AD Ally/FDA Scientific Workshop
March 13, 2008
TRANSCRIPT

AGENDA

8:00-8:15 Joint Welcome

- Eric Hall, Member, ACT-AD Advisory Committee, President and CEO, Alzheimer's Foundation of America
- Bill Thies, PhD, Vice President, Medical and Scientific Relations, Alzheimer's Association
- Robert Egge, Executive Director, Alzheimer's Study Group

- **Moderator:** Dan Perry, Chairman, ACT-AD

8:15-9:00 Current FDA Standards for Defining Clinical Meaningfulness in Alzheimer's Disease Treatments

- Russell Katz, MD, Director, Division of Neurology Products, FDA

9:00-9:30 Issues and Challenges in the Context of the Current Standards for Defining Clinical Meaningfulness in Alzheimer's Disease

- David Knopman, MD, Department of Neurology, Mayo Clinic

9:30-10:00 Options and Alternatives for Defining Clinical Meaningfulness in Alzheimer's From Early Diagnosis through the Disease Spectrum

- Jeffrey Cummings, MD, Director, Alzheimer's Disease Center, University of California, Los Angeles

10:00-10:30 Meaningful Changes as Viewed by the Clinician, Patient and Caregiver

- Howard Fillit, MD, Executive Director, Alzheimer's Drug Discovery Foundation

10:45-12:15 Challenges Facing Stakeholders, Regulators and Industry
(Panel discussion)

- **Moderator:** Sid Gilman, MD, FRCP, William J. Herdman Distinguished University Professor of Neurology, University of Michigan
- Bill Bridgwater, FDA Patient Consultant,
- Twyla Bridgwater, FDA Caregiver Consultant
- Meryl Comer, Caregiver and President, Geoffrey Beene Foundation Alzheimer's Initiative

- David Knopman, MD, Department of Neurology, Mayo Clinic
- Jeffrey Cummings, MD, Director, Alzheimer's Disease Center, University of California, Los Angeles
- Howard Fillit, MD, Executive Director, Alzheimer's Drug Discovery Foundation
- Russell Katz, MD, Director, Division of Neurology Products, FDA
- Dale Schenk, PhD, Executive Vice President and Chief Scientific Officer, Elan

12:15-12:30 Discussion and Q&A

12:30-12:45 Summary and Next Steps

- **Moderator:** Sid Gilman, MD, FRCP, William J. Herdman Distinguished University Professor of Neurology, University of Michigan

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8:02 am – WORKSHOP BEGINS

Mr. DAN PERRY: Well, good morning. And thank you all very much for attending our workshop this morning. My name is Dan Perry. In my day job, I'm the Executive Director of the not for profit Alliance for Aging Research. But I'm here today in my capacity as Chairman of the ACT-AD alliance. We have a very full schedule. So we're going to keep things clipping right along. And I want to, first of all, begin by thanking the co-hosts of today's workshop, in addition to the ACT-AD coalition, the Alzheimer's Association and the Alzheimer's Study Group. And we will begin with some welcoming remarks from all three organizations. And we'll start with my friend and colleague Eric Hall on behalf of the ACT-AD Coalition. Eric.

MR. ERIC HALL: Good morning, everyone. My name is Eric Hall and I'm the Founding President and Chief Executive Officer of the Alzheimer's Foundation of America and a member of the advisory council here at ACT-AD. The Alzheimer's Foundation of America is a national not for profit organization that focuses on providing optimal care to individuals with Alzheimer's Disease and related illnesses

and their families. Our objective is to address the educational, emotional, medical, practical and financial needs of the millions of Americans dealing with Alzheimer's Disease and related dementias on a daily basis as well as to raise awareness of the disease and the needs of the dementia community through our own advocacy efforts and in collaboration with our 850 member organizations and growing.

On behalf of ACT-AD, I would like to welcome you to this important workshop on clinical meaningfulness and Alzheimer's Disease. Our thanks especially go out to the FDA for making this event a reality and for all of the vital work you continue to do in this area. In particular, I would like to recognize Dr. Russell Katz, Captain David Banks and the others from the FDA who are here today. we also want to thank ACT-AD's co-host from the Alzheimer's Association and the Alzheimer's Study Group as well as all of the members of the ACT-AD coalition for their support in this forum.

For those of you who are not familiar with ACT-AD, we are a coalition composed of fifty national organizations that represent patients, caregivers, researchers, health care

professionals, employers, consumers and other health related groups committed to bringing interventional therapies to individuals with Alzheimer's Disease within the next decade. With the sense of urgency very real, ACT-AD's member organizations are committed to moving forward and collaborating with appropriate parties. So that we can improve the quality of life for those living with this devastating brain disorder.

For the past few months, we have been working with the FDA on putting together today's AD Ally FDA Scientific Workshop which we hope is the first in a series of meetings about how best to address the growing Alzheimer's Disease epidemic. Our goals for today's meeting are three-fold. We want to share the latest scientific debates to enhance evaluation and review of innovative therapies. We want to proactively engage in dialogue about obstacles experienced by those developing new treatments. And third, to ensure that the agency is equipped to make swift and informed decisions about new treatments.

ACT-AD wants to do all we can to help ensure that the FDA is best prepared to review emerging treatments. As we all know, currently there is no cure for Alzheimer's Disease.

But there are promising treatments being tested that will perhaps control symptoms, slow, reduce or reverse mental and behavioral symptoms and prevent or maybe even halt the disease. The potential of treatment in the pipeline that would modify the underlying pathology of this disease gives tremendous hope to individuals with Alzheimer's Disease and their families, hope that effective treatments will be available when it can still make a difference in their own lives as well as in the lives of the millions of Americans yet to be diagnosed.

ACT-AD's leadership and member organizations believe that delivering meaningful treatments to patients must be a top national priority. We hope that today's workshop will serve to advance the dialogue regarding how best to measure the clinical effectiveness of emerging therapies while opening the door to future discussions. We are encouraged that the FDA has agreed to explore alternative ways to approach how clinical meaningfulness is defined. And we look forward to a productive exchange of ideas this day.

Again, thank you all for being present and for coming out for this important gathering. It is my incredible honor

now to introduce Bill Theis[?], Vice President, Medical and Scientific Relations of the Alzheimer's Association.

MR. BILL THIES: Thank you, Eric. It's a pleasure to be here this morning. And I'm happy everybody else is in the room as well. It's a good group. And I'm sure that we will make some progress today. I would like to open with a few comments that particularly reference some history. So the Alzheimer's Association has a long history of interaction with various agencies here in Washington. And there is an underlying philosophy to all of those interactions. And that philosophy is simply that it does very little good to stand outside and throw bricks. What really helps is to develop a collegial relationship inside that allows you to actually look at common problems and deal with those common problems.

So historically, the association has had very strong relationships with the NIH. In fact, the association has sometimes been referenced as the poster child for relationships with the national institutes. In fact, I like that. Because anything that refers to me as child like as opposed to childish is a good thing at my stage in life. We've had a long history with CMS working on

complicated issues of how reimbursement works for patients with Alzheimer's Disease. And that's been very valuable. And we are working with the FDA in a continuing capacity.

So this even is really just part of an ongoing conversation. So over time, we've been able to develop things like the internal coordinating committee for Alzheimer's Disease which the FDA really has developed with their internal staff. There's the addition of patients to the advisory ... patients and families, to the advisory effort of FDA which includes Bill and Tawala[?] Richwater which you'll hear from later. And it includes a regular presence of FDA at our research roundtable scientific meetings which is now going on for years chaired by Dale Shank that you'll hear later.

And finally, we are working very hard to be one of the first organizations to work with the new Reagan Udall Foundation to actually create a fellowship program that will deliver actual workforce inside the FDA. So all of those things, it seems to me, increase communication between all of the scientists that are involved in trying to solve the Alzheimer's problem. And scientists work in different kinds of organizations. They maybe in academia.

They maybe in regulatory agencies. They maybe in corporate structures. In fact, many of them, virtually all of them, have the same goal. And that is to find better ways of dealing with Alzheimer's Disease.

The definition of that is sometimes complex. So I've got a couple of simple ideas. Number one, what everybody wants is something that changes the life of people with Alzheimer's Disease. And that's a fairly simple concept. When you go to try to figure out how you're going to measure that, the simplicity immediately disappears. So we've had multiple meetings about that topic. And this is one that has just continued. The other thing that is really essential in today's world is that whatever agent it is that creates this meaningful change has to be proven safe and effective. Rolls right off your tongue, easy as pie.

But in fact defining what is safe and what is effective is really a complex negotiation that tends to vary over time. So these continuing conversations are really critical to our coming to closure on standards that are acceptable to everybody in the community. And so I applaud everybody that's in the room being a part of this, particularly the

FDA being willing to send staff for this particular meeting. Because, in fact, I heard a reference to a day job. All of those folks actually have a real job which is evaluating applications. So this is really an important event.

I would just like to close by saying we've heard from some FDA staff that actually one of their favorite terms is risk-benefit ratio. They calculate that out to seven digits. This is a little bit of tongue in cheek. Because for those of you who know Rusty, he usually gets up and says there's no such thing as a risk-benefit ratio. But the relationship between the amount of risk that we would be willing to take to create real change and the amount of benefit it generates is at the crux of this whole discussion. And I hope that we will get at some of that today. So thank you all for coming.

I'm now completely free of any instruction. But it seems to me that learning on the fly that I should introduce Robert Egge who's the Executive Director of the Alzheimer's Study Group. Robert.

MR. ROBERT EGGE: I want to briefly pass along greetings and thank you from the Alzheimer's Study Group. The Alzheimer's Study Group is something I should maybe mention for a few seconds. Because it's a new group. And to this point, it's been a relatively quiet one. It's a study group that's co-chaired former Speaker Newt Gingrich and former Senator Bob Kerry. And it's organized around the mission of producing a national strategic plan that focuses on a few pivotal big ideas that would advance the conversation around Alzheimer's Disease.

One thing that I like about the group is its diversity. There are eleven members of this nonprofit, independent organization. Many of them have been touched personally by Alzheimer's and have lived through what an important terrible impact it has. Some of them have been very public about that. Like Merrill Comber who we're very pleased to have with us today. And like Justice O'Connor who has been in the news recently and is very passionate about this.

Other members ... and these groups overlap ... other members have been thinking about this and related issues from the health policy perspective. And so you have the co-chairs from a Congressional perspective. And former

heads of federal agencies like Dr. Satcher from the CDC, Dr. McClellan from FDA and CMS and Dr. Welmesh from NIH. So it's that vantage point as well.

And then just as importantly, some very accomplished leaders from business, from academia and from the medical community. So it's an interesting group of eleven people. And one interesting point about it is why this group came together. I think as they sat down together two days ago in Washington for an internal working meeting, they were struck from their own participation in many groups like this that this is an unusual coming together of different personalities.

And so the question is what did motivate them to do this? One thing was that they all share a perspective. First hand or from different perspectives on what a critical issue this is for the nation, for individuals. A second thing that unified them I think as they came together around this issue is that Alzheimer's is an extremely important and powerful lens for looking at some of the toughest but most important issues that affect us today as a nation in terms of health policy. And so if we can solve some of the issues and make headway around Alzheimer's

Disease, we'll probably come up with some very important insights that will apply more broadly.

And the last issue that motivated many of these people was their instinct that this was the right time to be contributing to this dialogue as well. That there are great problems, but there are also great opportunities. And I think each of them has a very strong appetite to be part of this ongoing work of producing solutions around Alzheimer's Disease.

I mentioned that their sense is first of all that they don't see themselves as a group that wants to invent ideas. They want to find the great ideas that are out there through meetings like this one and to encourage them. And they're looking also for pivotal ideas. In their meeting two days ago, clinical trials was a very important topic of ongoing conversation. Justice O'Connor couldn't make it to the meeting two days ago. But she is with Speaker Gingrich out in Arizona with the Alzheimer's Research Consortium a few weeks ago with Dr. Ryman, Dr. Cario and others. And again, with the Justice and the Speaker, much of the conversation was on clinical trials. It's really where

they focused, recognizing that it's such strategic, pivotal importance.

And so those introductory comments, I just want to first of all say, again, thank you. That the Alzheimer's Study Group is looking forward to continue to work with many of you. As I look around the room, I see many people have been extraordinarily supportive in many different ways to the Alzheimer's Study Group. And I won't make the mistake of starting to thank people and inevitably not doing a complete job of that. But thank you very much.

And finally, I know they are extremely interested in the outcomes of this meeting and are excited to hear what comes out from it. And are very encouraged that they expect this will be a continuation and not the beginning of the end of an ongoing conversation. And so they are looking forward to working very closely with each of you. So thank you, very much.

MR. DAN PERRY: I thank very much Eric, Bill, Rob for helping extend the welcome this morning. Just for a moment, let me share with you about a week ago, I was present at an awards ceremony for Alzheimer's researchers here in Washington,

there in Washington. And one person that stood up in the audience was the honorable Paul Rogers who many of you know a venerable and legendary member of Congress who when he served in the House of Representatives back in the '60s and '70s was known as Mr. Health. And as he looked around in that room and saw these esteemed scientific leaders, he said that he wished that if he could just get everyone together in a room, all of these smart people and lock them up somewhere, that we could probably solve Alzheimer's Disease. Coming from that generation that remembers Los Alamos. You just get the smartest people in the room and just lock them up.

Well, Robert was only partly serious. And we're not going to lock you up today. We are even going to serve you food. But first, we're going to have a feast of some intellect. We've got very esteemed scientists who will be speaking to you over the next few hours. And we're going to begin with Dr. Russell Katz. I think known, highly regarded by everyone in this room. Dr. Katz is the Director of the Division of Neurology Products within the Center for Drug Evaluation and Research and has many other layers of titles I won't begin to take the time to go into. But we're very pleased to have Dr. Katz be our lead off. And again, Dr.

Katz, and to all of those from the agency, we so appreciate your partnership in bringing this group together today. So, Dr. Katz.

DR. RUSSELL KATZ: Thanks, Dan. I maybe esteemed. But I have no idea how to work this. Anyway, it is a pleasure to be here and to discuss this very important topic. What I'd like to do is just sort of walk you through how we got to where we are at the moment and why we have sort of imposed the requirements that we have for clinical trials for drugs that treat Alzheimer's Disease.

It's I think very useful at this time to sort of reconsider the standards. We've been doing, as many of you know, the same thing as far as clinical trials and outcome measures for a long time. And now that we are hopefully on the verge of the introduction of a whole new set of treatments with presumed different mechanisms of action, I think it's worth reconsidering how we've been doing business. And if there's a better way to do it, to learn what that better way is. Or at least to discuss possible alternatives.

I think what we've been doing has a real rationale behind it. I think many of the elements that we have incorporated

into clinical trials to date I think still are and will be useful in the future. But it is certainly worthwhile figuring out if there's a different way to do it or an amended way to do it.

So let me just start with how we got to where we are. In the early '90s, we convened a meeting of our advisory committee. Most, if not all of you, know that our advisory committee is a group of outside experts who are experts in various fields of neurology. But we got them together for a two day meeting, supplemented with experts in Alzheimer's Disease, to discuss what should trials, clinical trials, designed to look at the effectiveness of drugs that treat Alzheimer's Disease should look like. And what are the outcome measures? What are the elements of the various ... what are the various design elements to be?

So we had this advisory committee meeting in the early '90s. And I think the main point that emerged from that meeting, a lot of discussion about outcome measures and how we should discuss these drugs. But the main points I think that emerged were these. Which is that any drug that we would approve for Alzheimer's Disease ... there was none at the time ... should be demonstrated to do two things. One

is the drug should have an effect on cognitive function. I think the view was that if the drug is going to be a specific Alzheimer's Disease drug, it really should have an effect on the core symptoms of the disease which are cognition in one form or another. So that was a very important criterion. Drugs should have an effect on cognition.

The other important, I'd say if not equally important, more important, point was that any drug that we would approve for Alzheimer's Disease must actually make a perceptible difference to the patient. That's not perceptible I should say to the patient who might be significantly impaired. But somebody should be able to assess more or less objectively that the patient is doing better. What we were most concerned about ... and this is, I think, a theme that you'll hear throughout ... what we're most concerned about is that a drug would be able to induce an effect which was reflected in a patient remembering one more word from a list five minutes later. But that would have no clinical consequence whatsoever.

So the idea was to have a drug show an effect on a cognitive measure, but also show an effect that actually

could be perceived to matter to the patient's functioning. And those were the two requirements. So what does that mean operationally? So how do we actually require that that happens? Well, so this basically evolved into a requirement that there be two what we call co-primary measures. That is to say two instruments that would both by themselves or each by themselves have to be statistically significantly better than the control group which at the time, and to this day continues to be, placebo for reasons perhaps we can talk about later. But I think that's fairly straight forward.

So, all right. So there had to be a formal measure of cognition, some formal test of cognitive function. Whatever that was going to be. And a formal global measure. And that was understood to mean some measurement that could just assess how the patient was doing. Now, when we first actually talk about it, we talked about ... we even used the word holistic which if you knew the person was involved in this, Paul Levy, you would know that that was out of character for Paul. But the point was that there wasn't necessarily going to be imposed a requirement that a patient be specifically improved on a particular function or not. That would be acceptable.

But the idea was are they just better globally? Can someone tell? Can the caregiver tell? Can the physician tell that the patient was just doing better in some way? Even if it was not explicitly clear in what realm they were doing better. They just had to be doing better. That was commonly understood. But in any event, it could have been what I'll call a true global which is this sort of holistic how's the patient doing measure or a more explicit functional measure of activities of daily living?

And here's the point, from the point of view of clinically meaningful. And this requirement for an effect on two co-primaries is entirely directed at trying to define an effect that was clinically meaningful. But here's the point. This was our ... these two outcome measures serves as an operational definition of clinically meaningful. In other words, if you had an improvement on a cognitive measure, if cognitive foundation was improved, and a global function was improved, by definition, this meant that the clinically meaningful. And I'll talk about this throughout.

But the point here is that we didn't mandate any particular size of an effect on either one of these outcomes. Take two valid measures of these two functions, show that they are statistically significantly better on drugs compared to placebo. That meant, in our definition, that the effect was clinically meaningful. And that global measure was there specifically to ensure that whatever effect you saw in the cognitive test was in fact clinically meaningful. And that was our definition and it continues to be our definition to this day.

Since we didn't know what a very small effect on a cognitive measure meant, apply the global. And so what's happened since? Well, almost all sponsors have used and continue to use an instrument called the ADAS-Cog. I'm not going to go into great detail of what this is. Probably everybody, almost everybody, in the room knows what this is. This is a seventy point scale, higher scores are worse. And almost everybody uses as this global measure. That's changing a little bit, this so-called civic plus. Which is a seven point scale. And I'm going to talk a little bit about that actually. And higher scores are worse.

This is the clinician's interview based impression of change. And originally, we had proposed just what we call a civic. In other words, an independent expert would assess the patient's functioning. This, by the way, would be someone, a rater, who was unaware of what the rating on the ADAS-Cog was. The idea was that this was supposed to be entirely independent of the cognitive change. And so, of course, if the rater knew what the cognitive change was, they might rate the patient according to what he or she knew about what the cognitive change was.

