewed as intermediate endpoints or biomarkers without a proven role in a natural history of this disease. Symptoms are of course the most readily available and least expensive measure of therapeutic response that we have. Now the question is, are symptoms the only factor that really concerns our patient? This was looked at by a clinical psychologist in our group, Tiffany Taft. She was doing interviews with our patients in EoE, these are all adult patients, and ask them about quality of life trying to develop the quality of life instruments, a specific quality of life instrument, and she identified that adult patients had five separate domains of altered quality of life in EoE. The first domain was impact on eating and dietary habits. Patients often felt that they had to be cautious about eating or spent a lot of time thinking about food or planning meals.

There is a social impact of this disease. Patients were often embarrassed by the choking episodes. As you know, many times these dysphasia or food impaction episodes occur when you're eating out that's why it gets the name ‘steakhouse syndrome’. One of my patience a young woman and people thought she was bulimic because she kept leaving the table to go vomit in the bathroom every time she had a food impaction, so many people thought she had bulimia. Emotional impact, patients report that EoE can be a stressful disease that makes their life less enjoyable. There is disease anxiety, patients worry about their disease as well as long-term consequences of a long-term therapy and there’s anxiety because this is the new disease. Many times patients will ask you questions and you won’t know the answer because there is not a lot of medical literature to back up our statements.

Finally, there’s the domain of choking. In the terms of how common are these impacts on quality of life? These are some the domains. It turns out that the majority of patients had these concerns, concerns for taking medications for my life .Over fifty percent the centers of disease could

worsen over time over fifty percent. Fear or panic during dyphasia episodes, over fifty percent. This embarrassment or social distress, seen in over sixty percent. An alteration in eating habits which could be something as simple as having extra water during meals, chew your food extra carefully. Two extremes were patients who were avoiding meat before their goals from their diet were seen in over eighty percent of patients.So, I think it's important because these aspects of life are not really directly assessed by current systems of assessment, which for the most part is are you having trouble swallowing or not, and patient concerns and dietary modification behavior are important consideration when looking at outcomes for this disease.

The second question is, what system assessment tools are available? This is a laundry list.. I heard Brad Conway tell me he's going to have available the slides from this handout from this session, so they will be available to you after the session. There are a number of system assessment tools that happen; you'll look out for this particular disease. I'm not going to go through every one of these but I'll touch on some of the major symptom assessment tools that have been used.

The first one is the SST or symptom scoring tool that was developing at UCSD. This is the pediatrics assessment tool, so you see the questions here pertain to kids, not to adults. They're asking about heartburn symptoms, regurgitation, abdominal pain, nausea, vomiting awakening at night with belly pain, and an interesting symptom of blood in her rectum, which I didn't realize was a symptom in kids with EoE. They also asked about dyphasia odynophasia difficulties for swallowing both liquids and solids. So this was the simple question that they developed the maximum point score was fourteen and they use this SST, symptom assessment tool for the randomized controlled trial of oralfiscus that was published in gastroenterology. Again, pediatric study, twenty four children randomized to either get or placebo for period of three months and as you can see here is that the histologic response was quite robust. Here's the eosinophil counts before the orificousbendeconide going down to five with the active drug. With placebo, no change in the degree. Tracking along very nicely with the esophageal resolution were symptoms of improvement, one month, two month, to three months they showed a significant improvement in the SST symptom score. The symptom fell from three point five to one point two with active treatment and two point seven one point eight it with placebo. So again, significant reduction of the drug but not with placebo. However, there are some limitations. The SST has not been validated. The timeframe for recall was not specified this is really not a patient reported outcome because the questions are provided by a provider or a patient's surrogate, most often their parents, provided the answers to the questions. Another symptom assessment tool has been the has been DAT or dysphasia assessment tool that was developed by Alex Straumann from Switzerland, one of the first people to describe on Eosinophilic Esophagitis and the DAT consists of only two questions. You ask about the frequency of dysphasia, how often have trouble swallowing and the intensity. What do you do when the dysphasia occurs? Do you just have to swallow some water? Or, do you actually have to regurgitate the food? Or, do you have

to undergo an endoscopic food dis impaction? Scores range from zero to nine and for their clinical trial that the clinical response was defined by a decrease in to the DAT by three points or more.

The data from Alex Straumann and randomized control trial again published in gastroenterology so this is an adult study that was a published in gastro. Thirty six adults with EoE, randomized, either got placebo or budesconide by swallowed nebulized formulation for fifteen days only, so not three months like the pediatric study only for fifteen days and very similar to the pediatric study, marked reduction in degree of esophogenaphilia, with active drug going from sixty two to four EoE's. Placebo, no change in the degree of eosophogenaphilia and along with this histologic response that showed a reduction in the DAT score, significant reduction with active drug, change with placerbo. Now, limitation to the DAT, it's again not a validated instrument. The real clinical significance of this three point drop in scores is really not clear. Now the NDQ ,MAYO dysphasia questionnaire 30 is one of the few validated instruments for the assessment dysphasia. I know Romero is sitting in the front row, so she'll probably harass me about presenting this. But this is one of the few validating assessments that we have for evaluating the presence of dysphasia.

