Dan Perry: Welcome, I'm Dan Perry. I'm the chair of the ACT-AD Coalition. As most of you know by now that's an acronym that stands for Accelerate Cure and Treatments for Alzheimer's Disease.

Ours is a coalition comprised of over 50 national organizations that represent the interests of patients, families, caregivers, women's health, senior citizens organizations; a broad array of not-for-profit, patient-centered organizations that are all very concerned about the looming threat of Alzheimer's disease.

I'm welcoming you this morning to what is now the fifth of our annual gatherings that we call 'The ACT-AD Alzheimer's Allies Meeting' because this is an opportunity to bring together our friends in government, in regulatory science, in academe, industry all under the umbrella of this broad, vigorous coalition representing the interests of patients and caregivers.

And we are very pleased today to be co-hosting this meeting with the Critical Path Institute and especially its internal program The Coalition against Major Diseases. And in a moment I will turn the mic over to Dr. Diane Stephenson, who is the executive director of that organization, and she'll talk to you a bit more.

A few weeks ago the ACT-AD Coalition hosted a session on harmonizing regulatory standards for Alzheimer's disease between Europe and the US and internationally generally – and this was at the meeting sponsored by the Clinical Trials in Alzheimer's Disease Group that was held in Europe a few weeks ago. While the rest of the people on the East Coast were facing Hurricane Sandy we were in a nicer place.

But the discussion – especially during sort of an open-mic period that we hosted – you know, this was at a time just a short while after rather disappointing results across the community in a couple of phase-three trials, to a degree at that very important meeting, the entire amyloid cascade hypothesis was somewhat in the docket, on trial.

I think it's fair to say that the jury is still out a bit but the theory is now being perceived as not discredited but now being looked at through some different lenses, different ways to approach that same phenomenon.

And increasingly we heard, just a few weeks ago, that the next real important step – the new approach to understanding how Alzheimer's and TAU work with Alzheimer's disease – is going to

be through different approaches from different therapies aiming at different parts of that big elephant.

In short, Alzheimer's disease, like cancer, like HIV/AIDS, like tuberculosis and many other clinical conditions, most likely is going to benefit from combination therapies. And it was the foresight of Dr. Katz many months ago, very early this year, when we talked about what should be our subject for the 2012 meeting? He said, "You know, the FDA has put out a guidance on combination therapies but we're really looking for some clarity of how that's going to apply to Alzheimer's disease."

So that was a foresight that then was reinforced at the CTAD Conference and now here we are; so this is a very, very timely subject.

Let me just say that when we started six years ago forming this coalition we met with the commissioner of the agency, we said we thought Alzheimer's disease, given the population demographics, given everything we know about the increase and risk for the disease in the years ahead, this really needed to be a major priority for the agency. And quite frankly, at that time, there was at least a perception that Alzheimer's disease wasn't even really a fatal disease; it was more of a caregiver issue, it wasn't really a great target for accelerated medical development.

Over these six years we've seen a tremendous evolution in thinking, led my Dr. Katz and his terrific team in the neurological products divisions, and I think these annual meetings where we've looked at biomarkers, we've looked at risk/benefit, we've looked at clinical meaningfulness; these gathers – because it's sort of a – mean we meet here in a windowless room on Rockville Pike, I mean what else are you going to do?

These are really roll-up-you-sleeves kind of meetings. There's not a lot of slides, there's not a lot of pontificating, and we really are a bit ahead of the curve. And today I think is especially ahead of the curve.

You're going to hear this morning not a lot of talk about TAU and amyloid and aggregation, but you're going to hear about how precompetitive collaborations have worked in other diseases like breast cancer. How they work in other industries like semiconductors and automobiles. So this is really not your grandfather's Alzheimer's disease meeting; this is really about a

look ahead so that we can come at this problem from a different angle and really, hopefully, make some progress.

So, I'm going to stop there. Thank you all again for being here. Thank you all for being partners in the ACT-AD Coalition because together we have seen a lot of progress.

There's an across the FDA group in neurology, in part because of our efforts, there's now a patient representative program, we've been active in PDUFA getting more FTE's focused on regulatory science, we've been active on the Hill pressing for more appropriations to keep FDA head-above-water during these very difficult budgetary times; we've done all of that together, and this meeting is sort of the annual high-point of that.

So get ready for a very exciting, very provocative meeting. And now I'd like to turn it over to Diane Stephenson, executive director of the Coalition against Major Diseases, which has been an exemplar of precompetitive collaboration with industry and with the agency.

Diane, you're right behind me.

[Applause]

Diane Stephenson: Good everyone, and thanks to Dan, Cynthia and Sue for inviting CPATH to co-sponsor this exciting meeting. And I get to tell you a story to begin with, which will kind of set the table of why I'm so excited about today.

So a couple of weeks ago, I think it was the November 10th and 11th issue of *Wall Street Journal* there was a cover article and then a full-page spread entitled "An outcast amongst peers gains traction on Alzheimer's care."

This article features the long-historic battle or challenges that Dr. Claude Wischik has faced in his pursuit of TAU-based therapeutics and he now is leading a company, TAU RX that has just announced they're a phase-three candidate for Alzheimer's disease.

Many of us who have worked in this field for so many years have been fortunate enough to work with pioneers in the field of the amyloid hypothesis – Dennis Selkoe, Dale Shenk and others – at a very exciting time where the genetics were just found. We haven't completely ignored TAWUbut I must say I've witnessed first-hand

over the last many, many years this Baptist TAU-ist debate that often times felt like the Presidential debate.