But anyway, the civic, as we originally talked about it, meant doctor and patient. But there was a lot of push back from the community then because people felt that that's not really how a physician assesses a patient with Alzheimer's Disease. There's always a caregiver involved who can provide some input. And in an attempt to keep this as pure as possible, we thought we really just want the physician assessing the patient. But we became convinced that that might not be the best way to assess actually how a patient's doing.

Because again, the patient might not be reliable informant. And so, we did agree to have the caregiver involved into

the interaction. And that's the sort of pluses. That's the addition of the caregiver. So this is what people have used. And, of course, in drug development, of course, the first drug was approved on the basis of effects on these outcomes. And in drug development, I can tell you when the first sponsor picks a particular set of outcome measures and we say those are good outcome measures and we approve a drug based on the effect of those outcome measures, everybody who comes afterwards uses the same outcome measures.

And there's a belief develops in the community that this is what the FDA requires. What we require, and have always required, is the principles be met, the effect on cognition and a global functional measure. We have never required that these be the two measures. But everyone has used these more or less in patients with mild to moderate Alzheimer's Disease. For severe Alzheimer's, other outcomes have been used. But basically, this has been it.

So what does a typical study look like? I want to go through this. Because to give you an idea of what sort of treatment effects we are seeing that turn out to be statistically significant on these outcomes which serve as

the basis for approval. And I want to give you an idea of how large or how small these outcomes are. There is, of course, a belief in many quarters that the standards are very high for many drugs, in particular in this case Alzheimer's Disease.

So I just want to give you an idea of where we actually fall on these scales for drugs that actually turn out to be approved. So anyway, I said it's a seventy point scale. For most patients in the mild to moderate Alzheimer's population, which is what most of the drugs have been approved for, the baseline ADAS-Cog is about twenty-five. It, of course, varies. But, in general, it's about twenty-five. And that corresponds usually to a mini mental score of somewhere between fourteen and twenty or so, give or take. And that's how we sort of operationally again define mild to moderate Alzheimer's Disease.

And the studies are typically powered and they enroll sufficient patients, to be able to detect the difference between drug and placebo, which is what counts when you're approving drugs, of about two to three points on the ADAS-Cog. And about .2 to .4 on average out of a seven point scale on the civic plus. So you can see that sponsors

design trials to pick up quite small treatment effects. At least look at sort of from the outside on an absolute scale, a two point change against a backdrop of a 24, 25 point score is, I think most people would agree, relatively small. And a .2 to .4 change on a seven point scale is also, on average, is a small treatment effect.

But again, remember our operational definition of what's clinically meaningful is a bonafide effect on both. And that we don't mandate a particular treatment effect size. And these are the sorts of trials that we see. So the typical results. So usually, there's somewhere around 200 patients per group. Some of these studies have multiple additional placebo, multiple doses of the study drugs. So you can see the drug/placebo differences on the ADAS-Cog. Even though they're powered to pick up 2 to 4 point difference, sometimes differences as small as one, as minus is better. Minus one are picked up as statistically significant.

And drug/placebo differences as low as .2 or even smaller on the civic plus are typically detected with the sample sizes of about 200 people in a group to be statistically significant. And that's sufficient for us. Absent any

compelling adverse safety considerations to approve a drug for Alzheimer's Disease. And this is how we do it. This is just taken from a particular study that looked at placebo in two doses of a drug. So anyway, over 24 weeks, which is sort of a typical duration, the placebo gets worse by maybe two points and maybe one point improvement, improved because minus is better than baseline.

So improvement. So that's about a three point difference give or take. And that would be a good robust size of the treatment effect on the ADAS-Cog based on what we've seen. So this is what we consider to be clinically meaningful. I think it's very difficult for us. And we've always taken the position that knowing whether or not a particular change on a particular scale is clinically meaningful in the absolute is very difficult to know an average change of one, two, three on the ADAS-Cog, which of those are clinically meaningful. We don't make those choices. That's why we incorporate the global. And that's why we just more or less look at average scores without cut off scores.

I just want to go a little bit into the civic plus. I talked about mean change on the civic plus of .2, .4 out of

a seven point scale. Typically, that's not actually how we analyze the data from a scale like this. We look at sort of the categories and the shift. How many people did better on the drug compared to the placebo, that sort of thing. So this is sort of ... this is also taken for one particular application. But basically, this is sort of what we see. And these are the seven ... there are actually seven categories of change on the civic.

One is missing. It's a symmetric. So it's markedly improved, moderately improved, minimally improved. You can see nobody markedly improved in this particular study. So I just didn't put the result. So we don't usually see lots of people markedly improving. Again, this is in someone's judgment. The difference between drug and placebo and the percentage of patients in each category is displayed here. And this was a drug that we think has a real significant clinical effect. An increase of four percent of patients on drug compared to placebo were moderately improved. And you can see what these percents are.

So it's not what you might call astonishingly huge treatment effect. Four percent more patients on drug than placebo had the best improvement as rated by this scale.

So these are the sorts of effects that we see that we consider to be clinically meaningful. Because we don't know how to do it really any other way.

All right. So here are the important points about the current agency standards in my view. There is ... and I've mentioned these. There's no requirement that there be a specific difference shown between drug and placebo on either the ADAS-Cog or on the civic. They just have to be statistically significantly different from placebo. And I suppose it's possible if you ... and you've seen the sort of effects that we actually, the size that we actually see. I suppose it's possible if a sponsor came to us and said, well, I'm going to have 5,000 patients in each treatment arm.

So instead of picking up a difference on the ADAS-Cog of one or two, I'm going to be able to pick up a difference of .3 on the ADAS-Cog. Would we accept that? We'd have to have long discussions about that. So when you push us to the extremes, I don't know if we would put a limit on treatment effect size. But in a typical study, this is how it plays out. This is another important point. There's no

requirement that the patients on a drug actually improve over time.

It's quite possible and quite acceptable that at the end of six months, three months or six months, in a trial that a patients on drug on average will be worse than they were at baseline. That would be perfectly acceptable as an outcome. As long as they're better than the patients on placebo. So again, when we think about clinical meaningfulness, we are really defining that by statistically significant difference on outcome measures that we believe in. And that's the standard we've applied and continue to apply. And, we, of course, are very interested to hear what other folks have to say about that.

So what about other outcome measures? I say everybody has used the ADAS-Cog in the civic plus or almost everybody from moderate disease. Any valid instruments are acceptable. We've had discussions with sponsors about perhaps using something other than the ADAS-Cog, some other global cognitive measure. And assuming it meets appropriate and more or less minimal psychometric standards, we had been in agreement with that. Folks have been reluctant to do it. Other global measures we have

used, activities of daily living scales, more strictly functional scales, we have agreed to.

What about cognitive instruments that assess only a single cognitive function? This becomes of particular interest I think in the early disease where a particular cognitive function maybe the earliest change and the executive function or a particular type of memory dysfunction. So what about looking just at a single measurement? Because the ADAS-Cog covers a broad range of measures as do some of the others that people have proposed. There's no apriori reason to reject that approach I don't believe.

If we could be convinced that in fact, yes, patients at an early stage with a particular of disease have an early change in executive function, can we measure executive function? Probably yes. But nonetheless, it still seems to us that a global measure would be important. Because you do want to ensure ... remember, the first principles were ... and Dan mentioned it and it was mentioned by others ... what we really want to do is help patients. And improving cognitive function and the absence of any global I'll call it effect on the patient's functioning may not be that important.

So I think even if you had a measure of a single cognitive function, you still want some measure that that meant something to the patients. What about non-cognitive outcomes? Because now are thinking a lot about looking at the behavioral symptoms of Alzheimer's Disease. The one precedent we had was the development of the treatment for the psychosis of Alzheimer's Disease. And this was accepted by the agency because there was convincing evidence that the psychosis of Alzheimer's Disease is actually a specific syndrome, specific to Alzheimer's and different from the psychosis just schizophrenia or other types of psychosis.

So this required some work to establish that diagnosis as a real diagnosis. But it was done. And even so, even though this was done, I believe there's still a requirement in those cases to show not only that the psychotic symptoms were improved or at least improved compared to placebo. But that in fact this mattered to the patient globally. Well, what about early disease? People are beginning to look now as you know at studying patients earlier and earlier in the disease process, even asymptomatic patients

perhaps. And how do we assess whether or not a drug has a clinical meaningful effect on those people?

So these are at least the categories I could think of that people are thinking of looking at now and are looking at. So MCI, these are patients, as a matter of fact you know who are impaired. They're not severely impaired. They're not demented. But they are impaired. And, of course, many people believe that certain types of MCI are just precursors to Alzheimer's Disease. Well, so far, there haven't been too many, but we have asked folks when they're looking at rating scales as the primary outcomes, to also have a measure of cognitive function and a measure of global functioning.

It may be hard to do. These patients are not as we say functionally terribly impaired. And, of course, if someone is not impaired, it's very difficult to detect an effect on impairment. But, of course, over time, over the course of let's say a six month study, there might be a difference that emerges. And we have asked people to look at that question. I don't know that we've solved it entirely. But we still think that as a principle that is worth preserving. Because again, if you can improve a patient

with ... memory of a patient with MCI, but you can't tell that that mattered to them, there are issues then of the clinical meaningfulness. And we'll talk a little bit more about that in some of these other cases.

Another outcome measure that people have proposed which we think is perfectly fine is not a scale. But since, as I said, most of these patients over time progress to Alzheimer's Disease, looking at an outcome measure that is either the time to the diagnosis of Alzheimer's Disease or the proportion of patients over a given time who do convert with a diagnosis of Alzheimer's Disease. We would think that that's a clinically meaningful outcome. If we can delay the time to the diagnosis of Alzheimer's Disease, even if just for symptomatic treatment, that's a good thing. And we think in and of itself, that establishes the clinical meaningfulness of the drug.

Here again, I want to point out that we impose no requirement on the actual difference in the proportion of patients or the difference in time between drug and placebo patients who reach a diagnosis of Alzheimer's Disease. As long as that can be statistically significantly different without 50,000 patients in the study as I said before, that

difference to us would be clinically meaningful. Because remember any difference that we see on average reflects a wide range of distributions of differences. Some people are going to have a big effect. Some people are going to have a small effect. But on average, if it's better than placebo, that's our test.

What about asymptomatic patients who have evidence of impairment? Either there is some clinical matter ... I don't know how you identify these people. But people who are fine, report no problem. But, in fact, on subtle psychological testing or psychometric testing, do have a deficit or maybe someday we'll be able to say your CFSTAU is this. You have pre Alzheimer's Disease. Or your MRI looks like this. We know you're going to have Alzheimer's. Even though you're fine now. So it's possible that these patients could be identified.

But here again, if we can pick up a difference on some psychometric test or some other clinical measure, that would be important. But the question of clinical meaningfulness ... but again, we haven't been posed with this problem really yet officially. No one's come to us and said we want to study people who are normal. But this

is coming. Some sort of an independent measure of clinical meaningfulness is really what we're looking for here. And I don't think we had the answer for these people yet.

The problem is that if all you see as a change ... I've said this many times ... if all you see as a change in a cognitive measure, we can't be sure that that will ever be reflected in a change that's meaningful to the patient. Remember, all we have is the data in the study. If we are going to say, well, yes. This is an effect on the cognitive measure in a patient who's otherwise not impaired, in order for us to say that this matters to a patient, we have to go beyond the data. We have to say, all right. We can't tell. We can't measure the importance to the patient in this study. But we will assume that because it has had this effect on the memory test let's say, it will be reflected at some point in an effect on functioning.

But, of course, that's an assumption. That's going beyond the data that's saying we know that the effect that we've seen on the cognitive measures will predict at some point in the future that the patient will be functionally better. And the question is what sort of evidence would we need to

have to be able to predict that reliably? If you can't show it in the study, the rest is assumption. And so in essence, what this does is this turns the cognitive measure into what I'll call a clinical surrogate for the change we care about. Again, a surrogate marker is some test, as someone said, that you can measure instead of the test that you actually care about.

So this would be, I think in my view, a clinical surrogate. A cognitive measure. It's improved compared to placebo. What does it mean for the future? What does it mean for functioning? Given that we can't measure functioning now. Well, I don't know. But they're relying on surrogates, for many reasons we can talk about, can be quite unreliable. And so this problem is increased exponentially with regard to the interpretation in a biomarker alone, a surrogate marker alone. Like the MRI alone or some CSF biochemical measure alone or some blood test alone.

In the absence of an independent, explicit measurement of clinical change, clinical function, that matters to the patient, even if you had a biomarker and a cognitive measure alone and they both went in the right direction, you'd still have to extrapolate beyond the data to assume

that that somewhere down the road is going to have a functional ... translate into a functional change. And maybe that's a reasonable assumption to make or prediction to make in some cases, but typically it's treacherous.

So what about normals at risk? There's no regulatory bar to studying patients who are normal, who might be at risk by some family history or genetic markers, that sort of thing. Here we're really in the dark. It's hard to know what to measure in these people. These studies would probably be, if you were looking at a clinical outcomes, would probably have to be very, very long. It's hard to know what the outcome measures ought to be.

Here is probably the case down the road when we know more where surrogate markers by themselves might be quite useful. But I don't think we're anywhere near there yet. But I just want to close the loop. And here, just normal people. These are people who have not been screened and not known to be at risk. If we had a drug that really prevented Alzheimer's Disease, maybe everybody would take it. And there's, by the way, no regulatory bar to studying normal patients. But anyway, the problems are multiplied, multi-fold, on every level here. We really don't know how

to study these people at all I don't think. But again, we may be hearing more about it.

So disease modification. This is, of course, what everybody's interested in. The treatments we've approved to date are we believe symptomatic. The disease continues to progress even though the symptoms are treated. But what about drugs ... and a lot of people think we have those now ... that actually have an effect on the underlying progression of the disease. It's hard to know how to detect such an effect. And if we do, how do we know that that effect is meaningful? I'll talk a little bit about that.

Many people believe that a difference in the slopes ... and you're going to see this graphically in some of the other talks. But many people believe that if you have a change in the slope on some clinical measures over time that in and of itself that's evidence of disease modification. I don't want to go into great discussion about how you actually detect disease modification. But many people believe that the change in slopes is what counts. Many people also believe that in order to detect a change on slopes, on whatever the cognitive measure is, let's say the

ADAS-Cog, it would take at least a year and a half, a year, two years, to actually see that change emerge. Because patients only on placebo are progressing at a certain rate. And in order to see a difference that is statistically detectable, you'd have to go out for a couple of years.

So anyway, we as an agency or as a division anyway don't believe necessarily that a change in slopes actually is solid evidence for an effect on the disease progression. We don't think that it forces that conclusion. There may be other explanations for why you see that difference. Anyway, we can have a discussion about that if you like. But even if it did, let's say that we did believe that that actually was prima facie evidence of an effect on disease modification, it's fair to ask ... and again, we're talking about clinical meaningfulness here ... it's fair to ask how are we to interpret the clinical meaningfulness of a change that takes two years to emerge.

Again, a huge treatment effect won't take very long. But modest treatment effects, given the rate of progression in the placebo group, will take longer. And it's fair to ask what is the clinical meaningfulness of an effect that takes a couple of years to emerge? Again, it seems to me that

the interpretation of such a finding as being important seems to rely on the fact that we would expect that that difference that takes two years to emerge would grow greater in three years or four years, that the curves will continue to separate.

But, of course, that's an assumption. That's going beyond the data. And it's hard to know if that would happen outside the context of a controlled trial. So we shouldn't ... I guess here's the point I want to make or a point I want to make. We shouldn't take the fact that a drug has an effect on disease progression, assuming it did, in and of itself as evidence that the effect is clinically meaningful. Everybody thinks slowing down the progress of Alzheimer's Disease or preventing to or stopping it is a great thing of course. But, again, we're talking about effect size. We're talking about is the effect clinically meaningful?

We shouldn't take the fact that a drug has a progression effect, an anti-progression effect, in and of itself as being clinically meaningful. You might be able to get just as big an effect or better effect with the symptomatic treatment that persisted over time. So we shouldn't take

the fact that it's disease progression, therefore it's clinically meaningful, as a given. That's something I think that's worth talking about.

Surrogate markers. I went into great detail here. Surrogate markers again are a lab test that has no direct connection to how the patient is actually doing. But you think substitutes for how the patient's doing. And so, sometimes surrogate markers will change in six months. Whereas, it might take two years for a clinical outcome to change. And that's why people who have seen them ... that's one reason why people like to use them.

But the whole objection that we have to relying solely on a surrogate marker is that we have no idea, absent any other external evidence, that the effect that we see in the surrogate marker actually will translate into anything clinically meaningful. That's the whole objection to relying on effect solely on a surrogate marker. We just don't know what it means clinically. And that translates into a question of clinical meaningfulness.

Beyond what I'll call philosophical objection, you've got to remember the more sensitive the marker ... and the lab

tests tend to be more sensitive, less variable than clinical scales ... they might be able to detect a very, very small effect to be statistically significant, very small. You might see a very small change on let's say hippocampal volume on the MRI. We really have to think about what does that mean clinically in the absence of any concomitant clinical information? So that's a problem.

What about alternative outcome measures like client specific outcomes? In other words, not just looking at the average ADAS-Cog or the average civic. But take patients and say, well, this is my problem. I can't do this. And maybe I have a drug that I like to help me do this particular function better. You could have a client ... go to every patient and say what's your particular problem? Or assess what's your problem? And set some standard for saying, okay. You're a winner if you improve on that particular function by a certain amount.

In any event, that might be fine. But it's difficult to measure that. It's difficult to pick a success criteria in any given case. And it would be hard to know whether that was an Alzheimer's specific effect. Maybe it's just an

anti-depressant effect or a muscular effect. So, we have to think about it. But we don't rule it out.

Secondary outcomes. People want to describe secondary outcomes in labeling. This happens all the time. Studies have a primary outcome that we more or less live and die on. If it wins on a primary outcome, you get approved. If it doesn't, you don't. But there's a whole list of other outcomes that people assess that they want to describe in labeling. And our policy is that these secondary outcomes, they have to address a domain that is distinct from the primary outcome. If you're just looking at cognitive functions three different ways with your secondary outcomes, it clutters up labeling to describe those results. It's basically just redundant with regard to the primary outcome. So that's the idea.

Now, these secondary measures, a lot of them are functional measures beyond the let's say the civic plus. They're not exactly the same as the one that was relied on for approval. They're not correlated perfectly. They all measure slightly different things, slightly different functions. But more or less, they measure functional.

They measure more or less the same thing. Not exactly the same thing, but more or less.

So our view is that permitting the description of outcomes that more or less cover the same territory as the primary outcomes is not a good idea. Partly ... this is not the most important thing ... but partly, it's in a sense unfair to other sponsors. It's probably true that every drug that's been approved or will be approved for Alzheimer's Disease based let's say on the civic plus will more or less do the same thing on the ADCS-ADL or something else as every other drug. They just didn't measure it.

So in some sense, it's unfair. But the most important thing is that we report the results of six different functional scales in addition to the primary functional scale, it gives the impression at least as far as we're concerned that this drug is doing a whole lot more than just describing results of a primary outcome implies. And there's a sense that there is a clinical meaningfulness to this drug that above and beyond what we really think is an accurate way to describe it. So that's why we typically don't permit those things in labeling.