As you can see, they are a whole host of questions in the NDQ-30. It's quite a comprehensive look at dysphasia and what's nice about this particular instrument is it's not just asking about the frequency or severity of your trouble swallowing but it gets into the food avoidance behavior. So, you're asking about food textures are you having trouble with apples or bananas or oatmeal ground meat or bread or steak or chicken? So you're getting at some of this question about how patient's modified their food or even avoid food. The NDQ has not been evaluated for on Eosinophilic Esophagitis and this concept of a thirty day recall does have practical limitations. I know sometimes I have trouble remembering what I had for dinner last night. Ask me how many times I've had dysphasia over the past month, I probably would be inaccurate about that. So nevertheless, the NDQ-30 was applied to a randomized controlled trial published by Jeff Alexander for Mayo Clinic, looking at forty two adult patients with EoE, randomized to either get high dose fluticasone, eight hundred eight microgram, that's four pops twice daily or placebo for a period of six weeks and very similar to the bedeconide study showed a marked reduction in the degree of esphogilinaphilia. Seventy one percent of patience achieved their endpoint with fluticasone, only ten percent with placebo. The problem with this particular study that they highlighted was that their symptom response was that there was not a significant difference between placebo and after drug. Seventy one percent of patients with fluticasone had a symptom response and forty eight percent of patients with placebo, no statistical difference between placebo and active drug in terms of simple resolution. So this gets at this question of what have we really learned about symptoms from randomized controlled trials in this study? What I've done here is summarized six of the randomized controlled trials with on Eosinophilic Esophagitis.

You'll see the author of the study on the far left, what treatment they used, most of these are topical steroid preparations. There's one biological agent therapy in this pediatrics study. The number of patients in the studies listed here along with whether it's a pediatric or an adult study. Across the board all six studies of randomized control studies have shown a robust reduction in the degree of a eosphagenophilia. All of these have met their primary endpoint of this histologic improvement in the degree of the esophageal formation. The problem has been symptoms of half of the studies have shown symptom improvement this one only shown a partial improvement half of them did not show some improvement compared to placebo. So this highlights a significant association between symptoms histopathology in the assessment EoE activity. So why is this happening? Why are we see this association between symptoms and histopathology? This may be because every one of those studies has used a different recording instrument. As you can see many of them are invalidated instruments. The ones that were validated had a long recall period. There's a difference in how you rate the frequency or intensity of episodes dysphasia, whether your recording symptoms on a daily weekly or monthly basis. You have to account for the food avoidance behavior and dietary modification, and the addition of these weakly associated symptoms, if your asking about blood in the stool, or nausea, or vomiting in addition dyphasia you might be diluting your ability to detect your primary effectiveness with dysphasia.

Patient's selection can be an issue and I think another thing that's been highlighted is a high placebo response, which was quite surprising to me in this disease I thought there'd be a very little placebo response for dyphasia but it's become quite apparent in every year we studied itthat there's a high placebo response in terms of symptoms. This may be because the inclusion of patients with mild symptoms, patients will cope. They'll adapt by chewing more carefully, avoiding foods and they will feel better because of dietary modification. Other potential reasons for this difference, the formulation of steroids administration Fluticasone or Budesonide, with an oral suspension neubulized formulation, whether the study was adult or pediatric and how long you treat maybe another impact in terms of demonstrating symptom response. What I think is perhaps the most important reason why we certainly see this association, particularly in adult studies is fibrous stenosis. The fiber stenotic complications of this disease may not respond respond as quickly or as completely with medical or dietary therapy as we see the histopathology improve.

So, putting together this four by four, two by two table rather, we're looking at the response to treatment. Whether symptoms persist or symptoms go into remission and whether histology is active or inactive after our treatment. I think we all agree if patient feels better and there histology is normalized, this patient would be a responder. Likewise, persistent symptoms, histology's active, this will be a non responder. However, symptoms persist with the histopathology inactive. Symptoms may be driven by fiber stenosis, in other words the patient may have strictures in their disease and that may account for their symptoms in spite of inactive histopathology.

And finally, what about their histology being active but symptoms are better .This could be a placebo response, this could be the fact that they have modified their diet or could be again the idea of fiber stenosis. If you dialate the patients esophagus like Dr. Richter does, the patient will feel better when you've done nothing to their histopatholgy. So fiannly, is there anything better on the horizon, and fortunately the answer is yes.

One of the best tools that I've seen developed is to DSQ, this is an electronic Palm Pilot or iPhone type device that prompts the patient on a daily basis to record their symptoms. So I think you have less recall problems if you're asked to record your symptoms on a daily basis. The little device will beep and alert you at the end of the day and ask you only three questions. Did you have any solid food today? Getting at the idea food avoidance behavior.. Did you have any dysphasia today? Yes or no and if you had dysphasia, what did you do about it? Did you have to click, did you have to gag a little bit. Did you have to vomit the food or did you have to seek medical attention for a food impaction? Another system assessment tool that's in the works right now is the so-called PEESS, this is developed by Cincinnati Children's Hospital, is currently undergoing validation, as part of a national registry called rigid you can learn more about this by going to rigid.com, from the Cincinnati's childrens. Another symptom assessment group that's also in development is EEsAI activity index, being developed by Alex Straumann from Switzerland. What's nice about the EEsAI is a modular design activity index and incorporates not just patients reported outcomes but also endoscopic characteristics, histopathology, biomarkers of disease activity, physician questionnaire and quality of life, to give you an overall activity of the patients disease. The adult form EEsAI is currently in phase two and should be ready hopefully with the next few months pediatric form is in its early phase two development. So, just to conclude, symptom point and EoE. Symptoms are important but patients also care about their quality of life this fear about disease progression over time. There are several PRO's that have been using multiple studies but most have not been validated. The randomized controlled trials have demonstrated the importance of a placebo response in this disease and the existence of significant association between symptoms and histopathology, and finally, the DSQ, PEESS, and EEsAI are novel tools being validated for EoE, both in kids and adults. Thank you very much.