And although I was in the industry I remember going to these meetings where the key experts would have respectful but heated debates over these targets.

And in companies – those of you in industry know when it comes to project prioritization – in companies where there were active programs for both TAU and A-beta we would also have the scientific champions for those teams kind of try to dis the other target saying that their target was better; so it, again, felt like a scientific debate.

And in this article I found it striking to see the quote by Dr. Wischik saying that today, if we look back, science is politics and the politics of amyloid has won or has been the lead to date.

I would say, as I stand here today, what I find so exciting about this meeting is the recognition that it's probably not going to be one magic bullet. This is an incredibly complicated disease. We know that it's probably not just one pathogenic protein; both TAU and A-beta play pivotal roles in the pathogenesis of this disease.

And I want to say a few words around how the kinds of revolutions in drug development have changed our thinking of this disease. We're not there in terms of having an affective therapy but we've come a long ways.

And I'll use the examples of the revolutionary advances in human molecular genetics that have really change our thinking of how to think about disease targets across a wide variety of complex disease – oncology and others are such great examples.

And in Alzheimer's disease you know 25 years ago it was the FAD mutations that generated the enthusiasm for the amyloid hypothesis and just in July all of us who worked in this target space were so enthusiastic with the shot-in-the-arm publication showing that the mutation in APP gene that confirmed lifetime protection from Alzheimer's disease just adjacent to the gene encoding the base region is a very exciting finding, and it all renewed our excitement and enthusiasm for this mechanism.

But I also say that you may have seen just a few weeks ago the finding reported on the genetic mutation of a very high-risk gene in

tram-2, which is a gene involved in inflammation. Not specifically tower A-beta but inflammation.

We also have learned a tremendous amount, yet the targets remain allusive for why _____ presents a genetic risk factor for Alzheimer's disease.

These risk genes tell us that it's not one gene, it's not one target, and it's going to take a multiple-target approach to be successful for this disease.

As I look back and think that it's been 25 years to get to where we are with these exciting therapeutic trials for the amyloid hypothesis this field, and those of us who have family members who suffer from this disease, cannot afford to wait 25 years for one target at a time, so today we're just in an amazing opportunity to think outside the box.

And after all these years with my role in leading this Coalition against Major Diseases, the things that get my juices flowing and things that make me excited is to think outside the box, innovate, and do things that are non-traditional.

And so I've been in meetings for years where people have said, "Well, first we have to get one target to work and then we can think about putting targets together." But in a disease like Alzheimer's disease, if we continue to do these one-target-at-a-time approaches we may be sitting here in another 20 years and saying, "It may not just be one," and then the next and then the next and then the next.

So today I'm so excited to be here, just be working across a whole group that is so diverse in their thinking. And I'm also here with my colleagues from Critical Path Institute – Martha Brumfield and Deb Hannah – who also work on our tuberculosis consortium that's really in – their core to their mission is combining drugs at the onset to help battle tuberculosis in a very exciting and innovated way; we're going to hear from their group today.

And we also are going to hear from a variety of others today that really are thinking about how to tackle this concept and I want to acknowledge and congratulate my colleagues at the FDA for their thinking of a guidance on how to think about combination drug development and parallel.

So that's kind of setting the stage, and I want to thank all of you for coming and, again, think outside the box for this forum because I think we want to look back at today and say this is where it started. Thank you.

[Applause]

Dan Perry: Allow me just one more word before I introduce our next speaker. Obviously meetings like this take a lot of work, a lot of planning, and especially when you're reaching outside even the medical field to bring in experts about pre-competitive collaboration from other field and telling them this is about Alzheimer's disease, you don't have to talk about Alzheimer's but talk about pre-competitive solutions – and we've got a very diverse panel that's going to wrap things up later today.

But reaching out, planning, cajoling people to get together and then to make it possible for them to travel from all over the country to get here; tremendous job, virtually impossible to do without the leadership of Cynthia Bens of The Alliance for Aging Research, our vice president of public policy.

[Applause]

Thank you. She deserves that applause. Believe me, she does.

So a year ago those of you who were here when we wrestled with the subject of what's going on with phase-two, why are we getting signals and then moving into phase-three, and these signals aren't holding up, and we wanted to really think broadly – one of the most exciting speakers – we have many of them – was Mike Krams of Jannsen Pharmaceuticals.

And we thought if we wanted someone to really open our minds up around pre-competitive collaboration and how we tackle Alzheimer's now a year later with this onrush of new information, let's bring back Mike Krams because he's really the right person to give us that perspective. So let me ask Mike to come up and open it up with the kickoff talk. Thank you.

Mike Krams: Hopefully I can do justice to that introduction. Thank you very much for inviting me. I'm going to give the exact same talk I gave a year ago with some updates.

The updates are about how fast this field is moving and how exciting it is for us to be together here – friends, colleagues – not

to try to be disappointed by some of the events that we've announced around large-faced retrials, but really to take a step back and think about first principles and how to do good science.

I think the most important principle is for us to cooperate. Dean, listen in the back here; I'm your apprentice and you're a scientist who's taught me how to think about things that I don't understand. I'm a stroke neurologist; I don't really understand Alzheimer's very much.

But I have worked in drug development for more than 16 years now and I have seen in stroke how things can go terribly, terribly wrong – unforced errors – unforced errors they would say in tennis – and wouldn't it be good if we – in this field – can learn from things that we have done the wrong way in stroke?