So anyway, just to summarize. The requirement that the treatment have an effect on the patient's functioning, however defined, that seems like a reasonable thing. It may be difficult to assess in various patient populations. But it seems like a reasonable thing to do and not just to show some effect on some more and more sensitive cognitive measure, for example. But we think the best way to know whether or not the drug has an effect on a patient clinically is to measure it in the study. And to not assume that an effect on let's say a cognitive scale will translate at some point into a functional change. Or an effect on a surrogate marker will translate into a clinically meaningful effect.

We think the best way is to measure it. And certainly, the drugs that are approved which are modest in effect, are able to be detected, the clinical effect is able to be detected. So approaches that rely on them as indirect evidence, the assumptions that they will have an effect on a clinically meaningful outcome, is problematic. Because it could be wrong.

And finally, and don't quote me on this, the standard for drug approval, at least for patients who have the

diagnosis, is quite low in certain respects. And you've seen what I mean by that. A statistically significant difference on these scales is taken as evidence of effect. And you've seen the sorts of changes that turn out to be statistically significant. And they're quite modest on average I think it's fair to say.

The standards are high, of course, with respect to the rigor of the studies, the design and the conduct and everything else. But from the point of view, the size of the effect, which we don't mandate in advance, quite modest effects turn out to support approval. So I think I'm done. So I'll start there.

(END OF HOUR 1)

9:00 am –

MR. DAN PERRY: I'd now like to introduce Dr. David Knopman.

DR. DAVID KNOPMAN: Well, I'd like to thank ACT-AD and the sponsors for inviting me to speak here. It's always daunting to go after Dr. Katz. But actually, what I'm going to be talking about does mirror some of the things that he discussed. And I'll just go into a little bit more detail. And actually perhaps in some areas may jump over some because he covered them. Just mention my disclosures. I am the site investigator at Mayo for Nilan trial. And I'm on DSMB.

So the point I'm going to start with is just some principles. And I'm going to take the view that in thinking more broadly about the issues here, and a little bit of a wish list. And that is that I think everybody in the field recognizes that primary prevention really is our ideal. I think most of us recognize we're not going to be able to get there tomorrow. In turn, we would also be happy with the secondary prevention. But at the moment, we

are mainly dealing with trying to treat symptomatic disease.

Now, I'm going to take the position here, and I'm not going to spend more time talking about risk/benefit ratios or the degree of side effects that would be tolerated. I'm going to assume in the discussion here the kind of agents I'll be talking about in general terms are low risk. The key things in terms of talking about clinical meaningfulness, as Dr. Katz had mentioned, is how big is the effect? But also how enduring is it? And this is an issue that is really not trivial. A conceivably very large effect over a particular period of time, short period of time say, might completely fade out in a few months. Is that something that we really want?

Then the third point that Dr. Katz made was is the mechanism itself actually important in terms of clinical meaningfulness. I must say I think that many people think that it is. It's almost like a political point. And Jeff Cummings, after he will talk about the disease modification issue. And I'm not going to go into it further in the interest of time. I don't really need to go over these definitions here except just to make one point. I think

that we all need to keep clear that when we talk about Alzheimer's Disease, clinically, we're talking about a syndrome that usually involves difficulty with short-term memory. We've got to keep it separate from the pathologic diagnosis of Alzheimer's Disease. Because sometimes these two are ... they have different meanings. So that probably won't come up again.

Now, I want to just go back and reviewing some of the things that Dr. Katz talked about. Consider the natural history of Alzheimer's Disease and where clinically meaningful outcomes fit in. There are five general areas that I identified. The first would be taking people who are cognitively normal and looking for a delay ... I'm sorry, a reduction in decline in cognition during a period when people would be considered normal. And I'll talk about that midway through my talk. The second would be in patients who have symptomatic evidence of cognitive impairment usually in the form of short-term memory problems that meet the definition of mild cognitive impairment. I'll come back to that later. And using that point as a place ... as a meaningful outcome, the development of objective cognitive impairment.

But on the other hand, starting with those individuals, asking the question can we prevent dementia at this point here, Dr. Katz led his discussion, and I'm going to move there in a second, in starting with people who have mild to moderate dementia and asking the question can we prevent the development of severe dementia? Can we prevent progression? And the final point that I'm not going to talk about further would be to start with people with severe dementia and see if we can delay death. This one is not I think of great interest to us.

The point of the slide, in addition to showing changes in cognition and the more or less parallel changes in daily functioning is to point out that there actually are some differences between those two functions. In the stage of mild cognitive impairment, daily functioning maybe virtually normal and difficult to distinguish change in that kind of setting. It's certainly difficult to distinguish that change in people who are normal. The advantage of studying people in the mild to moderate stages of dementia are that the changes occur perhaps more ... not perhaps, definitely more rapidly than in any other phase in the disease. It makes it easier to measure in a shorter period of time.

Now, I want to just then bring up a point in thinking about the spectrum of the challenge that we have. And this is not an FDA limitation. It's the limitation of the disease that we are trying to deal with. That while symptomatic therapies in people with mild to moderate Alzheimer's Disease may take trials six to twelve months, perhaps eighteen months, that take 150, 200 subjects per group. Getting into these areas that are more substantive for us in terms of having a greater impact on the disease become much more difficult in terms of number of subjects, in terms of the duration that the trials have to run.

And this is the challenge for the field. This isn't something imposed by the FDA. It's imposed by nature. So to talk about mild to moderate dementia and the mild to moderate Alzheimer's Disease and clinical meaningfulness, I'm just going to focus on this area of the curve for a second. Russ went into this in detail. So I'm going to go somewhat quickly. As he mentioned, the cognitive outcomes and global assessments are considered the joint, the important primary outcomes in this area.

I'll just make the comment that I was actually at the first ... participated in the first Tacron[?] study in 1987. And when Russ's predecessor, Dr. Lieber, mentioned that we were going to do a global assessment, neither I nor the vast majority of the neurologists in the field had ever heard of it, it was something that had come from the psychiatry world. And I was exceedingly skeptical about it and critical. And I certainly remember having the discussions about having the family members involved.

But the point is that with some of the data from the thirty week Tacron study, I had an opportunity to investigate the global assessment and how it functioned relative to cognitive measures. I went in with the intention of throwing brick bats and came out instead throwing bouquets. I really think that the idea of a global assessment makes sense. It really does measure something important. And it has a face validity.

Now, the way that I want to try to depict it is here, to depict the differences between these various functions. Cognition is easy to demonstrate. And to neurologists, it has great face validity. But to the rest of the world, it has somewhat less face validity than global impressions of

actually seeing change or what really has happened in our world as a lack of decline in treated patients compared to placebo patients.

Daily functioning actually fits somewhere in the middle. I don't actually attribute this to having the greatest properties in the world. Because it too is subject to measurement error. Now, just a few words about cognitive function. It does have ... it's easy to measure. It's reliable. It's portable. And these are great advantages. It certainly is the case that a three to four point change on the ADAS-Cog is not very large.

This was something that I certainly learned with a bitter experience of being involved with Tacron and being involved with the cholinesterase inhibitors early in their development of explaining the results to primary care physicians and getting a blank stare when we said look at this. There was a three point change on the ADAS-Cog. And there's nothing. It's no response. So it is something that still lacks face validity. I will say though that over the last ten years, as primary care physicians have become more likely to do mammal status exams, it does have greater meaning. But that still is an issue.

As I said, daily functioning is certainly important. It clearly relates to what's important to patients and care givers. But it turns out, it's actually quite difficult to measure. And it varies greatly from person-to-person whether you ... in my community, a Catholic Sister who lives at Assisi Heights who has everything done for them versus a woman of the same age who is a widow who has to do everything in their own house. Those kinds of differences make it actually much more difficult to measure.

So I do want to just show an example. And Dr. Katz alluded to this type of thing. But this is from a study that actually Rich Mose was the first author on. He's here in the audience. That used Dinepacil. I had nothing to do with it unfortunately. I think it's a great design. We'll talk about it in a second. The study took patients who had mild to moderate Alzheimer's Disease, evaluated their cognitive function and then asked the caregivers at the beginning of the study to define what they thought was a clinically meaningful change or loss of ADLs and IADLs.

This was a double blind study. And the number of studies who hit that end point was tabulated. And these are the

results which I think really quite adequately depict the true benefits, but also the very modest benefits of Dinepacil and the cholinesterase inhibitors. That in patients who received Dinepacil, 49 percent of them had lost that amount of pre-specified function that was decided at the outset. Whereas, 62 percent of subjects in the placebo group had declined. And I think that this shows the effect of the drug in an honest way.

I'd also like to make the comment that as a one year study that was placebo controlled, it also protected subjects by allowing them to be in a double blind trial. And if they did decline, they had the opportunity if they hit end point of going on an active treatment. So there are problems with this study. I think there are some strengths though. One, I think it's easy for primary physicians and families to understand that kind of data. I think it's a clinically meaningful outcome and it's ethically sound.

The problem with it is it probably took a fair amount of expertise to develop these kind of guidelines. As Rusty said, there's some question about the specificity for dementia. Although, I think that could be obtained. This is just an example of the kind of design that I think

should receive more attention and actually I don't think has. The global scales, I think that perhaps I won't go into in more detail. Except they really have validity. It's purposefully insensitive. And I think that perhaps the FDA's criticized for that. But this is a good thing. Because it allows an agent that has benefits to rise above the crowd. And it also, the final point, is that it is translatable into practice. Because it ultimately is a gut feeling. The clinicians feel that their subjects actually have not declined versus declined.

The one thing I will say about it that's important to recognize here, it would be very nice if the drugs that we had were ones that brought about genuine improvement. But generally speaking, in daily functioning and certainly in our experience right now, what we see is delay in decline. And that's actually much harder to see. It's very difficult for any clinician, and especially a primary care clinician, to perceive. And it makes that notion of perception of change much more difficult.

So I think that I as well as the other panelists feel that there is a fair consensus in terms of mild to moderate Alzheimer's Disease, that the dual outcomes are a fair way

of assessing efficacy of drugs. As Rusty said, there isn't any minimum in terms of duration of study. I think that most people in the field feel like a study of twelve months is needed. But that's sort of just pulled out of the air. The question is whether a positive biomarker and other clinical outcomes would allow the stronger labeling, stronger meaning the disease modification. And Jeff Cummings will speak about that.

The question is from the point of view of efficiency of getting drugs to market would a six month study be adequate if it showed benefits? The issue, of course, is is the effect enduring? And that's the problem with a six month study. But the longer the study, not only does it take longer to do, but the problems with attrition and interpretation of the results because of dropout become an issue.

Now, I want to switch gears and kind of work as Dr. Katz did actually and go back and talk about earlier treatment in the disease which at this point is largely, but not completely theoretical. One of the big problems here is though this disease is common, its incidents, the number of new cases per year, is relatively low. This slide shows

the number of new cases per thousand people per year. And even in an 80 to 84 year old group, the number of new cases is only 38 per 1,000, three per 100.

And those kind of numbers make doing a primary preventions study very challenging. With this kind of incident rate of one to four percent, doing a study where the onset of dementia was the outcome takes a large number of subjects. And the point is that there's really ... it's like being out in the ocean. There's nothing in between being on the coast of California and getting all the way to China. It's kind of a long jump. And the problem is numbers and power. And I just made some very rough calculations here that wouldn't survive a statistician.

But assuming that you needed five years with a two percent conversion rate for four years of the study, assuming that you have dropouts, older patients, you need a minimum of 3,400 people per arm. And the point is ... you can argue about the exact numbers ... is that we just can't do many of these studies. Even though these are the most important and have the biggest payoff in the end, we just don't have the resources either in terms of investigators or patients or money to do these kind of studies.

So the question is is there some other way to do it? Actually, I just wanted to make the point though that these studies aren't entirely theoretical. There have been a couple of them. I've mentioned one study of an anti-hypertensive that I think had 10,000 subjects in it actually has a standard that we don't know if this is important or not of actually reducing the incidents of dementia by ten percent.

Now, many of you know or you know that the women's health initiative memory study was one of these primary prevention studies as well that was intended to show reduction in dementia incidents. That study had roughly in the estrogen progesterone arm of it 4,000 women per arm, placebo, estrogen progesterone. Took years to do.

And the other point I just wanted to make about it that in terms of thinking about clinical meaningfulness and using an example from another field. In the principle study of women's health initiative or the main study, they were shooting for 20 percent reduction in heart disease. Is that what we should be shooting for, 20 percent reduction

in dementia? The problem with these studies is that they are just so resource intensive.

Now, one of the alternatives I'm getting to is that ... and Rusty alluded to this ... what if we look to people who are cognitively normal and asked the question could we delay cognitive change or cognitive decline in these people? Would that be an indication? Would that be important? Say it's for dementia. But would it be important? We'd like to link it to dementia based on this logic. There's no question that Alzheimer's Disease produces cognitive changes that precede the diagnosis by a decade or more.

It's also the case that lower cognitive function is a risk factor for dementia. And that's fairly well established, in the epidemiology literature, consistently established. And so, if you were to be able to intervene in cognition before people were symptomatic, would that be important? Presumably if you could have people at a higher cognitive level, would that reduce their risk of dementia?

I'll just give an example of a study that didn't make that claim but took normal people. It was a study of foliate. And I have nothing to do with this study. I'm not passing

on its methodological rigor or whatever. But this was a three year study with about 800 subjects, fairly young people. And they actually were able to demonstrate a slight change statistically on a memory test with foliate therapy. This was actually in Europe versus placebo. And one of the real challenges here, and Rusty alluded to, is what the heck does that mean?

A change in Z score of 1.32 on a memory test. I didn't tell you what the memory test is. We don't have time to go into it. But is this important for the field to be working in? If there's not an approvable indication, presumably industry wouldn't be interested. But this is something that we need to think about. And just in the interest of time, I think I'll just skip over these. It would be nice if we could find at-risk people who were cognitively normal who had some marker that made them at much greater risk to develop dementia, but we're not there yet.

So I want to close and just talk about the mild cognitive impairment in the last few minutes. The reason that this area is important is again this problem of trying to find outcome measures that are doable and that can be achievable in a reasonable period of time. As we talked about, when

you start with primary prevention, it's a very daunting exercise. And the question is is there something between normal cognition and dementia that you could measure as a milestone. And the answer is that there really isn't. Other than this entity of mild cognitive impairment. I want to just talk about that a little bit.

The point is that if you could identify people reliably, and if primary care physicians could identify people who had this entity of mild cognitive impairment, that it does in fact identify a subgroup of individuals who are at much greater risk for developing dementia than people who are cognitively normal. As I said a few minutes ago, the incidence of new cases of dementia is about one to two percent per year depending on the age. In mild cognitive impairment, properly defined, the rate of dementia is about twelve percent. It makes it much easier to use dementia as an outcome in a study with mild cognitive impairment.

But what's the problem? Well, unfortunately ... and we don't have time to go into the bigger arguments around this ... it's not as cleanly defined as we would like. Maybe it can't be. Because ultimately, this is a continuum. We talk about mild cognitive impairment as if it were a

specific entity. But those of us who work with it every day recognize that it is a spectrum. And it's a point that we draw a line in the sand. And we know it's artificial.

There are also some other problems, even if you could define it as an initial state, defining when somebody changes from mild cognitive impairment to dementia has been somewhat challenging. Because again, it's a continuum. However, using MCI to define a group and using the development of dementia which was almost always due to Alzheimer's Disease as an outcome measure did work. I was part, as was Jeff, of the Alzheimer's Disease Cooperative MCI trial. I'll just mention it only took about 250 subject per group. But it took three years. With the criteria we used, it did show changes between Dinepacil and placebo.

But the more important point here is that the rate of conversion, the number of cases of dementia, was exactly what we predicted. It didn't work with other sponsors. I believe it was because the sponsors were in too much of a hurry to enroll people and actually took people who are cognitively normal. But that's another topic. Is there an alternative with mild cognitive impairment? There is.

Again, it gets into the question of is this a ... what do we call it? Just another surrogate.

A study that was done by Pfizer ... Steve Salloway was the first author published in neurology ... used MCI patients. And instead of looking at dementia as an outcome, jus simply use cognitive change. Though there's probably going to be discussion about the ADAS-Cog isn't sensitive enough in very early disease. In fact, it worked here. The problem was that these guys ... and again, I had nothing to do with the study ... had defined delayed recall using the NYU paragraph test as their primary outcome. And so the study was negative. Because that's where they put their money. But the ADAS-Cog actually worked better than the memory test which obviously wasn't their expectation.

And the question is is this kind of outcome clinically meaningful in mild cognitive impairment? One has to make certain assumptions. And we can talk about those as to whether they are reliable in terms of the things we really want to know about, namely the progression to the dementia. I will just point out just with one slide only that imaging and looking at structural changes in the brain is very consistent in the clinical literature that people with

Alzheimer's brains and people destined to get Alzheimer's have brains that shrink. Either their ventricular volume increases or their whole brain volume decreases.

So in principle, volumetric change on MR should crack with the disease. As Rusty pointed out, it may not on a short-term scale ... you didn't say it that way. I'll say it that way ... on a short term scale. But over the long-term, this is what the disease does. And if I think we in academia need to do more work to try and show what the correlations are here between change on MRI and change in cognition. Actually, there's not too much literature on this. There's a paper that will be coming out in neurology that in fact shows that changes on CDR and changes in whole brain volume are correlated with our values in the .5 range.

So finally, my last slide. So I think that we in the field generally have agreement that the guidelines and the notion of clinical meaningfulness in mild to moderate Alzheimer's Disease is a reasonable standard echoing what Rusty said. Getting to these other areas is still out in the unknown because we don't have experience with success. But I think that having an open mind in terms of not ... in terms of

looking at outcomes that are somewhat easier to obtain, that might get promising agents available is something that needs to be considered. But we need to recognize that the notion of clinical meaningfulness still remains to be established. So thank you very much.

MR. DAN PERRY: Thank you very much, Dr. Knopman. Well, Dr. Knopman certainly fulfilled his role of showing us what some of the challenges are. And they are daunting indeed. And now we're going to hear what some approaches we might want to consider in dealing with those. And our next speaker will be Dr. Jeffrey Cummings. He is a Professor of Psychiatry and Director of the Alzheimer's Disease Research Center at UCLA. He is an acknowledged expert in clinical trial design and drug development. He also manages to find time to train fellows in behavioral neuroscience and dementia research at UCLA. Widely published, not only in Alzheimer's Disease, but also Parkinson's Disease which I know is of interest to some in the audience. Dr. Cummings, thank you.

DR. JEFFREY CUMMINGS: Thank you, Dan. Thank you to ACT-AD, to the Alzheimer's Association, to ASG, to FDA. This is sort of an alphabet soup of meetings, mostly with A and D in

them. It's a pleasure to be on this panel. It's an honor really to be asked to discuss some of these issues that I think are of extremely great importance. I've been asked to talk about options and alternatives. And I've concentrated on disease modification here in my disclosures. We are at a kind of a nexus in Alzheimer's Disease therapeutics.

We have substantial advances in understanding molecular mechanisms. We think we have potentially exploitable pharmaceutical targets and that disease modifications will evolve. These represent new circumstances for drug development, including an impact on disease course. These impacts are slowly evolving and progressive. This is a challenge then in terms of measurement.

We need to start therapy as early as possible. We want to maintain cognition at the highest possible level, not start therapy when cognition has already substantially declined. The trial design and end points vary from those for symptomatic agents. And biomarkers maybe needed to support that effect. And we may have to consider alternative outcomes and analyses.