Role of Endoscopy in Treating EoE
Dr. Evan S. Dellon

Ikuo, thank you. Our next speaker is Dr. Evan Dellon. He is an assistant professor of medicine at the University of North Carolina. Evan's going to talk to us about the endoscopic endpoints in on Eosinophilic Esophagitis.

[Dr. Evan S. Dellon] I'd also like to thank the ACG and the FDA for organizing this event for Joel for inviting me to talk. My topic is to take the next step after symptoms and talk about the role of endoscopy and possible outcome in EoE.

To get started I want to just put out there, what is the role of endoscopy in this condition? When you think about it there is actually several things that we doin EoE with endoscopy. First of all, we use it for diagnosis so we characterize the endoscopic findings, we assess complications, such as strictures or narrow esophagus, and of course we obtain biopsies. We use endoscopies for treatment, we will food bolus impaction and we will perform endoscopic dilation. We also use it often for monitoring treatment response, either with dietary or medical therapy. The real question is is can you use as an outcome or an endpoint for clinical trials. So I'm going to talk today about first off the endoscopic findings of EoE. What are they? So we're all talking about the same thing. Then talk about the prevalence and sensitivity and specificity of predictive values how reliable are these when you actually look at the data and then talk about a new scoring system to see if we can improve how we characterize the symptoms, and then I'll spend a little bit of time talking about the diagnostic techniques specifically biopsy and functional luminal imaging.

So, let's talk about the endoscopic findings of EoE. These are the esophageal rings right? It's not so easy to make EoE jokes but I try. So, these are called your typical pictures for my practice esophageal rings and narrowing and what you'll be struck by is that this is huge variation in what you see and in the top left, this is more of a classic picture that were familiar with . Almost a fixed esophageal ring, relatively narrow caliber esophagus. This is a picture of what would be termed filization of the esophagus, so these rings are transient. If you fully insufflate the esophagus these will disappear, so that's another manifestation that may not always be obvious. This is a patient with very subtle rings, and these are three patients with very narrow caliber lumens the adult endoscope won't not pass theses areas stricture and this is one where even a pediatric endoscope won't pass, it's so tight. There's a wide variety of rings that we see in this condition. These are examples of linear frozen plaques in the esophagus so you can see these crevices or train track appearances running parallel to the long axis of the esophagus in all these patients and you see a new degree of white plaxi; from very severe to more mild here and you can imagine this might be confused with candilesphoghitits. This is a patient I only saw a few months ago but the brushing were all negative for Canada as were the biopsies. The other thing you can notice which is a more subtle finding is that all of these images, the esophaghil mucosa has lost the normal vasculartur e . Its congested, it's endeminous appearing, this can often be a subtle sign of EoE that we may not be always reported. Lastly, these are examples of what's called crate paper mucosa, the EoE is very fragile and you might pass the scope and appreciate resistance or sometimes not appreciate any resistance and as you come back into the esophagus you get cardiff when you see these hug rips running down the long axis of the esophagus this is a very typical hallmark of EoE.

Now, can the esophagus look like this? Can it be normal in EoE? I'll show you some data I think as we're getting more and more familiar with the conditions as we're using scopes with higher resolution and better optics were seeing less and less patience with a completely normal appearing esophagus in the EoE but it can still happen and if you have a high clinical suspicion you'll never make a diagnosis without doing biopsies. Now, getting towards the end points these endoscopic findings improve and these are some examples of patients who were treated with topical steroids in a trial that I did and you can see before topical steroids, everybody has very clear prominent findings in many cases a mix of multiple findings, and after topical steroids on it looks close to normal not completely normal for all of them but very close to normal. These are pictures the Northwestern group showing similar improvements with dietary therapy before diet elimination, very nice improvement after dietary elimination although not completely normal in all cases and in recurrent symptoms after reintroduction. So, you can see very clearly how things go back and forth.

So how come they are these findings? If you read the articles and if you talk to people who do this you think that all these findings are present every single patient that are universal. It turns out that's actually not the case. This is a study that I did with Hannah Kim, who was one of our student research fellows and she did a systematic review the analysis from a hundred articles in its tracks more than forty six hundred EoE patients and twenty seven hundred controls. Now, as you can imagine there was a huge amount of heterogeneity in all these studies and how they were conducted and in the time frame over which they were conducted, but I think that the information is still very useful. This is a summary of some of the main findings. Just direct your attention to the first row to start. These are columns with seven different findings, rings and strictures, narrow caliber of plaques decrease vascularity and normal esophagus and as you can see, for any individual finding it's not all universal and the prevalence of some of them are actually quite low. However, only seventeen percent of all subjects in these studies had a pool prevalence of seventy percent that was for a normal endoscopy, so the majority of people had at least one abnormality. Now because these studies were so heterogeneous in different populations we broke it down and look that different sub groups from the study and there were differences between adults and children, esophageal rings were more common in adults than children possibly indicating as you've heard before that as you get older you have more fibrotic complications. Strictures were more common in adults versus children. White plaques and decreased vascularity , more inflammatory appearance was more common in children. Also, when you've broken up by retrospective versus prospective studies findings were more common in perspectives studies. Well, why is that? Well, most prospective studies have a clear protocol your tracking what's going on at the time that the endoscopy rather than rely on a report that was done ten years ago and so it's not surprising that the findings were more common in prospective study actually found only seven percent of patients in a prospective study would have had a normal endoscopy. So, the prevalence of findings are not universal but still very common for at least one finding.