So this was the title page that I presented a year ago; it contains all the things that I want to talk about, but of course it's not so easy to read. This is the title and this is what's happening in the Alzheimer's field – a snapshot that was taken two years ago – lot's of stuff happening. It's like the title slide. It's lots of things happening and these things don't talk to each other.

What if instead we constructed this solar system where the core, the sun, is the problem and we want a solution for that problem? So maybe it's an indication, it's the space of doing something about Alzheimer's; maybe around this there are planets that we know have some influence on this disease, maybe these are targets that we discuss, and maybe around these planets there are moons and each of these moons might be independent compounds that we pursue.

But now let's look at how we work in the pharmaceutical industry. We make the compound the sun, and somewhere down the road there still is a problem. And often we develop compounds before we have the faintest idea of what's really going on. That is why I'm so excited to also have Don Berry in the back, who's going to give the real talk – there is so much we can learn from oncology.

One big difference I think in oncology is that clinical trials happen after there is a really sound, profound understanding of basic biology, which is then translated into a clinical trial process, which might at times make more sense than what we do in neuroscience.

And so the big theme is to change the experimental unit away from 'Here is a trial on a compound' to 'We as a society have a problem and how can we all work together to solve that problem?'

Now in physics they do things differently. They run an experiment which takes a microsecond and afterwards they debate for decades whether the speed of light is faster or slower than they thought before. It also takes decades to get the funding for billions and billions of dollars to build these accelerators; so it's a very different funding model.

And I want to propose not that we do that thing; but I want to propose that we take on the perspective of engineers. Engineers want to solve a problem. And so I think we will move very quickly from the stage where, right now we still have our laptops in front of us, but very quickly we will have one common universal of knowledge – people call it 'the cloud,' I don't know what that means – but I think it's going to happen.

And here is the thought experiment: Can we think of building solutions to dementia? Not Alzheimer's but dementia as it presents itself to a clinical neurologist, or any clinician who sees a patient who is going downhill with cognitive abilities, as an engineering problem.

Deconstruct that problem. It's going to be very apparent that if we deconstruct it looking at the patient, there's not just amyloid; there is of course amyloid but there is so much more. There are vascular issues, there are – you know the whole cascade of things that are involved – so let's deconstruct the problem. Let's have a roundtable – let's have a week together, where we say we want to solve that problem.

And let's start by saying what is the biology of, and the different pieces of the biology, as they come together? And then we come out at the other end of this meeting – and it might be here today – with a roadmap, a written document that says, "Step number one is deconstructing. The final step is putting it together again and having an approach on how to do things right."

And I believe that the solutions will require a coordinated program effort. This is not just I run a trial on compound X and hopefully it all works. This is bigger than that, and we need to work together on this.

And rigorous planning and central project management; very different from how we function. Now all of us who sit here in pharmaceutical R&D, often we can't really talk to each other. How crazy is that?

And you know there are companies who develop amyloid clearance mechanisms, they have competing programs; why don't these programs live in the same database? There are people who develop base-inhibitors; why do these people compete with each other as opposed to cooperate with each other?

There are people who have base-inhibitors and amyloid clearance mechanisms; why don't they put these things together? There are others who talk about _____, load; why doesn't that also go into the mix?

People say, "Oh, there is IP," and "Oh, we know best; we don't need anybody else." All of that – can be park these thoughts and listen to what Don has to say when he tells us what's already happening in breast cancer.

So I was reminded the other day that the Empire State Building was put up in a very short period of time. Do you know how long it took? Well it took 13 months; one-three months. Extraordinary short time.

But imagine that there had been a builder saying, "I have windows," somebody who had said, "I have steel," somebody says, "I have concrete," and somebody would have said, "I have the helmet so that we don't get hurt," and then let's pull it together and hopefully the thing will go up in 13 months. No way this could have happened.

I'm arguing that we can be just as good in planning around CNS drug development as architects who build Empire State Buildings. Empire State Buildings are much easier to build. Even more important for us to work together and plan carefully and apply this engineering perspective.

And so I just want to introduce the basic research questions and then let us all continue, and then I'd like to ask you for your help and to build some type of event – or week – where we spend time together and hash out this roadmap and publish it and get buy-in for it.

So here are some key aspects to this. Whom should we treat? With what should we treat? How do we actually observe if there's a potential treatment effect? When should we initiate the treatment intervention? And how can we efficiently prove to the world that it works or not? What type of clinical trial – methodology – does exist?

So whom should we treat – I'm going to very briefly flash up these pictures from Randy Bateman's familiar Alzheimer's cohort – and just arguing that the time of intervention is an open-research question – full stop.

So it goes into our deconstruction perspective as one unsolved problem. Right now people are a little bit saying, "It might be better to treat earlier," but really we haven't got a clue – or too late – so it's an open research question.

So is it 20 years before that we need to start? Five years before? Or less than zero years – that's what we have now tried – and some people argue that this discredits it – and I tell people "Of course it doesn't." They totally forget about this important aspect – the research question of what is the right time point of interfering is an open one, and needs to be answered – we need to think about clinical trial methodologies that can take that research question on.

So in Chicago, the Alzheimer's Association for – and roundtable – has organized a wonderful meeting a couple of weeks ago where we argued that we can actually borrow information – not along the lines of what the familiar Alzheimer's world has done – can we perhaps in a base-inhibitor world – think about Down's subjects? And can we take, in _____-type thinking, build a natural history study around Down – learn on how to observe Down patients – and once we understand to observe, from many different angles, take sentinel cohorts from that natural history study, and make a pharmacological intervention trial out of it.