These then are the things that I'll consider in this brief talk. What is the definition of disease modification that we'd be working with? And how is it established? What is a clinically meaningful effect in trials of disease modifying agents? That's the central issue that we were asked to consider today. But I thought it needed to be embedded in the larger context. How can early AD patients be identified? A new suggestion has come forward. And are there alternative designs? I consider my suggestions that I'm making today really options for discussion rather than fixed positions that I currently hold.

So defining and establishing disease modification, there are a couple of definitions that have been proffered. One, a drug that alters the disease course. And a cholinesterase inhibitor would meet that definition. I tend not to like that very much. An alternative would be drugs that affect the underlying disease process and impact the clinical course of the illness. So that there is a clinically meaningful standard that is added to the effect of the drug. Again, echoing what Dr. Katz says, one can imagine, for example, an anti-inflammatory agent with a measurable impact on a biomarker that would have no

clinical impact. So you could alter the disease. But you might not alter the disease course.

So I think it is important to have an impact on course. But I think for this class of drugs, we should be thinking about an impact on the disease process. And cholinesterase inhibitors, for example, would not meet this definition. How then could this be established? Well, two clinical trial designs I think have been seen as by themselves establishing disease modification. That is the staggered start and the staggered withdrawal design. Pharmaceutical companies by and large have stayed away from these designs because it is difficult to know what their parameters should be. How long should they be? How big should they be? How long should the withdrawal period be for observation? And therefore, there have been very few of these.

That means then that there has to be some support for some other clinical design. And therefore, you would have clinical trial evidence consistent with disease modification and perhaps biomarker evidence supportive in effect of the underlying disease process with an important correlation between the clinical effect and the biomarker

effect. I offer this as a basis for discussing how we would establish disease modification in the absence of the staggered start or staggered withdrawal design.

A nuance of this, which I would be interested to get Dr. Katz's feedback on, is Suzanne Hendricks proposition of the natural history staggered start and whether that by itself would represent evidence of disease modification. When we think that about integrating these biomarkers into clinical trials, I think we would not integrate this into the minimum clinical difference standard. That is we do not know how to put a biomarker into minimal clinical difference. Nor is it a clinical difference. In terms of biomarkers, none are validated as surrogates.

But some are well characterized in terms of their support for disease modification. Even though they could not serve as something that would be used to measure instead of a clinical outcome. So biomarkers could be shown to show a drug placebo difference to correlate with the clinical outcome. That clinical outcome should be pre-specified. But I'm raising the question whether it could be pre-specified to correlate with any of a number of clinical

outcomes. Episodic memory measures. That might be, for example, the most relevant to medial temporal atrophy.

Activities of daily living. Perhaps that is the best correlate for global atrophy. Behavior. Perhaps that is the best correlate for singular atrophy or global again perhaps a measure of global atrophy. So what is the clinically meaningful effect in trials of disease modifying agents? I think this is where we enter the unknowns. Defining a clinically relevant difference. The question is what is the smallest effect size that is clinically meaningful? I think we are trying to define here a lower boundary that companies could work with.

How small is too small? And therefore, we would not further pursue that agent. I think for me that's the question. And I would just point out that this is not a statistical determination. This is a clinical determination. And there would be various perspectives which I think Dr. Fillit is going to bring to this discussion. There would be a patient and caregiver perspective. There would be a physician perspective. And there might be a regulatory or drug development perspective

I'll point out that there's almost no empirical investigation of this concept. If you look in the literature on the definition of clinical meaningfulness in the Alzheimer's Disease literature, you find so far for me one study. In a survey of geriatricians and neurologists, about 400 of them, the minimum clinically important difference for them turns out to be 3.72 mini mental state points. A change in drug placebo difference we have never seen in a clinical trial. The confidence intervals were large and the range was astounding of one to twelve.

Most studies failed to meet this criterion. The study included a review of the few studies. Notice, it was published in '99. It included a review of a very few studies published until then that had included a minimal clinical important difference. They included Marty Barlow's study, three points on the ADAS-Cog at twelve weeks, a nap study of 2.5 ADAS-Cog points at thirty weeks. (inaudible) study three points on the mini mental at thirty-six weeks week. Or the Wood & Castleton 1.8 points on the mini mental at twelve weeks.

My point, no consistency in either time or magnitude in the existing studies that identified a minimal clinically

important difference. We will soon see more discussion from European taskforce consensus for Alzheimer's Disease therapeutic trials. This is not a regulatory body. This is a group of investigators who meet in Europe, who are interested in disease modification and clinical trials. And they published a number of papers led primarily by Bruno Vellis. They are going to publish ... it's currently in press in Lancet Neurology ... a minimal clinical difference for Alzheimer's Disease of two ADAS-Cog points at eighteen months. Pretty small. It's a minimal expectation.

The placebo problem enters into these calculations. That is the drug placebo difference in Alzheimer's Disease depends on the rate of decline in the placebo group. You do not get most of your action from a drug, from an improvement of the baseline. You get most of the action from the difference between drug and placebo based on how much your placebo declines in the course of a clinical trial.

Unfortunately, in the last decade, placebo decline has been very variable with some studies showing almost no placebo decline. There is some empirical investigation of this.

You're more likely to see a placebo decline with a longer trial. You are less likely to see if patients have a higher mini mental at baseline which, of course, is the direction we want to move because we want more modeled patients in clinical trials. If you do more evaluations in the trial, include more trial sites in the trial, you are less likely to see placebo decline. We see the methodological issues that David raised with large sample sizes in this study.

So here are some of the issues about disease modification then that we have to consider. Alzheimer's Disease progresses slowly. Therefore, the effects of progression in a disease modification trial would be seen quite slowly over time. If you assumed a too many mental state point per year loss, which is not unreasonable, then a 25 percent slowing by an effective disease modifying agent would give you one mini mental state point difference at two years. And two mini mental state point difference at four years. That's with 25 percent slower.

A 25 percent difference then would equate to six months delay after two years of treatment and one year delay after four years of treatment. I just offer these as examples.

If we can get this in our mind ... because again, we're trying to think about how minimal is minimal? So it would mean a 25 percent longer residence in each stage of the disease and perhaps a range around this figure could be considered.

So here's what this would look like. Here we've got patients going from a mini mental of twenty to twelve. Here's a four year period. Here's our base decline right here. These are the placebo group. Here's 25 percent slowing. So that at two years, there's a one mini mental state point. And at four years, there's a two mini mental state point difference with this kind of intervention. You see that more extravagant interventions would be arrest, 75 percent or 50 percent decline. I'm interested today in the minimum. What is the lowest boundary that we would accept for drug development?

So robust drug placebo difference must be balanced against the problems associated with very long trials. You see that the longer you go, the more you see. But the longer you go, the fewer patients that you have. And the more variability and measurement that you have. So you're trying to balance the length of the trial against the

increasing size of the effect. And I would say that around 25 percent slowing may represent the minimum. This is one individual practitioner's opinion.

Let's move onto how patients with early Alzheimer's Disease can be identified for trials. Here are the issues. Early identification is of great importance. And more so than with symptomatic agents. Symptomatic agents actually worked best and had their biggest effect size in the middle of the disease. Our goal with disease modification is to maintain cognition and function at the highest possible level by identifying patients in the earliest phase of the disease.

So we need to identify patients with Alzheimer's Disease before they have Alzheimer's dementia. That is our goal. This is a change in terminology. We could do that by primary prevention trials. And David has addressed that very well. Or early Alzheimer's Disease. That is Alzheimer's Disease without dementia ... Alzheimer's Disease without dementia ... or mild cognitive impairment of the Alzheimer's type.

So here's a draft definition authored by Bruno Dubois and others. I was a co-author of this paper which offers a new definition of Alzheimer's Disease which I think has many advantages and will help drug development. In this definition patients must have an episodic type of memory impairment that must be progressive. This is the kind of thing that we see in every Alzheimer's Disease patient. Clinically, it begins by asking the same question again and again. And in the clinic, it is manifested by failing a three word memory test or a ten word memory test.

In addition, to meet this definition of Alzheimer's Disease, the patient must have a positive biomarker indicative of the presence of the disease. This would be medial temporal atrophy, biperadal hypometabolism, a positive amyloid signal, elevated amyloid or reduce tau or precinial mutation. They would have to have one of these, any one of these. So the definition would hinge on a specific phenotype supported by one abnormality consistent with the biology of Alzheimer's Disease. The important point, this patient need not meet criteria for dementia.

So this definition of Alzheimer's Disease allows us to extend the definition of Alzheimer's Disease back to

embrace the most mild patient who has at least enough change to have a positive biomarker. I think this is an important definition. Because it now allows us to talk about the therapy of Alzheimer's Disease more independent of the severity of the cognitive impairment and to embracing clinical trials those patients who had the earliest changes which is the ones we would like to include in disease modification.

So the idea here is that we would take patients with episodic memory impairment and identify those that have a positive biomarker, those patients now have a diagnosis of Alzheimer's Disease. And we put them into our clinical trial. I'll just point out that of those with a negative biomarker, 70 percent of these people still have Alzheimer's Disease, okay? Seventy percent. But thirty percent don't. And you don't want that mixed population in your clinical trial. Because you're washing out your effect of your anti-dementia therapy.

So for a clinical trial, I think this definition has much to recommend it. So now we would see Alzheimer's Disease increasing pathology from a state of no clinical symptoms. But we know that the amyloid burden is increasing. We can

see that on amyloid scans. Through it, a portion of the disease where there are mild symptoms that do not yet meet criteria for dementia to a portion of the disease in which they meet criteria for dementia.

Note that in this paradigm, you could still use David's suggestion of progression to dementia as an outcome. But it would be progression from the mild stage of Alzheimer's Disease to the dementia stage of Alzheimer's Disease. So the therapeutic clinical trial paradigm still works.

Okay. Alternative designs and outcomes. So I was asked to think broadly about how we might do things differently like David, I share the concept that the FDA has given us good guidance so far. But we are entering a new era here. Randomized clinical trials of anti-dementia agents. You're looking really for the drug placebo difference at the end of the trial. Some alternatives to be considered. The slope analysis. And I think Dr. Katz has told us why that is not a particularly strong approach. And David showed us the Richard Moses study which showed a slope analysis of a symptomatic agent. Showing that certainly slope analysis does not force the conclusion of disease modification.

Slope analysis is also subject to end point leverages that are statistically unsatisfying.

Survival analysis I think is an alternative. And this is time to a defined clinical milestone. David pointed out that there's difficulty defining these clinical milestones. You're looking for a situation in which a placebo group reaches some milestone prior to active treatment. And then you do a survival analysis showing that the patients on treatment do not reach that milestone as regularly as patients on a placebo group.

Time to event onset has been explored in two good trials done by the ABCS. Progression from CDR2 to CDR3 was the Vitamin E trial by Mary Santo in 1997. Progression from MCI to dementia. But again, I would say we could do early AD to dementia of the Alzheimer's type. And it was explored in Ron Peterson's trial. Our problem is that the survival analysis also cannot by itself distinguish between disease modification and symptomatic drug effects. It's like slope analysis in that sense. Because one can delay a more symptomatic state by a symptomatic agent. Therefore, these would need to be bolstered by biomarkers.

Let's come to the dual outcomes that Dr. Katz discussed, cognitive effects and global or ADL effects. Now, what this ignores is behavior. So I'd like to talk about the stepchild of dementia for a moment which is dementia. Because there are three domains of Alzheimer's Disease expression. They are cognition activities of daily living and behavior. And the global assesses all three of these things. So drugs proven to be efficacious for behavioral changes in dementia are currently lacking.

Indeed, the drugs that we use most often for severe behavioral disturbances carry an FDA warning about increased mortality and stroke. So the exclusion of behavior as an alternative primary outcome may discourage development of anti-dementia drugs with behavioral benefits. So I would like to put on the table the idea of behavior as a primary outcome in these trials. It can be done as a reduction in pre-specified behaviors present at the trial baseline. That is patients are agitated at baseline. And you determine whether they become less agitated. Or a reduction in the emergence of pre-specified behaviors during the course of the trial.

That is patients do not have agitation at the beginning of the trial and you determine whether the placebo group has less emergence ... whether the placebo group has more emergence than the treatment group. So alternative for the dual outcomes would be cognition plus a global or ADL or behavior adding that to our menu of possible outcomes. An example here would be the emergence of delusions in the placebo group prior to the emergence of delusions in the active treatment group with this kind of survival analysis.

Quality of life has been much discussed. The instrumentation is not well-developed. It's more patient and caregiver centered. That's a benefit. Caregiver input is required and therefore subject to the same kind of criticisms that David raised about ADLs which is that you're really assaying the caregiver in addition to the caregiver's view of a patient. That makes it complicated. But I think it could be considered if tools evolve.

Going back to the global for a minute, the global assesses function, cognition and behavior. And our problem is that function and behavior are minimally affected in the early patients. So it makes it difficult to show global effects. So this is one place I'm just very skeptical of being able

to get the global to work in the most mild patients. You can see a cognitive effect. I hear very clearly Dr. Katz's argument that we want to know that it's clinically meaningful and that the global is a good measure of that in some circumstances. But I don't think it's a good measure of it in this circumstance. And I wondered whether we could entertain some combination such that there would be an effect on cognition, a drug placebo difference, perhaps complicated by a delay in emergence of either a behavioral disorder or an ADL disorder. So you get the ADL in there. But you do it by a second alternative strategy which is delay an emergence. Because you're dealing with very mild patients. I think the current dual outcome maybe too severe for the early patients.

The NTB I think Dr. Katz has been cleared that other psychometric approaches are fine. Here I wander into territory that I probably shouldn't touch on. But I do want to bring this up because it brings us to the cancer analysis ... or the cancer analogy. We use the ITT, the Intent To Treat, analysis of all randomized patients. And this is the only way to have unbiased data available for analysis in a clinical trial.

On the other hand, it includes, of course, patients who do not get the drug and patients who do not take the drug and patients who do not take the drug throughout the trial. And therefore, it dilutes your trial effect. And the protocol observed case analysis reflect the patients who actually took the drug at the prescribed dose for the expected time. I think that's an important outcome. So I wonder whether the protocol of case analysis couldn't be considered for marketing pending some sort of implementory study or at least play some regulatory role.

Similarly, I wonder whether proof of the concept study. This would be more like the cancer analogy that shows benefit could be a basis for a temporary marketing approval pending confirmatory studies on enriched ... non-enriched populations. For example, taking familial Alzheimer's Disease or (inaudible) positive patients and showing a proof of concept trial with a secretase inhibitor. Then getting marketing approval with a lot of informed consist around the absence of safety data and moving ahead with ongoing safety monitoring in confirmatory trials.

So some recommendations. I'm suggesting that for the dialogue, definition of disease modification might include

effect on the underlying disease, plus an impact on the clinical course. This might include the clinical outcome, a biomarker and a correlation between the two and the clinical biomarker correlation should be pre-specified with many alternatives available. I'm suggesting that a 25 percent reduction in disease progression might be considered a minimum hurdle for drug efficacy. But I think there should be a range around that. And it certainly requires discussion.

I'm suggesting that these new Alzheimer's Disease research criteria that include patients with mild symptoms have benefit for clinical trials and should be seriously entertained. I'm suggesting that survival analysis be among the analyses used in trials about anti-dementia agents. I think they have benefits particularly in these early stages. I'm suggesting that behavior be considered as an alternative to the global or ADL as a trial outcome along with cognition.

That quality of life is not yet ready, but might eventually be an alternative. That the dual outcome might be too severe for early AD where the global does not appear to be measuring anything except cognition. And therefore,

perhaps cognition plus a delay to emergence might be a reasonable alternative to our current dual. And then as I mentioned, the NTB and other psychological batteries could be alternatives to the ADAS. I'll stop there and look forward to the panel discussion.

(END OF HOUR 2)

10:00 am

Mr. Dan Perry: Thank you very much, Dr. Knopman. I'd now like to introduce Dr. Howard Fillit-

Dr. Howard Fillit: Thank you. It's really an honor to be here and work with you on something that I know is really dear to all of our hearts as individuals and as citizens of the world. This is a problem that is really a tragic problem when we see it among patients. And I'm going to talk from sort of a bottom up perspective today about what it looks like in the real world of clinical practice, some of the things we're talking about, and try to give a perspective from that point of view.

Some of the things it turns out that Jeff and David have talked about, I'm going to talk about. Also some of the slides refer to the same studies, but from a different perspective. As a geriatrician, one thing I do want to say in terms of my perspective is that the average age of my patients for the last almost thirty years is eighty-five. And since the average age of onset of Alzheimer's Disease is somewhere like 76 or 79, we're really talking about a

geriatric population. So the perspective here is what does all this mean for a very old population who has to deal with these issues?

And so I think that the perspective here ... really one of my messages is the bottom up perspective from the clinical office versus the top down perspective, the population based perspective, that the FDA has to deal with, that that's the mandate of the FDA is to take a societal perspective. And so the patient, as we've heard, is often concerned about quality of life. The caregiver is often concerned is the primary issue about quality of life. How is this drug going to affect my quality of life?

The physician also concerns himself or herself about quality of life. Because the physician cares for the patient, but also has a scientific background and has to be able to interpret data from population based studies and translate them and apply them in a meaningful way in clinical practice. So in that sense, for the physician and also for the patient, one of the things I'd like to talk about is that clinical meaningfulness might include not only effectiveness, but also safety issues.

And finally, as I mentioned, from the regulatory and also the payer point of view, and this varies among societies throughout the world. In some cases, these agencies are often concerned about the same issues in our country, payers and regulatory approval agencies differ. Although that might change with Medicare Part D coming onboard and effecting other policies. But certainly, these agencies have a population or a societal perspective. And that's very different.

Now, one of the principles ... and I'm going to quote my colleague David Noppin here ... about what I want to talk about is that most Alzheimer's Disease patients are cared for by primary care physicians, either internists or family practice physicians. So let's just talk about what it's like in clinical practice. Because we're talking about complex clinical trials. But let's recognize that the average physician visit today is somewhere between seven and eleven minutes. And so that doesn't leave a lot of time for counseling. And yet, this is the time when the physician has to determine whether clinical meaningfulness is really there.

And as David mentioned, if you really think about it, if the average clinical practitioner in primary care has somewhere between 1,500 and 3,000 patients in their practice. And half their practice might be Medicare. That might be let's say in a practice of 1,500 patients, 750 people, older people. And if five percent of those people have Alzheimer's Disease, five to ten percent, make the numbers easy, say it's ten percent, that's seventy-five people. And if they're seeing that person every three to six months, you can see that on a weekly basis, that primary care physician is seeing three or four at the most patients with Alzheimer's Disease a week out of perhaps one or two hundred cases.

So when we're thinking about the busy day of a primary care physician where the incidence of data is, as David mentioned, is three or four new cases per hundred, the primary care physician doesn't really see this very often, a new case of Alzheimer's Disease. I remember going to Tampa, Florida because there was a primary care practice there with 15,000 people in an area which is the oldest area. The most elderly people in the country is in Tampa. And the practice was not prescribing any anti-dementia therapy, very minimal amount.

We met this doctor. We pulled into a mall, little mall, go in the back door. We had some Chinese food. Go into a room probably not a whole lot bigger than this podium. The doctor came in and he had a white coat on, no tie. Sat down with him. And I said, you know, if you have a practice of 15,000 people here, you must have about 7,500 old people. He said, yeah, that's about right. Maybe more. Because we're in Tampa. And I said if you have 7,500 old people, you must have 750 or 500 people with dementia down here. And he said, you know, we don't see it. And that was why he wasn't prescribing Alzheimer's drugs for anybody.