Now, what about the sensitivity and specificity of the endoscopic findings? Well, it turns out the findings unfortunately are not specific. Most of the studies that looked at endoscopic findings compared the findings to control group with patients with GERD and for the main findings here the sensitivity is actually pretty low. The specificity's are actually a little bit better but when you again look at any abnormal endoscopy, the sensitivity improves quite a bit.

What about the predicted value? So, if you see a finding, what's the likelihood that they are actually going to have EoE? So, the predicted values are pretty moderate, sixty to seventy to eighty percent predictive value is not good enough to use endoscopy alone as a diagnostic test in EoE. Switching perspectives a little bit, what about the reliability endoscopic findings. What that means is, if I see of this certain endoscopic findings how likely is Dr. Hurano or Dr. Richter have the same findings? This is a study that we do one of our GI fellows Ann Perry, and we set an atlas of thirty five endoscopic images out to a large number of gastroenterologists, if any of you got this, thank you for filling it out a couple years ago. We looked first at inter observer reliability, how well did those gastroenterologist fill out the survey agree with themselves? The way you measure this is with cappa and just as a reminder this is a measure of agreement between observers zero is what you'd expect by chance or a coin flip. One would be perfect agreement and then there's a range of values in the middle and so overall these levels of agreement for these findings were fair to sort of good, not great. Not great inter observer reliability, even for something like rings. You would think everybody would fine. We also look to intra observer reliability, so how likely am I to call something a ring then two weeks later call a ring again and this is very interesting. The inter observer reliabilities were relatively spread out and could be quite poor, particularly for plaques are people who are very bad. They will call it plaques one time and look again and not call it plaques. So, with still images at least the reliability is sort of middling.

Now Dr Hurano and his group just published an endoscopic assessment looking at a new scoring system and try to classify the endoscopic findings in a way that would be more reliable. They did this by showing people actual the video footage of an endoscopy, rather than still images with a thought that that would be more accurate. What they came up with was the EoE endoscopic reference score or the Erefs score and so its the abbreviation Endoscopic Reference Score but also conveniently highlights the endoscopic features that are included in this score. Exudates, rings, edema, furrows, and strictures. So, this comes with an atlas that you can download and take a look. I've summarized here and basically for every finding you have a score and so you could have exudates that involve less than ten percent or more than ten percent of the esophagus. You have rings that can be very mild or subtle, rings that are more prominent that allow passage of a regular upper scope and rings that are more severe are an adult upper scope that will pass. Edema, or decreased vascularity normal verses decreased. Furrows, mild furrows without much depth or severe furrows with cleared depth and indentation of the esophageal mucosa and strictures and if they're there, you would estimate the luminal diameter.

So they went ahead and also looked at cappa scores agreement and reliability endoscopists, and they got mostly results in the good range. Still, not perfect, but possibly slightly better than what we found with the still images and this provides a very nice starting place to try to standardize the reporting endoscopic findings in EoE.

I'll give you an example of how this might work. So this is before treatment and if I have this totally wrong to let me know. So, this is a patient before treatment and you would look at this finding in your endoscopy and say well they've got some mild exudates in less than ten percent of the surface. The rings are prominent but this scope passes. There's decrease vascularity in edema. There are some mild furrows without severe amount of depth. There's no clear focal stricture, so we have a total Eref score of five and you can actually have these five different sub scores as well. Then you have an after treatment, you go back and you don't see any findings of all and so the total score has improved to zero and all the sub scores have improved as well. So, this is one way we can see this might be very useful in a clinical trial we can get very granular detail about the endoscopic findings rather than relying on rings yes or no which might not be good or global improvement score.

So switching gears a little bit let's talk about diagnostic techniques using the endoscope and the main diagnostic technique that people are going to use of courses is biopsy. This is a quote from the most recent consensus guidelines for diagnosis and treatment of EoE and it says endoscopy remains the only reliable diagnostic test for EoE and the authors recommend two to four mucosal biopsies of both the proximal esophageal to maximize diagnostic sensitivity. I want to unpack this statement a little bit for you.

The first things to realize is esophageal biopsies are really small. I'll illustrate this with a simple schematic but this is if this is..your esophagus is a tube , maybe twenty centimeters long with the two centimeter diameter. You open it, it's got about a surface area of say a hundred twenty thousand square milometers. Well, the service area of a biopsy might only be three millimeters so when you take one biopsy, your sampling a tiny tiny fraction of the esophageal mucosa.

This is important because EoE is patchy, it's not uniformly distributed throughout the esophagus and this one patient that I have demonstrates this. This is a high powered fuel from one of his biopsies, where you see the esophageal mucosa and it looks relatively normally. You can't really find any eosinophils there. This is an adjacent high power fuel in the same biopsy, that's just full of eosniphils and this kind of finding is not uncommon and so you have to be careful in how you are sampling the esophagus and make sure you sampled enough. A couple other studies to point out I think are pretty interesting that kind of demonstrate this. This is a really interesting report from the Utah group, where they were fortunate I guess is one word but anyway they had a esophagectory patient who had on Eosinophilic Esophagitis. The patient obviously was very fortunate, and what they were able to do is a very careful detailed histologic assessment where

they sectioned the esophagus circumferentially and counted high power fields longitudinally around the entire length of the esophagus. What this shows is they tracked eosinophil density over here, this is the count for high power field and this is the actual density by millimeters and these are all the different sites. As you can see, every high power field they look at, there's a huge variation and even adjacent sites have a lot of variation. So, similar to the patient I saw and interestingly they found that only eighteen percent of the whole surface of the esophagus had more than fifteen eosinophils. So, if you do the math, you would need maybe nine biopsies to make the diagnosis in this patient. So this was one patient with a lot of high power fields. This is some data that I presented last year at EDW of twenty five patients before treatment in a randomized trial and what we did was we analyze every single high powered field was examined for those patients, a total of more than five hundred high powered fields.