It would be very fascinating to see whether something that reduces the production of APP products is actually of value in a population where the over-production of APP is part of the problem.

So whom should we treat? It's an open question. You all know more of it, but it will have to be chapter one in our roundtable.

Now with what should we treat? Definitely with more than one thing. It's absolutely obvious that there is no such thing as a pure amyloid pathology; it would be a rare thing I believe.

So we can learn a lot from cancer, from HIV – and there are cooperative approaches now where academics, regulators and the health industry work together to establish proof of concept – targets – to establish appropriate targets all the way to proof of concept in pre-competitive open space.

Chas Bountra and others are spearheading this. I want to talk about that – you all know about it more – but the conjecture is it might be necessary to combine more than one thing; how can we actually do this?

Now how do we observe a potential treatment effect? I would argue we haven't got a clue as yet. So A-4 of course is helping, others are helping, but we still don't really know.

So what I argued a year ago is let's build a biomarker-based GPS system to identify the position of a subject on the trajectory to it's developing dementia.

And a very simplistic perspective. Let's take this idealized graph, that of course is very much too simple, but just for argument's sake let's say there are all these satellites, they travel on trajectories, we need to identify what these trajectories are; let's do this, let's learn about each of these biomarkers, let's learn the trajectory over time that the readout will take in an individual patient – let's do this for many biomarkers, and then eventually let's look at the fingerprint of many biomarkers relative to each other to understand the position of a patient.

So if you look at these different crosses, that fingerprint might help us to say 'This patient is in this position of the trajectory.' Here the fingerprint has changed; it's the same biomarkers but the relative position of them to each other have changed, et cetera.

And then once we have built that we have one of the tools required to go into a clinical trial intervention.

Now, how do we get there? The familial Alzheimer's efforts are very active in this field. I think we should do the same in sporadic Alzheimer's. So an update report is that the European Union has put together some – in excess of I think 24 million euros to sponsor a project which is called 'IM I EMIF.'

And the idea is to take available cohort studies and pool them together and morph them together with electronic health records.

Is it what I want here? No. But it's a first step in the right direction.

And when we were in Chicago I asked, you know, how can we put this Down longitudinal study together? But the real dream is to build a _____-like, Framingham-like study on steroids – really big – with the right end points – biomarker endpoints – and do a really long longitudinal observation.

Now, when should we initiate the treatment intervention? All I'm going to say is it's an open research question. There's a nice review paper that Eric Karran has produced where he points out that what we have tested so far is the idea that amyloid might be a driver, but we haven't tested whether there's a threshold or whether it's actually a trigger, and these things require early intervention.

So the flavor of the month right now is to think of early intervention, but what does that mean? How early is early enough? I would argue we shouldn't just say 'This is the right time point.' I think we need to look at the entire spectrum.

A great opportunity with familial Alzheimer's, but equally great opportunity if only we can think big and work cooperatively in sporadic Alzheimer's.

How can we officially prove to the world that it works? That is what Don Berry will talk about. It will be the idea of taking the problem as the center of the universe – dementia, I would argue, not just Alzheimer's – and then deconstruct it, think about the targets that live around it, compounds that we can populate this solar system with, and then think about how can we combine different aspects of this to create knowledge on how to help patients.

So I won't go through these slides because Don will talk about them, but I will summarize my main points. I think there are so many open questions, and there is such a great opportunity, if only we could extend this meeting for a week. If we were to close these people in in some sort of Vatican-like, you know, white smoke/black smoke thing, I really think we would get somewhere.

Whom should we treat? We would have good ideas about that. With what should we treat? There'd be appropriate first steps around what that should be. How do we observe a potential treatment effect? Great stuff already happening, but how can we

be even more focused on building the Empire State Building – what's the right end point? When should we initiate the treatment? And how can we efficiently prove it?

So my big idea and hope is that we will be able to launch these very large, longitudinal natural history studies that are an ongoing project – a little bit like the Framingham, only bigger – with the right end points from the get-go, which are going to siphon off sentinel cohorts that will become pharmacological intervention trials where we now understand how a subject has behaved before and after an intervention – it's going to be very different from the type of thing where we as an industry say, "Here is compound X," I take a baseline measure and then I look afterwards.

So let's move from the title slide to the actual title and thank you very much for inviting me back. And this was not much about combination – combination is one aspect of it – this is all about us working together. Thank you.

[Applause]

Dan Perry: This is a very open format, so if there is a question for Mike Krams we'd be happy to take it now. Tony?

Audience: *[Inaudible comment.]*

Mike Krams: We're talking to different groups. We're talking anywhere from 1,000 to 130,000 patients. Of course you'll call this crazy – the 130,000 number – but if we are not allowing ourselves to dream nothing will ever come there.

Look at me 30 years ago, who would have predicted that this would become one of the most creative, productive sources of knowledge in this field?

Dan Perry: Thank you very much. I was just told that we're not taking questions, so you got one in Tony; consider yourself lucky.

And as for the suggestion that we find some hermetically-sealed room where we could go for a week, I have to ask; have you seen Dr. Katz's schedule? I don't think a week is going to happen, but still…

I think the idea of moving beyond the normal way we do things and begin to think of some way that we can really think of this in a different way is very much in order.

I've said that we're going to talk and learn what's happened in other disease areas and that's why we've asked Don Berry to speak to us about the experience in breast cancer and in oncology broadly.