So this is really down in the trenches that we're talking about. So what I'm saying is that clinical meaningfulness based on the statistically significant population based data from clinical trials have to somehow be translated into clinically meaningful information for individual patients, caregivers and physicians in the office. And also, that clinical meaningfulness in clinical practice varies with individual physicians, patients and caregivers' values. And that therefore includes some consideration of safety and effectiveness or risk benefit.

Now, there are some principles of geriatric medicine here that I think are important to consider. One is that as we all know, quality of life and not life expectancy is by far the most important outcome. Patients in my practice and geriatric patients in general would rather die of a heart attack in the middle of the night than suffer the many ravages of Alzheimer's Disease over time. But we also have to remember that in clinical practice for geriatric patients, co-morbidity is the norm.

We know that even in clinical trials, 90 percent of people ... this is a geriatric population ... have at least one medical co-morbidity and that about 65 percent of these patients have two or more medical co-morbidities. And many of them have five or six or ten diseases. And so, understanding the impact on the role of Alzheimer's Disease in the context of this kind of patient is complicated. These patients are on multiple medications. And sometimes they're on ten or fifteen medications. And so we have drug/disease interactions and drug/drug interactions and disease/disease interactions that often are not considered in clinical trials that play an important role in the

meaningfulness of drugs for Alzheimer's Disease in clinical practice.

And the other thing that we've talked about that, I kind of want to talk about from a slightly different perspective, but really reiterate that function is the most powerful predictor of outcomes in this geriatric population. So the reason is that when you consider a geriatric ... this is a principle, a basic principle of geriatric medicine, that when you consider the patient who is eighty years old that has five or ten diseases and is on ten or fifteen medications, that there's no way that anybody or any computer program or any clinician can understand the many, many ways that all of these diseases and drugs are interacting to ultimately go through what I call the function funnel of all these black box interactions to come out with how the person ... who they're going to interact to result in the person's ability to function.

But from the other side, when you're trying to evaluate that person in clinical practice, the most important thing is their function. Because function takes that black box and gives you an outcome measure of how all of these different interactions that we can't understand in their

full amount result in the patient's ability to maintain independence in the community. And if you look at geriatric studies, a function, for example, what is the most powerful predictor of hospital length of stay or hospital discharge or hospital readmission or mortality in geriatric patients? By far, it is the ADL, the Activities of Daily Living scale. Can the patient bathe and groom and dress and so on? Do they have incontinence?

More than the principle admitting diagnosis. More than if they have congestive heart failure or pneumonia or anything like that. And it's because of all these drug interactions. So function really, really is an important determinant of outcome in the geriatric population. And, you know, the ADL scale was developed by Sydney Katz at Columbia more than thirty years ago. And it's been studied in over 20,000 patients. So this is not like, hey. We're just asking people about whether they can bathe or dress or groom or if they're incontinent. But it's really a very ... as I think, a very objective measure in fact of outcomes in geriatric patients. And it is measurable. And it is the primary determinant of quality of life.

Now, from the bottom up perspective, for an Alzheimer's drug to be clinically meaningful for patients and caregivers, its effects have to be obvious or observable. And I agree with what Jeff and David and Rusty have said, I understand. I am a scientist. And I think that these statistical outcomes are very important for us to get drugs to market. I'm not objecting to that at all. But I'm saying that the challenges that we have in using those population based clinical trial data and translating that information into clinically meaningful information for patients and caregivers and doctors is very difficult. Because they're looking in that seven minute visit for a clinically obvious outcome.

And so in addition to adding the clinician's perspective, we would like it to be not only observable, but also measurable in some way. Now, that could be the gestalt of a civic. But we know that even to the extent that doctors in practice are not using the mini mental, I can tell you they're not using the civic either. And so, they're just basically coming in. And the patients comes in. And the doc says, hey. How are you doing? You know, how's he doing? How's your husband doing? How's your wife doing? And, you know, what are they going to say?

They don't measure function objectively, patients. They don't measure cognition objectively. They have really no idea. I mean, you see patients that can't count backwards from a hundred by seven. And they're undiagnosed because family members have been watching this happen for three years and never bothered to think that there was a problem. The patient can't draw a clock. They can't tie their shoes. And they're coming into my office at this point and saying what's the diagnosis? Because patients, lay people, cannot make an early diagnosis.

And basically, doctors can't either. As long as social personality we know in this disease is maintained until fairly late. And so as long as social personality is maintained, Mary walking down the street, hi Mary. How you doing? Oh, I'm fine, great, terrific. Mary has moderate Alzheimer's Disease. And nobody's picking it up. So what I'm saying is these data, for example, that we've used for drug approval are terrific. They're statistically significant effects on these global measures and on function and on cognition. But the general impression in the community, in the practicing community and in the lay

communities, that the drugs don't work. The drugs don't work.

So I think that's our challenge. Why is that? And are we failing to communicate properly? Is the effect size too small? Or is it something else? I don't really know the answer. I think it might be an effect size issue. But that's the impression. I mean, sometimes we do see patients come in where they're responders. They're big responders. And family members will say, yeah, he's better. And that's the outcome measure. But most of the time, we're kind of going on hope and faith.

And the doctor has to end up of being in a position of saying the drug rep or I read the study and it says that the drug works. So let's keep them on it. And really to be honest I think selling hope to patients. And it's hope based on clinical trial data. But it's not clinically meaningful. So it's not that we're doing something wrong by selling hope. But it's just that the clinical trial data don't translate well. And yet, the drugs do work. And here's where I think geriatrics, the geriatrician's point of view if you will, or the older person's point of view becomes quite important.

Because if you look at a numbers needed to treat analysis which is derived from clinical trials and is the inverse of the odds ratio, you can see that for geriatric outcomes such as hip fracture with alangini, you have to treat fifteen people for four years to prevent one hip fracture. Or even for something like a myocardial infarction, you have to treat 28 people for four years with Estatin to prevent one myocardial infarction. Or a well-established outcome measure of hypertension to prevent a stroke or a heart attack or a death, you have to treat somewhere between 30 and 86 people for five years to prevent one of those outcomes. Which is great. I mean, these drugs work and it's terrific and in fifty year olds and sixty year olds and forty year olds, that's terrific.

But if you're dealing with an eighty year old that has a life expectancy of five to ten years, is this really a highly meaningful way to look at when they have Alzheimer's Disease. And if you look at then the translation of numbers needed to treat based on what we currently have, the drugs that are perceived as they don't work and the chief statistical significance in clinical trials, you can see that repeatedly everyone of these studies translates

into something like you need to treat about five or ten people with Alzheimer's Disease for about three months or less than a year depending on the outcome to get kind of the equivalent of a eureka response in the clinic. Which's when the patient comes in, the caregiver says, yeah. He's better.

So we're not just saying this was measured on an ADAS-Cog in the clinic, but it was really sort of based on is the patient observably better and the family member says yes. So the numbers needed to treat would tell us that the drugs do work. And I think this kind of approach to it both based on the numbers needed, but also the values here. Because if you were eighty years old and you had a limited pharmacy benefit, and now we have Medicare Part D. But you've still got the doughnut hole. And you said to the patient, well, here's two drugs, you know.

And you've got Alzheimer's Disease. And you can take this one and you have a one in twenty-five to a one in eighty-six chance of preventing a heart attack from now and dying in the middle of the night. Or you can take this drug and you have a one in five to a one in ten chance of improving your cognition for a year or so. Which one would you take?

And maybe we need to educate doctors about that. And similarly, if you take this sort of ageism, it's almost ageism in my mind, perspective that's out there, we're approving drugs for cancer where people's hair fall out and they vomit.

And the drugs cost $80,000 a year. And we're getting improvement in life expectancy of three months. And everybody applauds. This is the greatest things since sliced bread. And here's the data. Stage two and three breast cancer. Breast cancer is almost a disease that with prevention has been cured. And you've got to treat ... and it's a disease of elderly women. And you've got to treat four to six people for ten years. Well, my patients don't have ten years. Their life expectancy is five years. So again, is the breast cancer outcome worth it compared to the cholinesterase? Which drug would you take if an Alzheimer's patient walked into your office and had breast cancer and dementia and had a limited pharmacy budget, which one would you want to give to your mother?

So let me just talk about the bottom up perspective on clinical meaningfulness of disease modifying therapies for a minute. We have symptomatic benefit. We have slow

progression. You've all seen these before. Disease arrest and disease improvement. The problem is that for what's going to probably happen in our clinical trials, if I give you this scenario that where the cholinesterase inhibitors at three to six months and maybe as long as a year actually improve function, and yet their effect is not perceived as from the clinical trials, translated into clinical practice, they're not seen as clinically meaningful, right?

And now we're going to develop disease modifying drugs that have as Jeff said perhaps a 25 percent improvement in the disease progression. So it's going to be probably somewhere in that green line ... the grey line, sorry, of the slow progression, right? And let's say that time out there is somewhere around one year or whatever. The problem is that these patients in this box in the office are worse. Bottom line. They're worse. And not only are they worse, but they're demented. And everybody, it's terrible being demented. It ain't a good thing.

So what happens in my office or in anybody's office is ... or in the primary care doctor's office where he's seeing two or three of these among a hundred people in a week. So it's in and out ... is that we're going to give people

disease modifying therapies that have statistically significant benefits, 25 percent, 50 percent, rate of improvement on a slope, whatever. And then they're going to take the drug. And not only is the patient going to suffer this terrible disease over time, but they're going to get worse.

And at six months or at one year, they're going to come into the office. And the doc's going to say how's he doing? And the caregiver's going to say he's worse. And not only that, he's still demented. And he's more demented. And why the hell am I taking this stuff? And the doc's going to have to say, well, you know, in clinical trials, this drug slowed the rate of progression of the disease by 25 percent and the FDA approved it.

Now, all I'm saying is we have a problem in lost in translation here between the real world and what we're talking about here today. I don't know how we make that message effective. I know I've worked with the company. I didn't show my consultancies and everything. But, you know, on education of doctors for over thirty years about Alzheimer's Disease. And the message is very hard to convey. And I don't know how we're going to do it. We can

get drugs to market. But how are we going to make them clinically ... you can get disease modifying drugs to market. But how are we going to make them clinically meaningful?

Is the marketing material enough to make them clinically meaningful in practice? And so if patients remain demented, skepticism will remain. And I think one of the problems is that the patients are evaluated on a gestalt or a subjective basis. And perhaps a practical suggestion is that although the civic seems like a practical end point. And as Rusty said, and it's very thoughtful, it's an end point that includes the caregiver's opinion which is something we want to do. It's not the kind of practical end point that will translated from these population based clinical trials readily into the clinic to obtain some sort of objective measure that the doc can say, well, you know. If you didn't take that drug, you would have been worse. How are we going to do that? That's part of the problem.

And I think if would be ... I personally think it would be very valuable then to have a surrogate marker. I mean, if you think about the hypertension model or the cholesterol model, we're selling hope with statins. And we're selling

hope with blood pressure medicines. Because let's say I take a statin at whatever age, fifty-nine, right? And, you know, if you look at the numbers needed to treat with statins, okay. We're advertising a 30 percent reduction in the risk of heart attack which is great. But the fact is that we're reducing the absolute risk from 22 per 1,000 to 17 per 1,000. And I have no idea if I'm one of those five per 1,000 who's not going to get a heart attack.

So at the end of the day, you know, you can sell me whatever you want. But I don't know. I'm taking this drug on hold. And not only that, but we know that Lipitor and the statins only account for thirty or forty percent of the variance in risk of getting a heart attack. And not only that, but when I take Lipitor, I have one of two outcomes clinically. One is I don't feel any different. Or two, I feel worse. Because I get tendinitis or myealgis or whatever.

So I know the clinical trial data. And I don't know why I'm taking the statin to be perfectly modest. And it's the same thing with blood pressure medicine. Patients take blood pressure medicine to prevent a stroke ten years from now. And they don't feel any different. The only feel

either the same or worse. But their number is better. Their cholesterol is down. And the docs, you know, three minute visit. I got your number. It was 240. Now it's 150. Everybody's happy. Yea. That's terrific. Your number's better.

But I think it's important. I think that's kind of going to be the value of a surrogate marker for us. We want to mainstream Alzheimer's Disease. And I think with a surrogate marker of some kind, it will help us in communicating the effectiveness, the clinical meaningfulness of the drugs that we want to develop. Until the day comes along we can prevent the illness. And as has been said, probably for people, the most clinically meaningful outcomes are to prevent or halt or reverse the progression.

But slowing I think ... if it's going to have clinical meaningfulness, while I understand and I agree with the regulatory approach that it can be just 25 percent slowing, I think that I'm worried that a 25 percent slowing won't have clinical meaningfulness. And I think we have to have sort of some kind of obvious slowing of progression. And I don't know how we do this. So one of the questions kind of

comes to how do you manage expectations in the clinical management of these therapies?

And we had a panel of experts that you all know not too long ago with clinical guidelines. And one of the things we addressed was, you know, from a practical point of view, how does all this therapy and management play out? And I'll just show you two recommendations out of about twenty. One was that the panel said that in clinical practice, the issue of mild to moderate and so on has very little meaning for a doctors and patients. Again, because of the subjective nature of this, the whole issue of mild to moderate and the indication for stage of disease is much less meaningful in clinical practice.

And I'm not sure that it's a good way for us to go. I don't think that doctors say, oh, yeah. You're in this particular stage. Because patients have so much heterogeneity. I just saw a patient the other day who on the mocha scale which is a scale I use instead of a mini mental. But it's a scale of zero to thirty. And she scored like three or four. And it was the first time they were ... and these were intelligent people. I mean, this guy was a partner in the leading law firm. His son-in-law

was a partner in the leading law firm in New York City, very intelligent people. And they were bringing in the mother with like a mini mental of zero and asking me if she was demented. You know, it's just mind blowing.

So, one of the things we came up with was like maybe we should somehow recommend to doctors that they need to counsel patients and caregivers about what is a realistic response? And I won't get into this, but I think again in translating clinical trials data into the marketplace, into clinical practice, it is creating meaningful information that what is the value of these different kinds of responses? What is an effective response?

I'll just say that in this study function is important. And it's important from the point of view of I think active life expectancy. Functional life expectancy is something that I kind of like as an outcome measure. If you want to sort of bridge this gap between life expectancy and function, you can look at a geriatric concept called active or functional life expectancy. And just in this study from Dodge et al, it was published a few years ago, you can see that the average life expectancy, for example, of an eighty year old person who's a healthy female is about nine years.

If they're non-demented, but they have zero to one impaired IADLs, their life expectancy goes down to six years. But if they have AD and 1 ADL, their active life expectancy, not their total life expectancy, but their active life expectancy, is 1.2 years.

So they have a 75 percent reduction in functional life expectancy. And again, in the spirit of trying to communicate what the value of our therapeutics are and what is clinically meaningful information, this means that if you could prevent the decline of one or two IADLs, you would increase functional life or active life expectancy. And that's the key principle. Geriatric patients again don't care about overall life expectancy. They care about functional life expectancy.

And so David showed you this study from Richard Mose. Here's another way that Pfizer has chosen to present it or that the data was presented. And it shows that functional life expectancy is 72 percent longer in patients. Now, that's meaningful in a person that has a one or a two or a three year active life expectancy if you reanalyze the data, you're giving them a thirty or a forty or a fifty percent increase in active life expectancy, you know.

That's better than taking a drug that makes your hair fall out and you vomit and you get three months increase in life expectancy with cancer. This is a better deal. You get more time with your grandkids.

And yet, on the other hand, there's this concern, and we get this pushback that we're going to develop disease modifying drugs. And they're going to increase years of disability and progressive decline. And I don't know from the community how we can really deal with that expect to say that if you take that point of view, then everybody should be prescribe five packs of cigarettes a day. Because that's going to decrease years of disability.

And I'll briefly go into caregiver burden. I think that we don't use this enough. I think caregiver burden is a very important outcome measure here. I don't have to tell you what it's all about. And we've demonstrated in multiple trials with multiple co-esterase inhibitors impact of these drugs on caregiver burden. And I think that this is a very meaningful clinical outcome that might be included. In clinical practice, it's a clinically meaningful outcome that shouldn't be set aside as necessarily even secondary outcome. Because I think it's very meaningful to

caregivers who are coming into the office. And the doctor's talking to the caregiver and saying how's he doing? But the caregiver is very concerned about their own quality of life and health as well. And I think to the degree that these drugs improve caregiver burden, it's very amazing. Because I think it really talks to the efficacy of the drug.

Okay. I have to wrap up. I would say that there are several of these outcome measures that are in my package that are clinically meaningful that are derived from clinical trials that we would talk about that have meaningful clinical outcomes. I think the surrogate marker could be used to look at these. And I just want to talk for one minute about the issue of risk and benefit. We have various approaches. But we have to consider in the clinical practice, in the one-on-one clinical practice, between patients and clinicians, their values and what goes into their values when they think about a drug for any condition or in particular for AD.

I've had patients who want everything done with Alzheimer's Disease. They want care. And I can keep them alive for fifteen years. And I have ... good nursing care. And I

have patients who say this is the worst thing that ever happens. You know, throw me out the window when I get diagnosed. I don't want to go through it. I don't want to be cared for. So there's a lot of value issues here that really impact on the clinical ... the perception, the perception of the clinical meaning of drugs. And so if we look at risk benefit ratio, as risk goes up or the ratio goes up, then generally we think that individual risk tolerance goes down. And that's probably true. But when you consider that individual patient in the office, that varies very much by their values.

So the point is that a patient who has an aggressive set of values that wants to really take risk will have a very different curve on this spectrum. And the problem for us is that how do we incorporate this kind of issue into our regulatory process? There's a huge disconnect between the regulatory process and individual patient values here. How do we allow a patient who has aggressive values choice and access to drugs? That in the position that the FDA is in today where the back is up against the wall on safety, we're not allowing choice for these patients.

And just to close here, this is illustrated very much by ... this chasm is illustrated very much by this study where we were able to participate with a group funded by Elan here to look at a new concept that Ray Townsend and Ray Johnson came up with called the willingness to accept risk as a way of evaluating risk benefit in individuals. So it was a survey of over 2,000 people. And basically, the bottom line message here, the sound bite, is that about 35 percent to 40 percent of people said that if there was a drug on the market that could halt the progression of Alzheimer's Disease, the question was if there was a drug on the market that could halt the progression of Alzheimer's Disease, would you be willing to accept the risk of death or stroke in order to gain access to that drug?

And roughly let's say, to make the numbers easy, 40 percent of those people said, yes. I would want to take that drug. So Rusty and I were talking. And Rusty has a great sense of humor, but also represents the population perspective on this issue. And when I told Rusty about these data, he said, Howard, that's great. Those data are great. But if there are five million people in the United States with

Alzheimer's Disease, I can't approve a drug that's going to kill two million of them.

And I think that really in cold heart ... not in cold heart, but in cold reality, illustrates the chasm between this population based perspective that Rusty has to take and the bottom up view that we want to incorporate patients' values into access to drugs even if they have certain risks. So I think the value of therapeutics is common concern. Clinical meaningfulness should include values. And we have to address the issue of a process of clinical decision making.