What this shows you is the proportion of all the high power fields this is the eosinophil count so what you can see here is that this is the cutoff for fifty EoE's, only a third or so of high power fields have more than fifteen EoE's for high power field. We stratified here in different colors and just the location of the biopsies and regardless of where you biopsied in the esophagus, this variation were seen. So, whereas the autopsy study suggests the case of one patient this suggests is the case in many more patients. We also have data from others to support this one is from a study by Dr Gonsalvas, who looks at eosinophil count variation, proximal versus distal esophagus, and what you'll see is the patients with very low counts of proximal and higher counts of distal and conversely look counts in the distal and high counts in the proximal. This is like a needle in haystack graph that I made from a predizone versus fluticasone but if this is the around the cutoff of fifteen EoE's, it makes the same point.

Some people have high counts in the mid and low in the distal and vice versa. So, there's a lot of variation in the eosinophil counts. How many biopsies do you take? Well, again Dr. Gonsalvas had a very nice study where they went back and looked at all the biopsies taken and asked the question, well if you have one biopsy was likelihood of making diagnosis? So on the Y axis the percentage of biopsies, if you are just taking one biopsy you might make the diagnosis in fifty fifty five percent of the time. But as you increase the number of biopsies, you increase your diagnostic sensitivity and when you're up to about five, your up to above ninety five percent chance of making the diagnosis. So this is some of the data that informs that recommendation to take a lot of biopsies from a couple different places. Well, what can we do with endoscopy that's beyond biopsy? I'd like to briefly mention the functional luminal imaging technique and this way that you can assess esophageal dispensability in compliance during endoscopy. What this is is a ballon that you insert and you follow step wise inflation protocol and the balloon assesses tthe compliance of the esophagus by measuring the cross sectional area along the whole length of the esophagus.So,m this is an example of some of the images from this paper, this paper is also from Dr. Hurano's group at Northwestern. What you can see for a normal person is you get image of the esophagus that looks relatively open, like a tube and this is a graph of the pressure inside this

balloon versus the cross sectional area in the esophagus. As you increase the pressure the esophagus just stands in the area and increases. It's a compliant tube. In EoE patient visually you can see that there's narrowing but as you increase the pressure in this patient after a certain point the area doesn't increase anymore. You get to this plateau, this dispensability plateau, showing that the esophagus is not compliant, it's fibrotic and it's stiff. The group presented some nice data on using this to assess treatment response a couple years ago DDW as a pilot study and what they did was they had a group of patients and after treatment they said were they responding or did they have less than fifty EoE's, did not respond to treatment. For the group that did not respond to treatment and had persistent eosinophilia, you can see that the dispensability plateau, where that curve flattens out is the same before and after treatment. But for the group of patients who had a nice response, that curve improved nicely. They got more compliant in the esophagus so I think there may be a possible role of this technology for an objective quantification of how compliant the esophagus is for monitoring therapeutic response. So to sum up, classic endoscopic findings of the EoE are frequently present but these are not highly sensitive or particularly specific and in isolation cannot be used to diagnose EoE. The reliability endoscopic findings are fair to good but I think the Eref's classification will likely improve this and Eref's is currently being evaluated as a potential endoscopic outcome for treatment of EoE, it's one of the modules in the activity index. The functional assessment of the esophagus is promising but the role of this endoscopic outcome is yet to be determined. Thank you very much.

Evan, thank you. Our next speaker, we're going to Ikuo to do two talks for us. Dr. Gonsalves unfortunately got the viral syndrome her children were having, so this morning before flying over. So she's not going to be able to be with us. So, he'll go over the histologic endpoints of EoE.

Eosinophil Count and Criteria for EoE
By Dr. Nirmala Gonsalves * talk given by Dr. Ikuo Hirano*

[Dr.Hirano]- Sorry you have to listen to me again. I got a panic call from my colleague at about six o'clock this morning saying that she wasn't able to make it because of severe gastroenteritis. Too bad she wasn't at this meeting; she would've had a lot of doctors taking care of her. So, we'll be looking at histologic endpoints and disease. The question that's coming up is, why should we include histopathology as an important outcome of therapy in EoE? We'll get to the point that histology, of course, is an essential part of the diagnosis. You can't have Eoe without eosinophil. Eosinophil esophaghitis is a disease of mucosal inflammation, and a third point is that mucosal inflammation is associated with important clinical outcomes, the development of fibrosis for modeling and symptoms of EoE have been linked with a degree eosinophilia. We'll go through some some of the data for that.

First, the diagnosis of EoE. This is the consensus recommendation definition Esoinophil Esophaghitis, published in the Journal of Allergy Clinic in 2011. EoE has been defined as a clinical- pathologic disease with symptoms related to esophageal dysfunction for the adult patients that dysphasia, food impaction. Pathologically,one or more biopsy specimens must show eosinophil predominant information. This eosinophil predominant information is characterized by greater than or equal to fifty eosinophils for high power field, that's a peak value, not a mean value and that's considered a minimum threshold for the diagnosis. EoE needs to be confined to the esophagus, you don't want a patient with eosinophil gastroenteritis or eosinophil interius. It needs to be isolated to the esophagus. You need to rule out other causes EoE . The most important one there is gastro reflux disease and finally, as Evan nicely showed, you need multiple biopsies to be obtained and evaluated for all the pathological features EoE.