Dr. Berry is a professor at the University of Texas in the MD Anderson Cancer Center, but he is best known for developing the baysean-adaptive trial design in breast cancer, which has allowed us to get more information out of a smaller sample.

And in the spirit of Mike Krams talking about reengineering things, if there's anything that needs to be reengineered it's our big, clunky, clinical trials that require too many people, take too long, and then in the end, as we have seen through sad experience, the information we're getting out of all of that is not ringing the bell in the final moment when we need it.

So we're going to learn from Don Berry about how to do it smarter, better, faster, and thank you very much for being here Don.

Don Berry: Thank you Dan for that nice introduction. And I agree whole-heartedly with what you say about clunkiness and getting rid of it. And thanks to Mike for some introduction. My financial disclosures include cooperative groups; so I work with something called The NETT – The N-E-T-T – Neurology Emergency Treatment Trials network – in designing adaptive trials, including some combinations in the emergency setting, and addressing the barriers associated with them.

So this is to dispel, to a certain extent, something that Mike said about oncology. I mean we all too frequently, in oncology, go into phase-three not know what we're doing and rolling the dice; I mean not too dissimilar from what happens in many cases in AD, you'll see they were actually worse in oncology than in neurology – 34 percent success rate in phase-three in oncology.

At the Alexandria Summit in neurology this year the many neurologists were speaking of 'cancer envy.' So you guys in cancer have the biomarkers, you know, the B-graph inhibitors and the like – but even that story, although it's really quite amazing – has a not-so-great ending in terms of the patient's survival.

And of course as you know – even though neurology looks pretty good – Alzheimer's doesn't look so good.

Dr. Woodcock a few years ago, at the time that the Critical Path initiative was getting rolling, suggest in lamenting that the sorry state of phase-three clinical trials that perhaps improved utilization of adaptive and baysean methods could help resolve the low success rate and expense.

In the last ten or so years we've designed over 300 trials at my home institution at MD Anderson, taking this perspective, but most of them in the early-phase setting and along the lines with what Dan was suggesting, getting better information with fewer patients; because we do something really revolutionary in medical research, we actually look at the data.

Medical device companies, following the 1997 FDAMA – the FDA Modernization Act – which used the term 'least burdensome' had a baysean initiative which they interpreted to be basion and there have been quite a number of successes in that area. And virtually every drug company is at least dabbling with the subject.

Why do we do this smaller usually – sometimes bigger – sometimes when you're looking at the data you see you don't have the answer. I don't mean you don't have the answer you want, you don't have – you don't know what you're going to do next; you're sitting on the cusp. And so in that circumstance you need more information.

More accurate conclusions, and along the lines of combination therapy, you address more questions. You address questions like, "What about these drugs together? How do they work?" Let's learn about that – and so I'll discuss some of that.

And depending on the circumstances you can focus on such as getting better treatment for patients in the trial, which is then attractive to patients, and certainly to patient advocates, which is a major thing in cancer – especially breast cancer, as you probably know.

Combination cancer trials – you know, we do combination trials to some extent in cancer, it's still not very great – I'll tell you about that – but in the early history it was horrible. So – I mean everybody knows in cancer, as in Alzheimer's, you've got to use combinations. In cancer we've got these pathways, you know, you can hit this pathway but cancer is a very creative beast and it finds another pathway; and so you have to hit lots of things. Everybody knows that.

So in a typical trial in the early days – back in 1980, for example – CLGB did a trial – Cancer and Leukemia Group B, a cooperative group – on stage-two breast cancer, about 800 patients – and they randomized combination therapy; CMFVP versus VATH.

Nine drugs – you see the V may be in common, but it's not; it's _____ versus _____ – we had no idea what contributed to CMFVP; none. It was just 'Well, let's put these together.'

So this is one combination therapy versus another combination therapy. It happened, if you're interested, that _____ won the battle, and we sort of feel now it was because of the A – the _____ – _____ – that caused the win, but it was a lousy trial.

In 1993 I designed a trial for CLGB using factorial design. It was a very difficult trial to get rolling because it was a great deal of reluctance to do a factorial design and we had to build it so that it would fall apart if patients didn't accrue it – it happened to be accrued more than the totality of all of the cooperative groups previously, so it was successful from a patient perspective, and patients liked the idea of contributing in more than one way, answering more than one question.

So Allan Fox last night mentioned – I heard him across the table mention Taxol; this was the study that gave rise to the SND NDA for Taxol in node-positive breast cancer and it addressed two questions; one was, suppose we increase the dose of doxorubicin from what we knew was an appropriate dose – that we were getting benefit at 60 mg.

And in those days, you may recall, there was a lot of interest in higher and higher dose, so _____ transplant, for example, as a support mechanism to deliver higher doses; so could we increase a dose of 60 up to 75 and 90 given with GCSF and get additional benefit? So we wanted to address that question.

We also wanted to address the question of Taxol after four cycles of AC and in a three-by-two design, so that there's six – I don't like the term – but there are arms – six arms – six different schedules – and it was successful in two ways.

One is this issue of Taxol, and the other is it nailed the question of dose. We had limited – there was absolutely no benefit to increasing dose above 60. And that was part of the whole aura of getting rid of this notion that more dose is better; there's a limit.

In 2010 lots of people complained about the cooperative system in cancer and the Institute of Medicine addressed the question of 'What are we going to do about the cooperative groups?' David Diltz was a member – probably the thing you read about that was it recommended consolidating cooperative groups – but it had a chapter on design, and this is a piece from that chapter.