And just want to close with this slide which is that this is a concern to all of us. You know, 2,000 years ago, Cicero said to live is to think. And Marcus Aurelius, a famous Emperor of Rome, said, in his twist on carpe diem for the 21st century, he said we must get on with our lives, not only because we are closing in on death with each passing day, but because our mental capacities may desert us before death decides to take us. And that's an expression of values.

But from a population perspective, the National Institute for Clinical Excellence in the 21st century said prove it. Thank you, very much.

(END OF MORNING SESSION)

10:45 am -- BEGINNING OF PANEL DISCUSSION

DAN PERRY – Welcome back from the break. I'd like to ask everyone to take their seats. (inaudible) Welcome to Dr. Gilman.

DR. SID GILMAN: I know Russ Katz very well and have great admiration for him. And I've worked with Paul Lieber before him. Second, I'm the Chair of the Safety Moderating Committee for two clinical trials in Alzheimer's Disease. These are sponsored by Elan and Wyeth. One is on Bapamisermad which is (inaudible) one, now in phase two trials and about to enter phase three trials. I've also chaired the Safety Moderating Committee for Schuyler and Osotal. It is ELN005 which is just starting in a phase two trial.

All right. With that, the organizers asked me to present a brief summary of the proceedings of this morning. I'll do very briefly. Dr. Katz made a wonderful presentation pointing out the historical development of two primary (inaudible) Alzheimer's Disease trials, the ADAS-Cog and another functional measure, and gave the rationale for this. I happened to be on the panel during the initial

discussion of this with the drug Tacron when that was discussed actually in this very ... in these very chambers in this hotel under its previous guise or name. I have a long history with this hotel.

He also pointed out that according to the recent developments with the disease and the drugs for the disease that it doesn't take a great deal of difference in these measures to show success. And then Dr. Fillit commented later upon this, bringing this full circle, that the drugs that are currently available, the symptomatic therapies, are not marvelous. That is it's difficult to see the effect. As a clinician, I can tell you that some patients respond remarkedly well to these drugs and some do not. It's just on the average one you don't see a great deal of change as a matter of fact. Yet, they achieve the required hurdle of difference between placebo and active drug and therefore should be made available to the general public.

Dr. Katz also went into some of the problems related to the earlier stages of the disease and Dr. Knopman took that up further. And specifically pointed out the problems with mild cognitive impairment or equivalent states when there is, as Dr. Knopman pointed out, a slower slope, a less

steep slope. That is the decline occurs less rapidly in the earliest stages when people transition from normal cognition to mild impairments of various kinds, particularly memory.

As opposed to the later time during the phase of mild or moderate Alzheimer's Disease where the slope is more steep. And therefore, it's possible to show a difference between placebo and active drug group more directly easily with fewer patients over a shorter time period. This is not discussed, or not directly discussed. But it's been obvious in recent years though that the population of placebo patients is different. That is that placebo patients are declining at a less rapid rate on average than they did a decade ago or thereabouts.

At least in U.S. and Western Europe trials, in recent trials with another drug called Delubon showed the early progression rate in Russian subjects who had no other medications aboard. There are various reasons why this may be true. But the fact of the matter is that the deterioration rate is now different than it once was. And this requires now that clinical trials be prolonged and some of them now the recent ones are going for eighteen

months to have the placebo group show the decline needed to show a difference if a drug works.

Dr. Katz also commented upon surrogate markers and felt that a surrogate marker by itself is a problematic end point. And then we heard that again from Dr. Knopman and then Dr. Cummings how one demonstrates disease modification. Dr. Cummings made the point that if one can show a staggered onset trial or staggered delivery of drug versus placebo trial and augment that with biomarkers, then perhaps ... and have a survival analysis as the other means of showing beneficial effects and disease modification, then perhaps we'll have the means of doing exactly that, showing disease modification.

That is the Holy Grail as far as I'm concerned. What I would like to see is medication that will slow the progression of the disease to the basic pathophysiology. Symptomatic treatment is obviously important. But even if a drug does not show direct symptomatic improvement even in a clinical trial, but a huge difference from placebo and a decreased rate of decline. Obviously not measured with the slope alone, but with other means. Then I think we will

have what we are looking for. That is disease, true disease, modification.

I really enjoyed hearing Dr. Fillit's comments. That is the real world. It's like a cold shower on a hot day. It was wonderful. Pointing out to us what it's going to be like for people or what it is now like for people in elderly age groups who have multiple different complaints, including dementia, and how infrequently they will be tested by the general physician. It's true in addition ... I don't think you mentioned the point that these people are commonly taking twelve medications. The average person I see, usually an elderly subject, is taking a dozen medications at minimum.

All right. Now, with that, my task next is to turn to our panel. And we will have initial brief comments from them, one to two minute comments, is what I have been asked to request. The first if Bill Bridgwater who is a consultant to the Alzheimer's Association and is himself a person with Alzheimer's Disease in the early stages.

MR. BILL BRIDGWATER: Well, my disclosure is I'm also a patient consultant to the FDA. My name is Bill Bridgwater. And

I'm here today to represent the Alzheimer's patient community, 27 million worldwide and growing. I would like to express my sincere appreciation to each of you for taking your time today to be here and continue to seek a cure for this devastating disease. As you can imagine, the subject is very near and dear to my family. As we talk today, I will offer you a glimpse of the emerging face of Alzheimer's, in my case, early onset, early stage Alzheimer's Disease.

My onset occurred when I was forty-eight years old and in the prime of my professional career. During my twenty-five year career in information technology, I held the positions of Vice President, Director, President and Chief Operating Officer of several ... or four separate multi-billion dollar corporations. Previously, Alzheimer's Disease claimed the lives of my grandmother, my father and my aunt. And although this implies a strong genetic link, we now know today that only three percent of cases are inherited.

I am hopeful that as a result of our conversation today, we will agree to place a stronger emphasis on Alzheimer's Disease, one that includes the fast tracking of all medications, similar to the methods previously implemented

for cancer and HIV/AIDS. Although I sit before you today knowing with medical certainty that I will die from this disease, I have committed the remaining years of my life to raising awareness and approaching ... as we approach the pandemic and working with you to find a cure.

Our goal should be to establish a process which results in a future without ... without Alzheimer's, pardon me. and to this end, if I may be of assistance to any of you in this room or the particular organization that you represent at any time, please call upon me. And in closing, I look forward to a fruitful conversation today and again a future without Alzheimer's Disease. Thank you.

DR. GILMAN: Thank you, Bill. Bill's spouse, Twyla Bridgwater, is herself an FDA caregiver consultant. She is also a member of the Alzheimer's Disease Advisory Committee.

MS. TWYLA BRIDGWATER: Actually, I don't think I'm a member of that committee. But I would like to acknowledge that I am doing some work with the FDA. First of all, I do want to express the thanks that Bill extended to you. I think it's incredible to have these minds in this room to address this

subject which is very near and dear to my heart. And I want you to know that you bring hope to the millions of caregivers and families who are impacted by this disease. And we're anxiously awaiting arrival of new and improved therapies. And from a caregiver perspective, of course, the ultimate goal would be a cure. But we're also in need of treatments which will halt or deter or even reverse the symptoms that the patient would suffer.

We need drugs that will allow a patient to stay at home for a longer period of time. This may not seem very clinically meaningful. But for that mother who may not recognize her sixteen year old son when he graduates from high school, a year, six months, can be a huge difference. So we'll take whatever you can put out there for us. But we also need more and better affordable diagnostics. For Bill and individuals like him with the early onset diagnosis, it's important to adopt an aggressive treatment plan. So that they can maintain a long and normal life for as long as possible.

And his typical program, you know, it's been daily medications which we all know and love, Araset Mendena or Exlon. And the supplements which we all just hinge our

hopes on. Because there aren't a lot of studies involving supplements. Of course, the rigorous exercise program and cognitive exercise. We're doing everything we can to help him have a healthy mind. And as you can imagine, extending the life of the patient provides an equally valuable benefit for the caregiver and the extended family unit. So we're all benefitting from the benefits of drug inspiration. And we appreciate all the work you're doing to get to a cure.

We don't know how long these benefits are going to stave off the disease in someone like Bill. Because I guess there aren't many studies for people of his age group with the particular groups which are available. But I can tell you that more people are going to be in this situation. We are in a situation where we see people on a regular basis around the country because we're all getting together to see what can be done. And Bill's gone from the primary provider for our family to being totally disabled from a work perspective. So this is a total role reversal for us.

And fortunately, we have the financial means that we're able to make this transition. But many Americans do not. And I'm sure worldwide, the numbers would be even more

staggering for those who aren't prepared for the onset of this disease. We know what we're facing. His father died of the disease. We saw how it ravages the body and the mind in the last few years. And more and more Baby Boomers are going to be diagnosed. As I said, the financial impact our health care system and the emotional toll on families can bankrupt the social services system infrastructure as we know it today. Time is a costly and unavailable luxury which most Alzheimer's families do not have. And this nation cannot afford to take the time. They need to get fighting against Alzheimer's Disease now.

My desire as a caregiver is that we move forward in the development of a process to make the cutting edge medications more immediately available to our community. We as caregivers are desperate and we're looking for ways to stave off this disease. We're looking to the FDA and you as research partners to help us in this health care crisis. And you are our hope for a nation without Alzheimer's Disease. Thank you.

DR. GILMAN: Thank you, Twyla. Next is Meryl Comer who has been a Alzheimer's caregiver for fifteen years. She's President of the Geoffrey Beanne Foundation for Alzheimer's

initiative. She's an Emmy award winning reporter, producer, moderator and talk show host for more than thirty years. Meryl.

MS. MERYL COMER: I'm really a desperate housewife. Just for a moment look at this beautiful couple. And if we could, wouldn't we all freeze this moment in time for them? If this was as good as it gets, would you take it?

MS. TWYLA BRIDGWATER: Sure.

MS. MERYL COMER: For as long as you could.

MS. TWYLA BRIDGWATER: Right.

MS. MERYL COMER: That's our goal. Two minutes to comment on fifteen years as a caregiver almost leaves me speechless. But those who know me, not quite. My husband was like many of you. Renowned scientist, a dedicated public servant. So I come before you with great respect. Your charge is monumental. You deserve to be celebrated and not maligned. But when I look around the room, know that I'm terrified for us all. Because when you witness early onset, it's like seeing the future and seeing what confronts all of us.

Diagnosed with early onset at the age of fifty-six, my husband's face was sealed. He was Chief of Hematology Oncology at the National Institute of Health for thirty-one years. Unlike Bill, he was in denial all the way into the disease. He maintained his brain and it just didn't matter. He was misdiagnosed twice. And by the way, you doctors are terrible. You just won't accept a diagnosis. After a two and a half month stay in the hospital where I actually put him in under a presumed name to protect his identity because he was so passionate about his work, he was diagnosed with early onset and a behavior disorder. And I was worn that he was too dangerous to come home. But no one wanted us, not even a $100,000 private pay.

Today, fifteen years late, at the age of seventy-three, he is late stage dementia, 24/7 care and still at home. I left my career to manage my husband. My husband survives. The man I married didn't. And last year, my eighty-six year old mother was diagnosed after five years of mild cognitive impairment. On the mini mental, she's thirteen. Ask her what's the name of the President, she says do I have to say his name? Now, that's a political statement.

But nothing has changed. Fifteen years later, the drug pipeline is full. But no new therapies are available to caregivers and families. So now I care for two at home, no relief, no hope, and forget about a cure. I just want to slow the progression. So when it comes to a definition of clinical meaningfulness, mine is simple. It's a hand that can lift itself to feed. It's a mind that doesn't see personal care as an assault. Very simple. I'm a caregiver, not a criminal. And I'm desperate.

And I'll give you a very quick example. Six months before the FDA approved Memontine, I went to Europe. I bought it over the counter in Paris and tried to get it in England. I was desperate. I brought it back. And it brought me, when you live in the margins, it meant the difference between my keeping my husband at home and getting some degree of compliance versus having him institutionalized where I knew he would be restrained and over medicated. Would I do it again? You bet. And I have managed any side effect. And I will take the side effect on because that's what families do.

Let me offer you just ... I've gone over my limit. But I'm a fearless woman and I'm too old now. I want to give you a

what if proposition. Because what you don't feel when I listen to scientists is an urgency about this disease. And the what if proposition when I look around the room how many are Baby Boomers? Raise your hands. All right. This is based on the notion that sixty is the new forty. And that we can't Botox this away. What if Alzheimer's was newly discovered, not 100 years old, driving fear through every Baby Boomer about the slow and tortured death it brings.

Politicians fearful for themselves and the tsunami effect on the health care system. The media broadcast daily casualty alerts with every POA outbreak. That's Prisoner Of Alzheimer's. Each and every minute that passes means another family is dealt this cruel and ultimately fatal hand. Right now, that's true. Every seventy-two seconds, someone else is diagnosed with this disease. Now, let me ask you this question. Would that scenario persuade the FDA with its societal charge to use its streamlined review and approval mechanisms for promising Alzheimer's drugs that it has used so effectively on conditions like cancer and HIV/AIDS. Would it revisit standards for clinical meaningfulness that are now twenty years old?

Let me state it one other way. How cruel an irony if the FDA for safety first to protect the public misses or denies the threat and inadvertently allows Alzheimer's to become the untreated epidemic of our generation? The fact here is that every one of our generation is at risk. It's about us and how more meaningful can that get? Thank you.

DR. GILMAN: Thank you. Dr. Dale Schenk is our next speaker. He's the Executive Vice President and Chief Scientific Officer at Elan Pharmaceuticals. He's been working in basic and clinical aspects of Alzheimer's Disease for over twenty years. It was his seminal demonstration published in 1999 showed that immunization in the transgenic mouse could remove beta amyloids. And subsequently, he and others went onto demonstrate that beta amyloid was not only removed, but the mouse which had difficulty negotiating a water maze could in fact relearn and function in that way yet again. For his work, Dr. Shank has won the Patamken Prize. Dale.

DR. DALE SCHENK: Thank you. I said I was praying that I didn't have to speak after hearing the very moving statements of the patient caregivers. This is a devastating disease. And it's something that effects us all. I think what I just want to make one or two key points, particularly from

the industry perspective. As Dr. Gilman pointed out, we have ... my colleagues and I have worked for about twenty years in this area. And it's a difficult area. But when you develop a drug ... and that's what we're trying to do. That's a piece of this puzzle that we do.

And the fact that you, all of us together up here who are sitting here, a team, as opposed to having different views, we're all part of a team. We have different roles. So our role is to make drugs that treat the disease. And I think we want to make a meaningful difference to patients. It's not about making a drug. It's about making a meaningful difference with the drug to patients.

So how do we do that? Well, again, just making one or two points here, there's 100,000 things I could talk about. But what we have to do is focus usually on a single target, a single hypothesis. That's what drugs do. They inhibit an enzyme or they block a receptor. Or they do whatever they do. And, in fact, the definition of Alzheimer's Disease is clinical. It's related to dementia. We heard about it today from our experts here. It's also pathological. And over the past twenty years, there's been a huge amount of biology that has taken place.

Some of my colleagues up here actually, we were involved in developing some of the first diagnostic tests involved in Alzheimer's Disease. Beta 42 and CSF and Tau. There's now 300 papers since those first observations supporting that those CSF markers work. And in fact, if you look carefully at the predictive value and specificity and sensitivity, they work essentially as well as a very experienced clinician can do. But they're not really used.

And if I look at successful areas of disease management and treatment, I see the marriage diagnostic tests and biology together with treatments. Dr. Fillit talked about hypertension and cholesterol. And although, it was somewhat discouraging some of the things you said about it, where would we be? One would not know to give somebody a cholesterol lowering agent if we couldn't measure cholesterol. One could not know to give a hypertensive agent if we couldn't measure it. I guess my key point here is that we have to marry the two.

And it's time for us to move the field forward and begin to use the biological markers even if slightly at risk. Because that's the path to disease modification. That's

the path to keeping somebody who is mild in a mild state and not progressing to moderate. That's the path to making a difference in everyday life. Can a person close themselves? Can they still lead a valuable life? Can they do all these things that we want to maintain in our function?

And so in closing, I want to make it clear again that I believe that's what we have to do sooner rather than later. I always hear that these tests, you know, that a test to a given marker's not validated 300 papers later. What do we have to do to validate it? I mean, I don't know what else we can possibly do. I can think of a few things. Honestly, as a scientist, you always can. But enough time has passed, enough work has been done. Let's move on. Let's move forward. Let's try and make a difference for the patients.

DR. DAVID KNOPMAN: Well, thank you very much. At this juncture, we're waiting for questions and answers not only from the panelists you just heard from, but also from our speakers from this morning. So to get things started, let me just pose a couple of questions. I will key off Dr. Schenk's last comment. And this will be for Dr. Katz. You mentioned that in order for us to ... it's not that bad ...

in order for us to show disease modification, we'll have to show some sort of clinical efficacy, clinical meaningfulness. But perhaps augmented by some other study such as a biomarker. You touched on that. I wonder if you could elaborate just somewhat to tell us what you think will be needed in the way of validation. How does one validate a clinical biomarker to be convincing to you?

DR. RUSSEL KATZ: First of all, let me just back off a little bit and say what the law permits or doesn't permit. Let me back up even further. When we approve drugs, invariably we approve them, as I discussed and as we all know, on the basis of some clinically phase valid outcome. When we approve a drug to treat epilepsy, we count seizures. You have fewer seizures on the drug than you do on placebo. That's good enough to get approved for epilepsy. So the clinical outcome is sort of the gold standard for the obvious reasons. We want to make sure we're doing something right for the patient. What clinical measures we've been talking about in Alzheimer's Disease.

We had a law that says that we are permitted, not compelled necessarily, but permitted to approve a drug on the basis of an effect on what we would call an unvalidated

surrogate. In other words, we could approve a drug on the basis of an effect on some lab test which is what a surrogate is, as we've been talking about, without any clinical concomitant, without any information at the time about what it's doing clinically. We could do it.

The problem is we're not going to know at that time whether or not the effect that you've seen on the surrogate actually is going at anytime to be reflected in the clinical outcome. And there are many examples in the history of medicine where a surrogate marker has been an outcome measure in a trial. And it has moved in the direction that we expected it to move in the correct direction. Decreasing arrhythmias, for example, for some cardiac drugs. But the clinical outcome either didn't change or it got worse on the drug compared to placebo.

So there's always a risk if we're going to approve a drug simply on the basis of an effect on an unvalidated surrogate. One that we don't know under drug treatment correlates with the disease. And sometimes ... but the law permits us to do that. We've been reluctant. We haven't done it in Alzheimer's Disease. Because we don't think we know enough yet about what the effect on a surrogate, a

drug induced effect on a surrogate will mean clinically without a clinical outcome.

And when Dale says that what else do we have to do to validate a surrogate, there are 300 papers. It depends, of course, what you mean by validate. It might very well be the case that there are 300 papers that say when the CSF Tau was in a certain direction or when the hippocampal volume is such and such, that's equivalent Alzheimer's Disease. We have a test that will do in diagnosing the disease as an experienced clinician. That's one form of validation. That's fine. Maybe we don't have to do clinical exams anymore. At least for diagnosis purposes.