Now where did this statement come from? Given this recommendation statement it actually brought together thirty three adult and pediatric gastroenterolgist together with immunologists' pathologists and researchers looking at the evidence base in the literature and also based on expert opinion. So what is the evidence that EoE casuses inflammation? This is the typical biopsy in EoE. What we're seeing is not just a degree of esophageal eosinophilia but we're seeing other characteristics of mucosal inflammation. You'll notice here that the eosinophils are clustered at the superficial layering shown here. You're seeing eosinophil micro formation which is defined by a cluster of four eosinophils or more in one particular area deceased. You're seeing spongiosis, since many of us noticed that gastro-reflux, dilated inter cellular spaces. The little gaps being created between the cellular junction's reflecting a spongiosis or leaking membrane. Finally, epithelial hyperplasia, also known as basal zone hyperplasia which is this dramatic increase in the degree of basal zone extending up to the upper margins of the between them other has lots more pursuit and the city include the graduation here's the essentials of the epithelial. Other histologic markers that can be seen include degranulation, having released there proteins into the intercellular space. Also, lamina propria fibrosis that is collagen deposition in the sub epithelial space as shown here. The importance of this is that eosinophils are normally not present in the esophagus, unlike all the other parts of the GI tract where you can find eosinophils including the stomach, the small bowel on the colon. The esophagus is normally devoid of any eosinophils, so finding EoE in the esophagus is typically a hallmark of some disease state.

What does eosinophil do when its activated by allergens or other stimulation through cytokines from other cells? It releases eosinophil granule protein that essential protein. Eosinophil derived neurotoxins, cationic protein, perioxidase. It releases cytokins, arachiodonic acid products, and also neurotransmitters that can have effect on gut function. This slide highlights some of the effects of these release of cytokines and mediators from the Eosinophil. At the center of the action here releasing the granulation proteins here. Some of the proteins such as TGF beta have effects, hyperplasia. Other granulation proteins can affect sub epithelial fibrosis. Other factors

can cause muscle reactivity or a high contractility, resulting in motility effects and there can be model effects on remodeling, including vascular remodeling within the esophagus.

So moving on to the third point which is that mucosal inflammation is associated with important clinical outcomes. What is the data here? This is a study done by Aceves from UCS looking at subepithelial fibrosis in children with EoE. What Dr. Aceves demonstrated is that over ninety percent of her children with EoE had evidence on biopsy of subepithelial fibrosis or collagen deposition shown here. If you did this fibrosis score, you could actually distinguish healthy controls from reflux patients by the degree of subepithelial fibrosisal . So the degree of fibrosis tracks pretty well with the degree of esophageniphila. A similar study done by the Mount Sinai Group Dr. Cherhade,again a pediatric cohort. Looking at, again this question of subepithelial fibrosis, markedly increased in EoE compared to patients with EoG , reflux disease or healthy controls were a substantial proportion the majority of the children had supper subepithelial fibrosis in contrast to patients with reflux disease.

What about the correlation between symptoms and histopathology? I think this is nicely shown in randomized controlled studies this is the study done from The Cincinnati Group, again a pediatric cohort using topical Fluticasone. This is the eosinophil counts before and after therapy with topical Fluticasone, from the proximal esophagus in the top end of the panel and the diastal esophagus at the bottom hand of the panel. So in this particular experience, using a low dose of topical Fluticasone, not every child improved as you can see some of the patients had marked improvement in histopathology, where other kids did not improve. Likewise, in the distal esophagus some of the biopsies improved and other patients did not improve their histopathology and interestingly, the symptoms, particularly of nausea, tracked with the histopathology. The patients that had their nausea improve had histologic resolution. The children who did not have their nausa improve did not persist. Another example of this tracking of histopathologies is again the UCSD Group experience of randomized controlled trial of OVB. Here you're seeing the eosinophil going from their baseline and after therapy and with a placebo, no change in the degree of eosophageniphila and tracking very nicely with the degree EoE since was an improvement in symptoms in these children with EoE. At month one, month two one, and month three where there is no change in the symptoms in the pediatric patients given the placebo. In the dietary elimination study done by my colleague, Dr. Gonsalves. Here's the biopsy results for the proximal esophagus and distal esophagus before and after the six food elimation diet, we see marked improvement in the degree of esophageal eosinophilia, both in the proximal and distal esophagus. Here's proximal and here's the distal esophagus and tracking again very nicely with the improvement in esophageal eosinophila was a marked reduction in symptoms of dysphasia. We use the strongest dyphasia with a DAT scoring system and you see that almost every patient had improvement in dysphasia. All but one penatient had improvement in dysphasia. We get the patient to go in for histologic remission and then we add that the food is introduced every two weeks. With return of the trigger food they have returned other symptoms, return of the

endoscopic findings and return of the esophageal eosiniphilia. With the reintroduction of the trigger foods.

Finally, there has been identification of a correlation between therapeutic response in the resolution of subepithelial fibrosis. This is work done again by the Mount Sinai Group, pediatric cohort, looking at histologic response in terms of the steroid therapy or dietary therapy improvement in the degree of esophageal eosinophila that track fairly well with improvement in sub epithelial fibrosis. Interestingly, what they're demonstrating is that you can improve not just the eosinophila but you can improve sub epithelial fibrosis and remodeling changes in a subset of patients with esophageal eosinphighitits nicely shown in this slide is two different patients for EoE. All this blue is showing the collagen deposition in the sub epithelial space and after treatment with topical steroids marked improvement in the degree of sub epithelial fibrosis.