This is a particular scheme for an adaptive factorial design to address drug A, drug B, combination and control, and to look at the data over time doing inner _____ – aggressive inner _____ – asking, you know, should we stop the trial completely because we've learned that everything is futile, or is drug A doing something good that we should be considering? How about drug B? And the combination?

And we might drop – we could be adaptively randomizing – but we might drop one of these completely at any of these points and hear from – just as an example – we drop drug A, continued with drug B and the combination, and at some point we decided to drop the combination and go along with drug B because the combination wasn't doing as much.

You can imagine this with a much bigger setting, with more types of combinations, you know, two-by-two-by-two-by-two.

So end points is the huge issue in AD – as you know better than I – and there may be different mechanisms that lead to different aspects of different biomarker effects in the longitudinal setting, and these may be measurable, and maybe that the different drugs have hit different end points that you can measure and that they come together in the end, you know, with the – you know, we lived happily every after with a combination therapy that was actually synergistic, and this can be modeled.

And it may be that for some patients drug B is effective and in other patients you need a combination, and you want to have a clinical trial that will address that.

So toward that end, in 2006, a Critical Path initiative said that they uncovered a consensus of the two most important areas – improve medical product development – or biomarker development – streamlining clinical trials. In 2010 Dr. Woodcock and others at the FDA wrote a perspective on combination therapies and they highlighted a trial called 'I-spy 2' which they indicated was groundbreaking in breast cancer drug responsiveness based on the presence or absence of genetic and biological markers.

In 2011 the FDA's driving medical innovation document highlighted this trial – and you can get my slides to read what they said. And I-spy 2 is highly hyped – perhaps somewhat over-hyped – but take my word for it, it's going to be very successful. I mean I know some things I can't tell you about what's going on with the data and it's really going to change the way we think about things, if it hasn't already.

This is a *Wall Street Journal* article on the study and contained a graph that I like very well. Of course I made it. It says 'Genetic profiles to highlight biomarker differences among patients and match drugs to patients with biomarkers that predict the benefit.'

The goal is – this is the old days. This is – and in cancer we design trials made with thousands of patients. The eye – and it's because in cancer we over-treat most patients. I mean I hate to tell you. And we've got to identify who we're benefitting and, of course the correlators who's not benefitting and not putting them through this horror.

So the goal is – in the blue – I'm a blue-Stater – this is the design – I'll tell you a little bit more about the design – but this is to highlight that we do MRI's along the way, even though – this is neoadjuvant breast cancer where you leave the tumor in, deliver systemic therapy and hope to do away with the tumor; that's the end point.

If at six months, roughly, after delivering – after pummeling the tumor – you got rid of it; that's a success. But that's a long time even for us to wait to adapt, so we build in modeling using MRI volume to assess what's happening to the tumor and how likely is it that this is going to – whatever the reduction is – that that's going to translate into a path CR.

So MRI is not an end point; it's a marker that we correlate with the end point. If it turns out the MRI is not affective, we'll learn that. I mean think about some of the things in AD; you model things – I was talking to Reisa last night about this – put them in the model. If they turn out not to be predictive; you'll learn that. That's one of the great things about being adaptive. If it turns out to be predictive; you'll learn that.

You liked that latter, but in the former case you fall back to what you would have done anyway.

So this is a cartoon; it's showing the trial. The big thing about this – there are several big things – but one is the patient population. The usual setting is that you have a heterogeneous population – you regard them to be heterogeneous – we specifically model their heterogeneity and the possibility that different therapies are going to be effective for different subsets.

And so we adaptively randomize within subset. What that means is if a drug is doing better within a patient subset it gets a higher probability of being assigned. And that means that the drugs that are affective move through faster. This is like a screening process – phase-two screening process.

And you see in this example five experimental arms. We actually have five experimental arms in the trial now and two others that are coming along. And on the precompetitive note these drugs come from different companies. They're experimental drugs coming from different companies.

Pfizer, Pfizer-Puma, Abbott, Amgen, Merck, Genentech; playing in the same sandbox, pulled together by the – and the IND is held by The Foundation for the NIH, which is a public/private consortium.

It's a new world. I mean it isn't completely new; there still are vestiges of the old days. But ten years ago I tried to do this study and I got pushback from companies saying, "No, I don't want to play in the same sandbox with Pfizer."

Today – especially at the higher levels of pharmaceutical companies – there's a great deal of interest in playing together, and this is an example.

So it may be that arm-two graduates in a small-focused phase-three trial, it may be that arm-three drops for futility, arm-five graduates to another subset, and there are holes you see here; as we go, we add arms. So we add experimental arm-six, et cetera.

In terms of combinations we can embed a factorial design within I-spy 2. So if you look at – you see this is A, plus-standard of care, B, plus – et cetera – the C the D, the C plus D and the control is a factorial design nested within I-spy two. And as we go – we adaptively randomize – it turns out that C is not adding much, we drop C, but we might end up doing adaptively comparing C plus D with standard of care and with the other arms, whatever they are.

So the goal is an 85 percent success in phase-three, specifically driving the trial, looking forward; what is the predictive probability of success?

Effects – and this is my last slide – effects of I-spy 2 approaches matched therapies with biomarker signatures. There's a savings from a common control, so before you do anything clever, the fact that you've got five or so arms with a single control in a controlled setting of the clinical trial comparable across the various drugs – if you've got six arms in a trial versus five two-armed trials; that's automatically a 40 percent savings in terms of sample size.