Another way that people talk about validation is that the marker, we know how the marker tracks with the natural history of the disease. And we saw some of that today. It's clearly true that various MRI measures track very, very well with the progression of the disease. The ventricular volume increases as the disease progresses. The hippocampal volume decreases. Very nice correlation. The problem is when you treat somebody with a drug and you see positive effect on the surrogate, does it also translate into a clinical effect?

And that's what I was talking about. There are many examples where there's a disparate effect on the surrogate versus the clinical outcome. Unless you check the clinical outcome, you don't know. So many sponsors have come to us and said, well, how about if we did a study which showed an effect on clinical outcomes? Let's say a cognitive measure and a global measure. And we have a surrogate marker or a biomarker. That also moved in the right direction. Would that be enough to get approval for a disease modification claim?

And we've said it's possible we would be willing to entertain such a package of information as supporting a disease modification claim. There are still questions about that. Because they maybe correlated. But they may have nothing to do with each other. There may be an effect on the surrogate. But the drug effect that you see clinically might be a symptomatic effect. So it relies a lot on what we think we understand about how the drug works, what we think the pathophysiology of the disease is. What we think certain changes on the biomarker are. It's complicated. But we've said we would be willing to

undertake that package for review and see what the field thinks.

So I don't think a surrogate by itself without a clinical concomitant in 2008 would be acceptable. Because we don't know what the clinical consequences are unless we measure them. And really we're talking about clinical consequences here. So that's what I think. I think we still have to take into consideration Howard's point which is we would approve a drug, as I said before, where everything gets worse over time. The clinical gets worse. The biomarker gets worse. It just doesn't get as bad as the control. We've approved drugs and we have approved drugs on the basis of that sort of information.

The question is at the end of the day do people want that if the effect is small? If people are still coming to the office a year later saying he's worse? It's hard to tell a patient, I gather, yeah, but he would have been even worse if he wasn't on the drug. Is that what people want? Maybe it is. And we've adopted that very de minimis standard for drug approval. It is de minimis. But the real question is is that something that people want? We're willing to do that. But is that clinically meaningful? And we've

decided it is. But we really have to I think seriously take Howard's comments that either it's not being pitched adequately to patients or they really don't want that. They want something else.

DR. GILMAN : Let me just follow-up with David Knopman about one particular biomarker. You mentioned that we see shrinkage of the brain MRI scanning in Alzheimer's patients as they progress, and specifically hippocampus shrinkage occurs and can be measured accurately, of course. Then as you recall in the AN1792 trial, the long active immunization trial which had to be stopped because of unfortunately meningoencephalitis, there was greater shrinkage in the people who had antibody typers[?] and who had relative preservation of memory, at least by the neuropsychological test battery. So what we do with a biomarker that goes the opposite to what we expected?

DR. DAVID KNOPMAN: Well, I think that sort of feeds into Rusty's point in that particular study. It is the case, just to backup, that the decline in brain volume and the increase in ventricular volume are very consistent across patients. It also occurs in normal people with again. And why that occurred in that study is unknown. I think that

viewing the cognitive effects in AN1792 as positive is going a little beyond the data frankly. All you can say is that the people who had the antibody response did have their brains shrunk. But that was essentially in my opinion uncorrelated with the cognitive measures. It was a subset of a subset.

I don't think that is necessarily interpretable. I think that was a problem. I think that particular finding gave us a lot to think about. It was little bit of a setback for the field to see that. But, you know, that study was stopped premature when those results were looked at. That was ten months later after most people only got two injections. I think it's very difficult really to draw any firm conclusions about that.

DR. GILMAN: Thank you. Question for Jeff Cummings. We've heard very little about safety today. We heard the comment from Meryl Comer that almost any degree of risk is worth it if one can preserve intellect. I'm paraphrasing badly, Meryl. Forgive me for that. We heard a bit from Howard Fillit also about risk relative to benefit. Can you tell us more what is tolerable in your community of patients with respect to safety of medication? Let's take the

extreme case in which a disease multiplying drug is extremely effective. What risk would you be willing to accept for your patients? Or would you be comfortable with for your patients?

DR. JEFFREY CUMMINGS: That's a data free question. So this is a speculation and not data driven. It is a terrifying disease. And I think my patients would accept a reasonable degree of risk. But there would be many nuances in it. For example, could they get sick but then recover to their current state versus get worse and stay worse, for example. So it's not ... while it is true that Alzheimer's Disease is inevitably progressive, it is not true that the Alzheimer's patient is without any quality of life. And I appreciate Bill being here. And I appreciate Bill as making an important contribution today. And that is contributing to your quality of life, Bill. Because you are helping all of us.

So I don't want to say that we would be accepting a risk ... I don't personally want to accept a risk in conjunction with my patients that would further complicate that quality of life. Because I think Alzheimer's Disease patients to a

certain level of severity continue to enjoy a certain quality. I'll stop there.

DR. GILMAN: All right. For Bill and Twyla Bridgwater, Bill, you have the disease you were fighting every step of the way. Twyla, you are the primary caregiver. If the FDA has the problem with public perception that it's allowing unsafe medications on the market, that it needs to be more risk averse than ever before, tell us about your personal risk tolerance for a drug, a medication, that would slow the progression of Alzheimer's Disease. Or you can get symptomatic benefit.

MR. BILL BRIDGWATER: Having been happily married for thirty years, I will defer this question to my wife. And I will follow-up on her comment.

DR. HOWARD FILLIT: Smart man.

MS. TWYLA BRIDGWATER: I think that, as Dr. Cummings said, that most families who suffer from Alzheimer's Disease would happily take a little bit of a setback to maintain the place where you might be in your life. Let's face it, I mean, function at home, being able to care for one's

personal needs, is monumental. Especially when you're looking at a 200 pound person versus 130 pound person. You know, it is a toll emotionally. But physically it's very exhausting as well. So as long as the drug would give you some stability to remain at home, as I said earlier, we're pretty risk tolerant there.

MR. BILL BRIDGWATER: I would just add that I'm in the early stages as you can clearly attest. Medications that I initially took, the menincept, complemented with Trazidone and Clamazapan to sleep, because insomnia was one of my earlier symptoms. I had fits of stuttering. I couldn't talk two years ago. And I've regained that through a lot of therapy and to some extent I'm hoping the medication is helping that as well.

But when I look at risk, I know the end stage of this from watching my father pass away over an eight year period of time. So, yes. I'm willing to take risks. And I would say the risks are comparable to individuals that early on took AZT with HIV/AIDS. And then the cocktail that ensued. Many of those people were not cured. Many of them were. We've learned a lot from those studies. Similarly cancer and the chemotherapy and radiation that cancer patients

undergo creates incredible hardship to those people and their caregivers. But in many cases, we've been able to mitigate, halt or even cure those individuals.

So that would be my perspective to you on risk. And if my comments weren't clear enough, I would say yes. I would tolerate a high degree of risk on the basis of knowing that it's a terminal illness today.

DR. GILMAN: Thank you. Meryl Comer, you heard people claim that Alzheimer's Disease is just as urgent a disease as cancer and HIV/AIDS and that these drugs deserve priority view just because they are AD cretin, potentially dangerous drugs that is, drugs with substantial side effects. So do you think that Alzheimer's Disease is bad, as bad as cancer or HIV/AIDS from your personal experience with your husband?

MS. MERYL COMER: All disease is cruel. But I would take any disease that gave me the ability to fight with my mind and make decisions about the course of treatment. And Alzheimer's denies you even that dignity. As the wife of a scientist, trust me. I did my homework on Ementine before I went to Europe. And I was most concerned about toxicity.

But I would take a chance on most drugs to buy a margin. And a margin becomes a quality of life. And trust me, the caregiver defines the quality of life for a patient. The issue is what happens if I wear out? Then I'm worried for my husband's quality of life. So the notion of risk, unfortunately we've had populations before that have defined it for you and demanded it, cancer patients. Well, they're going to outlive the cancer. And they're going to outlive the HIV/AIDS. And they're going to end up with Alzheimer's. It's not unlike children with, oh, the disease that ... it's the disease that starts early that was really how you discovered the first gene for.

DR. GILMAN: Cystic Fibrosis?

MS. MERYL COMER: No, not cystic fibrosis. Down's Syndrome. Look at the double jeopardy. All of the marvelous medications and pharmacology. They now live to be 45 years old. But they all get Alzheimer's. It takes your breath away. That's the other end of the spectrum. So risk tolerance has not been verbalized to a community because the caregivers are worn out. And it's incumbent upon the baby boom generation that is now taking care of their parents and says I see my future. And this is unacceptable

for our generation. That to me will help you define the risk and take the burden off of the scientists who have to say, well, be careful, be careful. This is a disease that is systemic for society. So, yes.

DR. GILMAN: Thank you. Dr. Schenk, there's been a lot of discussion about early detection of Alzheimer's Disease. From the industry perspective, can you tell us about trends in Alzheimer's Disease drug development currently? What do you think would help, would prepare us for future treatments that maybe coming forward?

DR. SCHENK: Thank you for the question. I think that most diseases ... you hear about this with diabetes, for example, almost any disease, they're all ... I like to think of it as organ based. I think by the time that a patient presents clinically with Alzheimer's Disease, the brain disease, if you will, has been going on for a very long time. It's not a new concept. We know this. And so what we are actually trying to do in the clinical arena with Alzheimer's Disease is treat a very advanced disease in the brain.

And so the best approach I think to that and the best one for society is to back up into early Alzheimer's Disease as defined clinically. You talked about it today. it was discussed today. Any way that we can better define early disease, in reality, I'm sorry to say this, that's probably going to be moderate disease in the brain. But there's going to be a much bigger progress and bang for the buck so to speak with all of these therapeutics if you can treat as early as possible. It's not quite a truism. But once neurons are gone, they're gone.

There is some replacement that's exciting in research that they can be replaced to a certain degree. What we really want to do, however, is the nerve cells that are ill, have them recover. And so we have to hit it early. I think that the most important thing we can do as society is to prevent it from occurring in the first place. That will actually reduce the numbers and reduce a huge burden on society. In my mind, it has to be done part and parcel with the treatment strategies that are obviously ongoing.

DR. GILMAN: Let me ask you further about the FDA and its large number of priorities currently. Do you think that the FDA needs to spend more time and resources focusing on

expertise in this area? Do you think there is a sufficient number of trials forthcoming that it will be a problem for the agency to handle them?

DR. SCHENK: I was going to say because I think the FDA is doing the best job they can possibly do. I think there's a huge number ... again, from the industry side ... there's a huge number of compounds that are going into clinical trials. I actually think the discussion today, getting back to the teen concept, we all have a role to play in this. We each have a piece of it. We all have to come together to do it. I think on the industry side, we have to put the very best compounds or potential drugs forward that we can possibly do.

I think we have to have metrics. We have to understand meaningfulness from a clinical perspective. All of these things have to come in place. I think we have to, as I said earlier, have good biologic end points. So that we don't have the lack of clarity that we currently have with our end points. Having said that, it has to work clinically. But we have to find a way to make it easier to measure.

DR. KNOPMAN: Can I make a point? To bring back the question you first asked Dale and the question that you had asked the Bridgewaters and Ms. Comer. In terms of, if we are getting into the early stage of the disease, and I think it's standard throughout medicine, the healthier the people are are the ones who we want to try to treat earliest. The risk tolerance there is going to be lower. No question about that. And if we're going to change that, that's really a huge change in public perception. As Howard said, he's willing to take Lipitor, reluctantly willing to take Lipitor.

But if it caused myalgias on a daily basis, I'm not sure he or I would be willing to continue to take it to prevent the disease twenty years from now however certain that disease was to occur. So I think that we have to keep it in perspective and industry has to keep in perspective that the earlier we move, the lower the risk tolerance. That's just a principle.

DR. KATZ: Obviously, there's been a lot of talk about risk tolerance. And let me tell you how we think about it. First of all, I would think about it in two separate phases. We haven't really talked a lot about the IND phase

or just starting with the development of a drug. But in the very early development, and this is sort of analogous to what Dave just said. In the very early development of the drug, it's a new chemical comes to us. It's never been given to people before. It's proposed as a treatment for Alzheimer's Disease.

Honestly, we tend to be fairly ... I won't say concerned, but we treat those drugs like a lot of the drugs that we deal with where we have at the moment no information that the drug is effective. There are certain animal studies that need to be done. There are certain chemistry information. The usual things that we would ask for in the very early stages. And we tend to ask for those things whether it's an Alzheimer's ... the purported Alzheimer's drug or whether it's an anti-seizure drug or whether it's an ALS drug, whatever it is. There are certain rules. And by and large, with rare exception, we apply them.

Sometimes that results in a delay in development. Because the companies don't have the appropriate animal studies. Or there's some other piece that's missing that we think would expose people to an unreasonable risk. Remember at this stage, we have no idea ... we don't know that it

works. We don't know how safe it is. We know nothing about it other than from the animal data.

So with very early stages, we tend to ... I won't even say risk averse. But we tend to apply the mutual rules. But when you get to the point of thinking about all the data's in now and we get to years later and we get to thinking about whether or not this drug should be approved for marketing, we tend to tolerate a great deal of risk. Not all risk. And I think that if I did say that to Howard in the past about the two million, I'd say it again. If a drug is to treat five million people, but we thought two million people were going to die, we wouldn't approve that drug. And I don't think people would want that drug approved.

So it is always, of course, a balancing how much risk and what the risk is versus how much benefit. To the extent that we can quantify either of those. And we don't do a great job of quantifying either of those. Because I don't think we can. But we tend as a general matter to approve drugs that have significant risks. So all anybody has to do is look at a random sample of ten of the drugs we've

approved for anything. And half of them probably have black box warnings. The diseases we deal with are bad.

And we recognize that Alzheimer's is as bad or worse than anything out there. Everybody who's involved in Alzheimer's regulation recognizes that. We tolerate a great deal of risk if we think we can inform people as to what the risks are. We don't tolerate every single degree of risk as we talked about. But I can count on the fingers of one hand, maybe of one finger, the number of drugs we turn down for Alzheimer's Disease because we thought they were too dangerous. It just doesn't happen very often. So we tolerate a fair amount of risk, even for the benefits that we have seen to date which are modest as most people would agree.

So I don't think we are particularly risk averse in that sense. Certainly there are new safety initiatives coming down the pike. And everybody I think interprets those ... many interpret those as meaning in the future the FDA will be more risk averse. I actually don't think that's true. But we'll see. We try to do the right thing on a case-by-case basis. This notion that as we treat earlier and earlier disease, the tolerance for risk will go down may or

may not be true. If we had a drug that we knew prevented Alzheimer's Disease or stopped it in its tracks or really had a meaningful effect, we might still tolerate a great deal of risk. Even though X percentage of patients who take it might never develop the disease.

As I said, everybody knows that Alzheimer's is as bad as it gets. And we would be ... I venture to say, although we obviously are not at that point, but I venture to say we would be willing to tolerate a fair amount of risk, even in very early patients or patients who are at-risk who aren't even symptomatic. Because it's as bad as things there is out there. And if we can prevent it, we'll tolerate the risk.

So certainly we think about risk, of course. But it's the rare case where the drug doesn't make it through that has shown itself to be effective by the current standards because there's some toxicity. It's a very rare occurrence.

DR. GILMAN: First, Howard Fillit and then Bill Bridgwater.

DR. HOWARD Fillit: I agree with Rusty. And I think the issue is not risk. I mean, as somebody said to me, being born is risky. You know, when you get born, you're at risk of death. Driving a car is risky. Taking an aspirin is risky. Buying insurance is risky. There's risk in life. So obviously, when you put a chemical in your body, there's going to be risk. So I don't think the issue is whether or not there's risk. It's really how we manage risk that I think is key. And I think it's how we manage risk through the approval process, post-approval and then in the office that is really a more relevant question.

I think, as Rusty said, most drugs that are effective, and I think for Alzheimer's Disease, we will have effective drugs that might have some safety issues. And if they do have safety issues that appear in the pre-approval stage and come to the approval decision, then I think if the risks are substantive, we've learned enough about managing risk in the community with drugs like Accutane or Tasovry to be able to put in place at the time of approval risk management programs that clinicians can use to make drugs available.

If the risk turns out in the post-approval process, I think that we can do a better job. Because this is where the agency has had press and so, Vituron, for example and Avandia and these others. Where after the drug's been taken by a million people, we find some death. You know, there's black box warnings post-approval to manage risk. There are also, for example, an Accutane post-approval mechanism for managing risk. So I think we definitely can manage risk. And that's what all industries do. When we manage risk in a car, we involve seat belts.

And then finally in the office, this issue about asking individuals about population data regarding risk. The way we manage risk in clinical practice is what's called the practice of medicine. We take the science that is given to us by the clinical trials. And then we deal with individual patients. And individual patients vary tremendously in their values and in their risk tolerance. And so my job as a doctor, it's not ... it's for me to have the knowledge. But I can't impose my values. It would be wrong for me as a practitioner to impose my values on a particular patient.

So let's say there was a drug out there that had significant risk and benefit. My job is to try to effectively communicate the data. And then somehow get a sense from the patient what their values are. And if they say I want everything done, my values are that I think that I have early AD and I'm willing to take those risks to prevent it or to treat it, then it's my job to prescribe the medicine despite the risks. If patients say to me, well, I don't want to take that risk. Then it's my job to say, okay. Then that's what we're going to do.

And I think that's where the practice of medicine comes into play. And I think that's where this translation of information that comes out of the clinical trials and from the FDA, we need to do a better job of transmitting the clinically meaningful information about these drugs. And if there are risk issues, then we need to implement appropriate risk management strategies like we did with the touch program for Tasabry.

DR. GILMAN: Bill.

MR. BILL BRIDGWATER: Just briefly to echo those sentiments. I lack the medical communicating style. But I will put

things in kind of a correlation perspective. Many of my friends that have developed HIV/AIDS over the years, twenty, thirty, forty years old, which would be considered very young relative to the Alzheimer's community, didn't hesitate to take the drugs knowing that there would be side effects. Similarly, I have many friends that are women and have had breast cancer or may even have breast cancer history in their family. And they responded by having radical mastectomies to avoid even the potential of having the disease. So I want to reiterate that I don't think risk should be an issue. I think education should be the issue. And if a drug passes with the ability to create improvement, then through the doctor consultation with the patient a decision could be made for that particular patient situation.

DR. GILMAN: One final question for Dr. Katz. The question is the following. Do you think that you have sufficient in-house expertise in neurology to handle Alzheimer's Disease first? Second, if Congress were suddenly to flood the FDA with funds and you were the recipient of them, how would you augment or change your staff?

DR. KATZ: Well, listen. I certainly think we have sufficient expertise to do the job we are tasked with doing. Sufficient expertise, that is to say the expertise per capita basis, do we have enough people who have expertise? No, of course, we don't have enough people. We are hiring people and we need more people. There's no question ... and I think that's a general becoming increasingly obvious to Congress and other people and bodies that we need more people. And we're trying to do that.

But as I say, I don't believe ... others obviously may have a different view. I don't believe it's a question of whether or not the people we do have have the expertise. I think we need more people. And again, I think much of what we're talking about here ... and I think the critical question is how do we assess the clinical meaningfulness in the future in early patients and for disease modifying agents and that sort of thing. I think there's a lot that's not known about that.