So, is it important to get rid of the eosinophils in the treatment of EoE? The answer seems to be yes. There are of course limitations in histopathology, as Dr Dowling nicely showed their limitations in how we evaluate the surface area of the esophagus. EoE is a patchy disease, you have to take multiple biopsies to adequately assess the degree of inflammation. Inflammtion may be present despite the lack of eosinophils and the fiber stenotic the changes may not reverse as readily as mucosal inflammation. I'll show you some of the information, Evan already showed this slide. Again making the point that you want to take at least five to six biopsies to make an accurate diagnosis because EoE is a patchy disease. This has been shown both to adult and pediatric cohort. Now this is an interesting study done by Glen Frereda in Colorado, it which this patient had sub threshold eosinophila. They thought this they patient had EoE but the number of EoE's was less than fifteen for high power fields. If you look at this biopsy, it shows you basel aone hyperplasia, tissue injury effects but they're really very few or no eosinophils on this biopsy specimen. However, when they did a special stain for an eosinophil granulation protein peroxidase, it showed marked activity of the eosinophils. So, it may not be as important what the number of eosinophils is to what the esinophils are doing. If they're all very active in the granulating of proteins that may be as important as a quantitative number of eosinophils.

Finally, the idea of fiber stenosis. Here's a patient who has been treated with topical steroids, biopsies have normalized but this patient still has dysphasia. They've got a high grade stricture.The biopsies have gotten better but the patient doesn't feel better and they still have a high grade stricture restriction in the esophagus. That's again because the fiber stenotic complication may not reverse as quickly or as completely as we can reverse the inflammation of the aforementioned esophagus. So again, should we include histopathology as an important endpoint? I think the answer is yes. Histology is an important part of a diagnosis. EoE is a disease of mucosal inflammation and mucosal inflammation has been associated with important clinical outcomes in terms of fibrosis, remodeling and symptoms. Thank you very much.

Review of FDA EoE Workshop (Sept 2012)
Dr. Robert Fiorentino

Dr. Fiorentino is now going to go over with us a recent panel that they had at the FDA and then I hope we'll have about ten to fifteen minutes worth of time for questions

[Dr. Fiorentino]- Well thank you to the ACG for reaching out to us and inviting us to join this discussion. Our interactions have always been very fruitful. I should say before I begin that the views expressed in my presentation of those of myself and not necessarily those of the FDA.

The FDA has taken a, more recently has taken an increased attention and has devoted more resources to ensuring that the end points that are used in clinical trials are objective and really are measuring what they intend to measure. We have an entire division that study endpoints and labeling team that actually works with manufacturers and sponsors to validate their endpoints. So when EoE started to come across our radar very recently, we noticed that there was no really accepted and validated endpoint, and that in a lot of ways they would have to start from scratch. So we'd look at these symptoms scales and the disease activity that had been discussed and as Dr. Hurano pointed out there were no scales that we can really accept as a valid endpoint to base an approval of a drug on. So this was not a unique problem to EoE as you know we have other symptoms scales and activity indices that we have used to approve drugs, such as the Mayo Score and the CDAI for Crohn's, which themselves are more activity indicies and are not really validated or had not been validated as clinical endpoints. So we decided to have this workshop and the great name means gastroenterology regulatory endpoints and advancing therapeutics, so it was a fabricated name but we we also have had all day workshop on EoE but we also had a workshop on colitis in adults from IBD in Pediatrics. We had a fourth day for parental nutrition associated liver disease, all diseases that had not had a valid endpoint developed. So, we really wanted to get together all the stakeholders to discuss how we together can move forward and identify really clinically meaningful patient outcomes and clinical assessments. This was not really intended as an advisory committee where we sought input then would somehow come to a determination of the path forward. We really wanted to involve everyone and you can see we had number of participants from the FDA for this meeting. We had on some very candid presentations from industry that was extremely helpful. We had, obviously, academia involved a number of experts in the field and we had a patient representative all contribute to an all day discussion. This occurred on September nineteenth, so only about four weeks ago. I apologize if I haven't distilled out everything from the meeting. So for this talk I want to give an outline on from a regulatory perspective on the level of evidence that's required to support drug approval, for people to keep in mind as we hopefully get the drugs approved for EoE. We can also discuss requirement for what we call clinically meaningful endpoints. I want go over the role of surrogate endpoint of drug approval and its relevance to EoE because of think EoE gives a really

good example of how surrogates can be used under the regulations. Finally, I want to give some take away points from the great meeting at the end.