Better therapies move through faster, and there's offspring of I-spy 2 in colorectal cancer, melanoma, lymphoma, HIV, acute heart failure, pandemic flues – the treatment thereof. You may think something like heart failure – we know everything there is to know – it turns out not. We don't know how to use vasodilators and diuretics. We don't know what patient sub-populations benefit from which combination therapy.

So the idea is – in I-spy 2 – where instead of biomarkers it's things like dyspnea – severity of dyspnea – renal function, blood pressure, et cetera.

So – I'll stop there. Thank you.

[Applause]

Dan Perry: You have to love a presenter who says of his own project, "It's over-hyped." That's a level of humility that I respect. Thank you very much Don.

Dr. Reisa Sperling, a neurologist at Harvard Medical School is well-known to certainly everyone in this room. She's been part of these ACT AD Allies meetings the past many years. She was one of the standouts on our dream team that published a consensus on bio – neuro imaging and CSF protein biomarkers in "The Neurology of Aging" publication a year ago from right now.

And at the meeting in Monaco Reisa, once again, was one of the – that was the most talked about presenters. And she came up to me afterwards and said, "You're going to be talking about combination therapies at your next Allies meeting; I really want to talk about that." So we've made room for Reisa, as we always will. So, Reisa Sperling. Thank you.

Reisa Sperling: Thanks very much, and it's true; I actually did beg to come. Partly because Rusty had told me about this meeting and because when I was trying to recover from my phase-three depression about the results I certainly moved towards trying to think about combinations.

So here are my disclosures; I'm working with many of you in the room.

So I'm not going to use the engineering analogy but rather the Mother-Nature-Fury analogy. And of course here's the tsunami – the original picture of a tsunami that I think is facing us in Alzheimer's disease, and I'm really going to argue that we're going to have to move to combination therapy very quickly.

So the rationale's already been talked about a little bit, but I'm going to get a little more granular, and yes, I am going to talk about amyloid and TAU. I guess this makes me a grandfather.

So, again, it's already been pointed out that Alzheimer's disease is complex and that we're going to have to go after this from multiple mechanisms, and I absolutely agree that ultimately we're going to have to go after both amyloid and neuro-degeneration; not just TAU, because there are other things that kill neurons.

But I'm also going to say that even within the amyloid world and the amyloid hypothesis I think we have to consider a greater amyloid reduction, which likely will require combination therapy there as well, because I think we've seen evidence that we may be limited in dosing anti-amyloid compounds of several different types, due to adverse events. And maybe in combinations we can get greater amyloid lowering without having as much adverse events.

And also I think we have to acknowledge – even if you're in the amyloid camp – that we have no idea really which form of amyloid we need to be going after; so I think we want to be a little ecumenical and think about multiple targets within the amyloid.

And although I absolutely agree with Michael that it's an open question when you need to intervene; I'm more and more convinced that you need to intervene more on the earlier side because the pathophysiologic process begins decades – and not just amyloid – I think we've seen in the familial AD that many of these things change prior to symptoms, so I think we're going to have to use combination therapy even if we go earlier.

So this is some work that Cliff Jack and Paul Aisen and I worked on a couple of years ago – mostly arguing that we had to move earlier – but also in this paper we said, "Wow, we need to move to combination therapy." So I'm so excited that we're really – I think – on the cusp of that.

And again, this is really just to point out that even though again I do believe we should work on combination therapy for the later stages of Alzheimer's disease; before you even get to the stage we recognize as MCI there's evidence that all of these markers are abnormal, so definite neuro-degeneration, lots of amyloid, and already subtle cognitive symptoms. So I think we have to keep thinking about moving left.

However, I think there's some major challenges in how we get there. And these relate back to some of the things Michael brought up – and I'll get a little bit more granular on this. So I think one of the biggest problems is how do we actually access synergistic effects of combination therapy in the earlier stages?

And in particular because I think biomarkers at the moment are a little bit behind what we hoped they would be in terms of predicting therapy. And I say this as a biomarker person, but I think the associations of the biomarkers and the clinical outcomes in phase-three have to make us wonder about what we're going to adapt on in these studies?

Again, the best opportunity may be to intervene earlier, but the earlier we go in the disease the harder it will be to adapt on a clinical measure; whether it's cognitive or functional.

And I'll just bring this up because it's already been brought up, that there may be ethical concerns. And I keep hearing, "Why would you possibly think about a combination therapy in normal people or near-normal people because there may be additive risks."

But again, if it is the case that these combinations would work best early on then I say that's the ethical place to test them because these individuals are at such high risk for moving forward.

All right, so I'm going to take heat for this slide again but biomarkers, shmiomarkers, what good are they? But I think we have to address that they've had some limitations and try to understand what they're telling us.

So I think that the data so far suggests that they do help us select participants potentially, especially for going after a specific mechanistic target. And particularly as we move earlier we're going to have to use these for selection.

And maybe they have some utility in helping us know whether we're hitting our targets mechanistically. I think there's some pause of evidence there. But at the moment I'm not sure which biomarkers, if any of them, really have what we'll 'theranostic utility' that actually track the clinical response, and even better, predict a clinical response.

And I'm going to make an argument here that we still need better markers of synaptic function – and I'll come back to this because I think that's fundamentally what Alzheimer's disease, and dementia, is.

And then I'll just spend a couple seconds talking about what do the biomarkers and the associations that we just saw in phase-three tell us in terms of how we would have moved earlier and in using combination therapy.