And I think we probably heard that from most of the folks here that we are entering a new age. I don't think anybody has the definitive expertise on those questions yet. And I completely agree with Dale. It is a partnership. It's the

academic community. It's the industry. And it's us getting together, trying to figure out with places like this what do we do next? I think we all bring a certain type of expertise to, as Dale says, the puzzle. And I don't think it's a shortage of expertise other than globally we don't really know what causes the disease.

And we don't really know how the drugs work. And we don't know exactly what to do about it. But that's a problem that everybody shares.

DR. GILMAN: Thank you. That's very helpful. Let me turn the panel over to the audience now for questions.

[off mike question, difficult to hear]

AUDIENCE QUESTION: We've heard that modification of the large (inaudible) therefore can be quite expensive. And a product that is ultimately (inaudible) return on investment. It's unfortunate that we don't have a care representative on the panel. I was just wondering perhaps what is the panel's perspective, what needs to be demonstrated? It is clearly demonstrated for care (inaudible) ultimately society in the future to (inaudible).

DR. GILMAN: Dr. Knopman.

DR. KNOPMAN: I think one of the issues right now that you're raising is pharmaco economics and cost-effectiveness. And clearly around the world, in the U.K. and Australia and places like that, cost-effectiveness is becoming part of the regulatory and payment process. In the U.S., we also have entities or constituencies that consider cost-effectiveness such as the payers, the managed care payers, the Medicare part, the Medicare Advantage plans, for example. And now we have Medicare Part D covering 95 percent of the elderly with the pharmacy benefit.

And I think the evolution of that would be, you know, we have an institute now for cost-effectiveness for comparative effectiveness it's called. And so I think that what we need to do to address the issue is not only kind of the way we've done pricing in the past which is based on experience and wisdom and those kinds of things. But I think ... and we're seeing that certainly in the field. A lot of these clinical ... I'd say most clinical trials today are incorporating health economic outcomes into the trials…

(END OF HOUR 4)

12:00 noon (Panel discussion continues)

DR. KNOPMAN: ... that we have to decide sooner rather than later before it really gets out of hand.

DR. GILMAN: Next, Bill Thies (from the Alzheimer's Association) wanted to make a comment about it.

MR. BILL THIES: Well, I've got a comment and a question. The comment is around this price issue. And what I really want to say is that I can hardly wait until we as an association have the opportunity to address this issue. We've got some experience from the existing drugs and the drug benefits. I know that we can make an impact on whether (inaudible) will happen or not. And (inaudible) take our shoe off and pound on people's desks until this s really taken care of the way it ought to be. And that's a terrific opportunity for us (inaudible).

The question I have actually goes back to the last thing that (inaudible) Rusty (inaudible) if you had the benefit of being able to (inaudible) and they haven't been able to fight back a little bit. So here's my question. Ask Rusty

if he had enough resources. So you've got a long career in training young researchers and physicians. My question to you is how many times have you said to a resident, you know, if you really want to have an impact on the field, get a job with the FDA in the neurology section.

DR. GILMAN: Oh, every day. It's a calling, Bill.

DR. KATZ: Let me just say it's a good question. But first, let me say that Dr. Gilman has given more time to the neurology division at the FDA than probably any fifty residents who've made a career of it. But it's still a good question.

DR. GILMAN: Other comments about that? Well, we really appreciate your fortitude and your being behind all of us very much. I can't see you taking off a shoe and pounding on a desk though.

DR. GILMAN: My question is about the issue of risk. And so far, we've discussed it. We've been talking about what we might call down size risk or the risk of harm. And as I've listen, the first question I guess is just an opportunity to clarify what I think I've heard is that there is quite a

bit of tolerance for down side risk. And as I listened to the presentation if I interpret it correctly, there's less appetite for upside risk. So, for instance, (inaudible) based on its impact on a certain marker if we don't really know, it's hypothetically there could be an upside. But we don't know. There's great uncertainty. And so my question in a sense is is that right? And shouldn't we be thinking about the upside risk in a way different from the downside risk? So no tolerance in the upside. We need certainty. Even if we're willing to tolerate a little bit of variance around certainty on the downside of potential applications.

DR. KATZ: That's a very good question, of course. I don't know that we need certainty. I think there has to be ... before we would approve a drug on the basis of again what I'll call an unvalidated, start with validated, you know, granted it's a non-issue, but an unvalidated surrogate. I don't think we need certainty. But I think there has to be sufficient consensus let's say at least in the field that we understand what this drug induced effect on this surrogate actually means clinically or will mean clinically. That's a tough burden.

It's not that we would never do it. It's just that I don't think we're there yet. It's possible at some point we will have sufficient understanding about the pathophysiology of the disease, sufficient understanding of the mechanism of the change induced by the drug on that surrogate marker. And what that all means clinically down the road for patients. It's possible someday we'll have enough information on all of those areas to do it. But again, one has to be humbled by the previous experience in many other areas with surrogates where the surrogate went in the right direction. And clinically, ultimately the patients did worse. Or the case with the vaccine, however it really should be interpreted. But where the surrogate went apparently in the wrong direction entirely. What does that mean?

To approve a drug on the basis of the effect of an unvalidated surrogate makes a lot of assumptions about the effects of the drug. The drug by the way may have the effect you want. But it also may have some negative effect that interacts that's there for the patient. So there's a lot of things you have to make assumptions about when you do that. And we may get to the point where we're willing to make those assumptions. But I think there has to be

considerably more agreement in the field before we'd be willing to do it.

It's not to say it wouldn't happen. And particularly in the earlier patients I think is where this is really ... it's where sort of surrogates came out of that world in HIV/AIDS. Where the outcome you really cared about was five, six, seven, ten years down the road. You couldn't do those studies. So you had to rely on a surrogate. That's what we're talking about here. That's the place where surrogates I think are most potentially useful. But even so, you'd still have to have more information than we have now.

DR. SCHENK: It's actually (inaudible) on this. Many of the ongoing phase three studies, certainly our phase three studies and other groups phase three and phase two studies, at last good clinical measures and the various biomarkers or imaging end points are being looked at simultaneously. There's been a bit of a history in the field where people doing imaging aren't really following the patients extremely close clinically. And people doing the clinical work aren't really looking at the biomarkers. The people doing the biomarkers aren't really doing the other two.

And so, the clinical trial work is forcing all these to come together. And I think some researchers are putting them together too. So we need that data as well. It's coming about very, very fast.

DR. FILLIT: Yeah, I think one of the things about surrogates is that before we can call something a surrogate, you have to have an effective treatment. I mean, if you look at the history of cholesterol, it was identified as a risk factor in epidemiology in the '50s. But it didn't become a surrogate for twenty, twenty-five years until we had effective treatments which had a proof of concept that by altering cholesterol, you put that in the disease. And then showing that with the effective treatment that the biomarker or the surrogate for that matter moved in the direction with treatment that one expected. So these are sort of postulates that have to be fulfilled before something is called a surrogate. We don't have effective treatments. We don't know ... I mean, we think that we're pretty confident that amyloid, for example, plays a role in disease. But we don't know that yet. And we don't have a drug approved or even in phase three it shows that if you move amyloid CSF beta or whatever in a certain, you know, if you treat the patient with the drug that the surrogate

moves. So I think part of the confusion here is for diagnostic purposes, I can order a CFS beta test, a beta 42 test today. It's available. And for diagnostic purposes, a lot of these surrogates in clinical practices are actually available. But in terms of using them as a surrogate, we first need a treatment on a target that gives proof of concept in humans that this target, like amyloid is valid. And then from that, secondarily we have to prove that the test related to that target like amyloid moves in a direction one way or another that's correlated with the treatment. And then you can say, okay. Now we're ready to say now we can approve a drug based on the way that that surrogate moves.

DR. GILMAN: Go ahead, question.

GREG MURPHY (audience member): Hi, I'm Greg Murphy from Eli Lilly. We've had some good discussion this morning relative to the length and the size of some of the clinical trials. But some a very practical aspect which is today slowing down the development of Alzheimer's with these compounds is the ability to enroll patients in clinical trials. I think this is a good news, bad news story. The good news is a number of pharmaceutical companies are

trying to develop new treatments. So we're effectively competing with each other for the same very limited number of clinical trial patients. So again, I think this is a partnership. From a patient standpoint, we need to encourage more patients to enroll in clinical trials. From a sponsor, FDA and academician standpoint, we need to design the trials in such a way that they don't play such a huge burden on caregivers and on patients that they can practically conduct a trial and participate in a trial. But that is, you know, it's not uncommon for trials of a relatively large size to take a year to a year and a half just to enroll patients. So there's a real need that I think in a short term has some practical solutions to it.

BILL BRIDGWATER: A dynamic that applies to that is the driving mechanism for a trial. And obviously, all the pharmaceutical companies are very familiar with that process. in my particular case, because of a very active sports career, I had thirty concussions. I also broke my deck when I was in high school. So I've had quite a bit of head trauma. And as a result, I'm excluded from most trials for that reason. I don't know that I would ever be qualified under those circumstances to participate. But if there could be a lessening of the criteria, I think you

would have a much larger and relaxing perhaps even of the age grouping. Although, the pathology of the disease doesn't change from your thirties to your seventies. And it's easier to get a statistically relevant differentiation at the elder age than you could for my age. I think that's one of the things that could give you a higher number of participants in the studies.

DR. GILMAN: Meryl Comer.

MS. MERYL COMER: My greatest concern is that the pharmaceutical industry, looking at the timelines, the problems with clinical trials, they run the numbers and they say we're out of here. We just cannot make any headway. So you have a patient population waiting for something and that you back away from us. Because the interim successes are not permitted. Whatever can be agreed on gets delayed and that to me is the big pending concern. We can talk to insurance companies about de-risking the front side of the disease. So if you get to earlier diagnostics, they open the window like amnesty. All right, between 40 and 50 buy in. Because they know that's the sweet spot. Because they know they're going to be paying out longer. But my concern is

the pharmaceutical industry will say, thank you very much. We're moving on.

PANELIST: I think it is an issue in recruiting. And we were talking earlier about risk. But when it comes ... and people were saying they're willing to tolerate risk. But it's interesting. As somebody who's been involved in recruiting subjects for twenty years, it's in fact difficult. People don't like the ideas of placebo controls. Many patients have acquired this notion from the cancer world where phase one and phase two studies are done usually without placebo under different circumstances where they think they can just get a drug. And we can't do it that way.

And so that's a matter of education. It is a matter of altruism. And we actually need to increase the tolerance for altruism. We need the Alzheimer's Association to continue to pound on the importance of participating in clinical trials. We also need to have the infrastructure of people and institutions and centers with expertise in recruiting validly diagnosed patients, not patients who've been retread through five different trials who may not have Alzheimer's Disease. So I think it is a problem. And for

all the talk about tolerance of risk, when the rubber meets the road in doing clinical trial, people are risk averse.

PANELIST: We have health educators who go out in the field and go to independent living institutions and various step-down units from there to try to recruit people for clinical trials, both placebo and for active (inaudible) groups, including people in the earliest stages of Alzheimer's Disease.

BILL BRIDGWATER: Just a follow-up on that if I could, Dr. Gilman. How many people in the audience represent pharma? How many of you take patients in their thirties, forties and fifties in your trials? That's my example.

DR. GILMAN: There's a question?

BILL THIES (audience member): Well, this is a comment on the clinical trials and the availability of volunteers. And the association feels that that is actually a serious problem already. And certainly if one projects out into the future, the first amyloid (inaudible) medication demonstrates that (inaudible) is like to trigger a huge spate of similar kinds of approaches to the disease. And

the population simply isn't ready for that. So in the last year, we ran five area pilot program to help recruit people for clinical trials. And the data on that looks promising, including some surveying of investigators in the pilot sites where those of you who deal with investigators know that they seldom say anything positive.

But they actually said it's easier to recruit people for trials this year than it was last year. I think that's encouraging along with some other data. We have in our budget to expand another ten areas coming up in this next year. And I anticipate this is a program that the association will be involved in for quite some time. Because if we don't do it, I don't think anybody else will.

DR. GILMAN: The Alzheimer's Association has been just a great ally in recruiting for our site actually. Let me ask if there are other questions at this point. Yes?

ROY CLEMEN (audience member): Hi, Roy Clemen. I'm from J&J. I think this is a question for Dr. Cummings on the diagnosis of Alzheimer's Disease versus dementia. And we've heard that the real benefit of the disease modifiers is for the really early population. So how far away do you think we

are from a true diagnostic. We've heard Dr. Katz say in the past they're not in the business of establishing new diagnoses. So it's community that will have to drive it. So how far away do you think we are from a true diagnostic that could be FDA acceptable and community acceptable for the diagnosis of early AD, be it an imaging assay or a blood assay or otherwise.

DR. CUMMINGS: When you say true diagnostic, I think you're meaning a biomarker diagnostic. Is that right? We have ... I think we have a true diagnostic now which is for Alzheimer's dementia that has been widely accepted and implemented in all the clinical trials. My point was to try to expand that backwards through the use of more modest phenotype in conjunction with a biomarker. I agree with Dale actually that the CSF markers when they are used have the same sensitivity and specificity as the clinician. They run in excess of 90 percent. So in terms of a true diagnostic for people who have a lumbar puncture, I think we're essentially there. I don't see any way to improve on that frankly.

PANELIST: Can I just ask a clarifying question?

DR. GILMAN: Yes.

PANELIST: Presumably, the CSF data are correlated in people who already have the diagnosis.

PANELIST: No, it's with MCI. There's a good paper that looked at the prediction of dementia in people with MCI. And the CFSI markers were really quite good in predicting future dementia.

PANELIST: But also amyloid imaging is another augmenting feature.

PANELIST: The next point I was going to make is that I think we have several that are emerging and very promising. Amyloid imagine is among them. If you look at the predictive value of medial temporal atrophy, even though that is mechanistically more distant from the Alzheimer's Disease process, in the person who has the appropriate phenotype yet has a strong predictive validity for the emergence of the dementia of Alzheimer's Disease. So I think the biomarkers from a diagnostic point of view are in pretty good shape. I think Dr. Katz's point of view is that we

still don't know how they predict a treatment tool response. Am I understanding that correctly?

DR. KATZ: Oh, absolutely. And that's the $64,000 question with regard to surrogates as outcome measures. But listen, I would applaud the attempt to develop the diagnostic techniques earlier and earlier in the disease. We still haven't solved the problem of how do we study those people? But certainly, if the field agrees that people with MCI really do have Alzheimer's Disease and we can tell that by some CSF marker, as long as that's a widely accepted way to make a diagnosis, we have no objection.

In fact, it sort of helps us out a little bit, at least in the future. Because we have not yet had to wrestle with the question of what do we call a treatment for MCI? Because we believe, like most people, in most cases it's perfectly defined early Alzheimer's Disease. And there's been controversy as to whether or not ... but if the patients are only diagnosed with MCI, the question is do you say this is a treatment for MCI? Or do you say it's a treatment for early Alzheimer's Disease? And there's arguments on both sides of that. If the field agreed it

was early Alzheimer's Disease, we'd at least know what to call the patient if we got one.

PANELIST: The problem is the field does not agree on it yet. Because there are so many different subdivisions of MCI.

PANELIST: But you went over the criteria though for adding if you take MCI and you add in biological criteria ... I'm going a little bit beyond the data. But if you take the substantive MCI for which there is additionally biological criteria, the specificity greatly improves as I think what Phil said.

PANELIST: Yeah, I think that's exactly right. I think those criteria which are newly proposed now need to be studied and academically accepted. I think they have tremendous promise based on the available information. And so I think we're close.

PANELIST: But the outcome in an MCI trial is dementia. And dementia due to Alzheimer's. So as an outcome measure, I don't think there's disagreement.

PANELIST: Well, that's one type of outcome measure. And we certainly endorse that. But it could also just be looking at some (inaudible) global. And then you don't know what you're dealing with.

PANELIST: I think also the value of the diagnostic has to come into this. Since we don't have any target based effective treatments and only symptomatic agents that are widely used for people with cognitive impairment, on or off label. We don't have specific diagnoses and clinical practice. The drugs are used for people who come in with memory loss. Primary care doctors are not meeting DSM4 criteria for dementia. So I'm thinking we're sort of laying the groundwork for the field here. We're building the field. The diagnostic is ready.

But until we have an effective treatment, particularly one that's target based, I'm not sure that the added value of the diagnostic except if it could be used in lieu of cognitive testing. Doctors are used to writing a prescription for a test and then the test comes back and you've got it. But I don't know that I'd feel comfortable with that in Alzheimer's Disease. Because if somebody ... if it got to a clinical paradigm where all people had to do

was a spinal tap and then the test results come back and the primary, you know, then it changes the whole pattern of practice.

Because the primary care guys aren't doing ... probably aren't going to do the spinal tap. So everybody gets referred. So there's a lot of issues about how this gets implemented in practice. Then you get who's going to pay for the spinal taps? If we're going to have spinal taps on a wide basis. And what's the value of that if there's no effective disease modifying therapy.

So we're working in parallel here. But I think the crystallizing point will be the FDA approval of a target based agent like an anti-amyloid agent. And then the field will crystallize around that I think in terms of changing clinical practice.

DR. GILMAN: We're almost out of time. Meryl Comer.

MS. MERYL COMER: Just quickly and onto the point that Howard makes. I really resent what I call paternalism. A decision made for me, whether that information should be mine to have because there is not an efficacious drug.

There are some people that feel information is power. There are some people that would like to know for life planning. And I think that that kind of paternalistic attitude among the scientific community is inappropriate in a day where you're shifting all the health care decisions onto the consumer. We're supposed to be empowered about our health. And I really find that it is pervasive. And I am very concerned about that kind of attitude. I find it ... don't make decisions for us about that kind of decision. Let's see what the science shows and let us make that decision.

DR. FILLIT: Yeah, that's certainly the individual's point of view. And you can get the test today. I mean, your doctor if you want it, you can have a spinal tap and get your CFSA data. But if we're trying to make a societal decision, which I think is kind of what we're talking about, then I'm not sure we're ready for that.

DR. GILMAN: We've just run out of time. So let me just conclude this very interesting discussion by saying we in the scientific and clinical community want to be partners with the FDA as we go forward and learn more about the disease, about biomarkers for the disease and means of

intervening earlier and earlier as more effective treatments come online. We're all available. We're available to the FDA as consultants or for any other purpose to try and speed up effective delivery of treatment for this terrible disease. Thank you all. And Dan Perry has some concluding comments.

MR. DAN PERRY: I just wanted to ... I noticed that after individual presentations, there was a tendency to applaud. And that kind of got stifled because we wanted to get through it all. But there were so many things said here and so many presentations that were very meaningful, very productive, very constructive. And let's give Dr. Gilman and the entire panel a big show of appreciation. [applaud] Dr. Gilman, did you want to make any other summary remarks?

DR. GILMAN: No, I think we're done.

MR. DAN PERRY: Again, my appreciation on behalf of the ACT-AD coalition to our co-host organizations, to all of you that have participated and a special thanks to the patients, the caregivers, the scientists, the regulators, industry, all of those that gave us this opportunity somewhat unique to really talk across the usual barriers that separate us. We

have recorded this. We will make a transcript. It will be available soon. I invite you all to go to the various websites of the various host organizations. Ours is at act-ad.org. And we will have the transcript available to all of you. And a special thanks to the officers and the employees of the Food and Drug Administration for meeting us in this kind of a forum. We really do think that this has moved things further towards the goal that we all want. Thank you all very much.

(12:45 pm -- END OF WORKSHOP)