Fifty years ago this month there were two very important events that forever shaped the course of American lives one was the Cuban missile crisis but a week before on a lighter note the Kieth Harris amendment was signed by John F Kennedy into law. What that required was that manufacturers establish a drug's effectiveness 'substantial evidence'. So before this you really only had to establish a new drug was safe to get on the market there were really no requirements that you needed to prove it was efficacious. There were other requirements and regulations in there with the other major one being that and there were limitations put on advertising of drugs so if you wander through the exhibit hall and you wonder why nobody's advertising fluticasone or budeconide for the treatment of EoE is because under the law they can't. So, the substantial evidence and of the largest taken from the line hard evidence consisting of adequate welcome to investigations into the clinical investigations by experts qualified by scientific training to evaluate the effectiveness of the drug involved. So, adequate and well controlled really goes down to something that we all take for granted now but it's really designing a trial to address confounding through randomization and to ensure that bias is not present, that the appropriate control is used and that's the regulations and has been pretty well adopted in modern clinical investigation. The other one word was effectiveness, what does it really mean to show effectiveness and the food drug and cosmetic Act is not directly stated what endpoints directly affect evidence of effectiveness so there's no way we can look to the regulations to really help us pick out what the most appropriate endpoint is for EoE. We use these terms clinically meaningful employment which Bob Temple, an institution by himself that the FDA says is a direct measure of how a patient functions feels or survive, so it's really something that's important to the patient that represents the meaningful benefit to that patient and the way that you determine what that endpoint is on is primarily through discussions with the FDA. If a company wants to say we think we have a drug that can treat EoE , we're not sure what to use , here's what we're thinking and we really have discussions that are pretty intensive about if it's purely a clinically meaningful employment data supports it. So using these clinical meeting of endpoints, now increasingly involves interactions with our colleagues internally who can validate them and can assert the objectiveness of the endpoints ,really measuring what it intends to measure. I think historically that level of involvement had not been done and I think that's why we see examples of drug approvals based on disease activity scales and symptom scales and not really validated endpoints. So, it's a paramount point instead that we develop clinically meaningful endpoints. There are regulations though that allow for deviation from that and I just want to quickly go through those. One is talking about the treatment benefit which is a clinically meaningful endpoint the other is if you're talking about basing improvement on a surrogate endpoint, which does not directly described how a patient feels functions or survives. So, just a definition of a surrogate endpoint, it's a measurement or a physical sign used as a substitute for clinically meaningful endpoint. It measures directly how a patient feels or functions or survives.

To quickly go over some examples. We do use certain endpoints to approve drugs and some examples of them are here, so blood pressure, LDL, HIV-1 RNA, hemoglobin A1C, these are all endpoints that if you just showed an improvement on these can get you to an approval.

The reason why they can be used to support approval is because we know the relationship between the given changes in blood pressure LDL HIV RNA and the more serious outcome it predicts. So, for blood pressure we know that high blood pressure causes stroke we don't need a company to prove to us that it reduces strokes. Reducing blood pressure is sufficient, so for an accelerated approval use of the surrogate is somewhat different and accelerated approvals where a company can get an approval based on a surrogate endpoint without really demonstrating an effect on a more clinically meaningful outcome. So, accelerated approval is limited to cases of serious and life threatening diseases and where there's no real satisfactory alternative that exists. They allow some uncertainty of its relationship to clinical benefit because they want to introduce a potentially promising drug to the markets sooner.

Like I said, the quantitative relationship between the surrogate d the clinical outcome has not been established, so there is no validated surrogate for EoE. Eosiniphils a reduction in a given amount of eosinophils has not been quantified to predict a clinically meaningful outcome. That has to be a very robust quantifiable relationship, that's typically established multiple randomized clinical trials that evaluate both the surrogate and the outcome. Also, an accelerated approval it's not clear at this time what surrogate is reasonably likely under the laws to predict a clinical benefit. Again, it's not even clear to us what a post approval study under an accelarated approval would look like to confirm a clinical benefit if we don't have a clinically meaningful outcome. So those are some of the regulatory considerations that we presented it at the great conference to frame the discussion. I think going over some of the other discussion points in again this was an all day session it's hard to distill it out in a short period of time but again the importance of understanding natural history to inform the study design the study population the end points was and interesting take home point. To quote one of our time one of our colleagues at the FDA, you have to begin with the end in mind to these natural history studies. You have to make sure that you're collecting symptom scores, your collecting disease activity scores in a way that will help you inform clinical trials and the choices of endpoints to ultimately support approval of new treatments. Ideally, we would like to have full and complete understanding EoE. I think as we said realistically, we have to do the best we can because people are treating this disease and they’re modifying it in the world. I thought it was very intriguing to hear about the different EoE phenotypes. The differences between patients with inflammation in the presence of fibrosis and structuring, which may actually require different study designs in these populations maybe that's the point of discussion. Also in understanding that what has to have to understand not just a relationship of going from inflammation to structuring but actually how are the symptoms evolving over that time period because mostly those are going to be the targets for approval. Then interestingly, the differences in Pediatrics and adults which may affect what we call

extrapolation of efficacy, which is leveraging adults to support pediatric approval. So it was encouraging to see that the clinical outcome assessments are being developed. There were examples discussed there that were already mentioned. I think that the validating these clinical outcomes systems is not going to be easy. There's a lot of unique characteristics of this disease that may make it more challenging to develop but I think it's the clearest path forward to identifying these clinical meaningful endpoints.

I think we will also need to show some effect on inflammation but as it stands now I think these PRO's are going to be really where our effort should be right now. As I said, there were some concerns expressed over the ability to assess a patient, patient modified behaviors, to address the placebo effects and all the different phenotypes of the disease that may be again make it more challenging than it seems. I think the bio markers there was the number of new bio markers presented that have a possible role in the prognosis the pharmacodynamic response to treatment and possibly identify new drug targets but again these are not going to be used as surrogate endpoints for approval at this time. I think the endoscopic and histologic scores havebeen discussed and presented are very promising and they could help provide some evidence that the drugs that are being treated actually have some impact on the disease itself rather than just a ameliorating the symptoms.

So, to conclude of understanding natural history is critical to defining a disease, designing adequate and well controlled trials and identifying clinically meaningful endpoints. Validating these PRO's or clinical outcome assessments for adult and pediatric studies is going to be critical to developing drugs to treat EoE. It's not going to be easy but academia, industry and regulatory bodies will need to work together to make this all happen. Thank you very much