So I think everyone in this room is well aware of this, but I really thought of it as a double-association a bit in terms of the phase-three results that we had _____ and modest evidence of target engagement and affects on both A-beta and some markers of neuro-degeneration and yet we didn't see that translate into clinical benefit.

So _____ had some modest but consistent evidence of clinical affect with slowing – particularly in the mildest group – some target engagement on biomarkers, but we didn't see evidence on the biomarkers we expected for neuro-degeneration that typically track with clinical.

So, what does this mean? So I think before we give up on biomarkers, and certainly before we give up on the amyloid hypothesis, we have to come back with this too-little-too-late question.

So although we did see on some biomarkers that we decrease the amount of fibular amyloid – that we've slowed the rate of increase – they really were not robust decreases from baseline levels.

And this said to me I think that before we give up we need to see if we can get more amyloid reduction to really alter the clinical

course. So the question is how much do we need to reduce? Do we have to go to 40 percent since birth – which is what I'd say the genetic data suggests – and what forms of A-beta do we have to drop down?

So – and again, this question of stage of intervention – I think dementia – particularly moderate dementia – more and more evidence from the biomarkers, but that may be too late to actually move the clinical course as well.

All right. So, how do we move forward? This is not just theoretical; we're actually trying to plan a trial. The only thing we have so far is the acronym; it's going to be called 'The Combat Trial.' And as a pacifist at heart I have to admit that I came up with the acronym but I don't like it because it's so war-mongering, but this actually is a war against Alzheimer's disease and we are losing, so we're going to have to get more serious.

So here are the things we've been thinking about, again, mechanistically, I'll talk a little bit about the issues of how we might design this; so one, again, staying in the A-beta space, because that's where we've got the most drug development so far, is maybe we need to simultaneously decrease A-beta production and increase clear _____ such as a _____tase inhibitor plus immunotherapy. And I think this is potentially ready to start over the next few months.

Maybe we need to increase clearance of multiple forms of A-beta – and I would say some day we might see multiple antibodies given together going after different forms of A-beta because we don't really know which is toxic – and maybe they're all toxic at different stages of the disease.

Ideally we want to decrease A-beta and neuro-degeneration and anti-beta anti-tau. I'd love to build the Combat Trial to be Combat Two and Combat Three so that we could stick in these arms when these drugs become available.

And of course any of these plus-neuro protective agent – inflammation would be great, although I'm not sure whether inflammation is a good thing or a bad thing based on the nature of the medicine article that came yesterday.

All right, but there are some real challenges – and I did have a great opportunity to talk to Don Berry last night because I think as we think about adaptive trial design in Alzheimer's disease – and

particularly in early stages of Alzheimer's disease – there are really some issues that we have to address.

So one is this; what do we adapt on? And again, I've already trashed biomarkers, which I don't mean to because I absolutely think we need them – but it's not clear to me which change on a biomarker right now is really going to predict clinical response.

And I would say that we built in an adaptive futility design in the A-4 study we're doing, and I realize that we probably would have made some mistakes based on that adaptive futility analysis based on the phase-three because so far they haven't been very predictive.

And especially as we move earlier what clinical or cognitive outcome could we actually use in 6, 12, 18, even 24 months in these very early populations that's going to tell us what's going to happen clinically, because these people are not imperative baseline, and they're changing very, very slowly.

So we have the horns of a dilemma; we have to go earlier but it's going to be harder to see short-term change in this group.

Two-by-two factorial – a more traditional design – although I love the idea of putting them together. The drugs that we're talking about are at very different stages of development; so some in phase-three, some in phase-one going into phase-two. How do we combine these easily in a two-by-two factorial when the needs for safety monitoring are different? And I'm hoping to get some input from the FDA on how we can do this better.

And of course how do we blind the placebo groups well if these drugs have different routes of administration and different needs for safety monitoring?

So here are some solutions – not many – but one is we need more biomarkers, not just in small subsets of subjects; we need them in everybody in these early-intervention trials so we can track them together and say which go with which and ultimately, hopefully, when we have a therapy that really works very clearly, how do you predict that with these biomarkers?

Again, I'm going to come back to this; we need biomarkers that tell us whether the brain is working better, that is not just a mechanism, but actually, again, if you suck all the amyloid out of

the brain, you prevent TAU, do you actually make it work better, more acutely, so we can see this.

We need to pick these leveraged populations – I hate to use the term 'on the cliff' especially in Washington these days – but people who are just at the precipice of dropping, I think is a very good place to look for individuals. That's early enough to still be able to rescue their neurons, but individuals who are likely to decline over two to three years in these studies.

And we still need better cognitive measures to detect these subtle changes, especially in earlier stages of AD.

So here again is this idea of a cliff – I although it's more of a hill here – but I think – so right now we're doing our trials at this cliff and I think unfortunately are already falling. I think we need to move back to this cliff and I think we need to move there with combination therapy.

Ultimately it may be that we need to be over here. Absolutely. But I think it may be tough right now to design a of combination therapies for that group.

Again, improving trial efficiency especially will get us I think closer to the combination therapy designs that would allow us to use an adaptive design, such as I-spy. So we're working on computerized cognitive batteries, more challenging episodic memory measures, CSF markers that are of neuro-degeneration but may not just be TAU and phauspho-TAU, which may not be as dynamic as we thought in that range.

And again functional imaging methods that maybe get us to synaptic integrity a little closer.

And one issue in this design, again, is how could we embed safety monitoring in these two-by-two factorial designs – or adaptive designs – in the middle of this cohort? So how can we do this in a short-term that allows us to continue long-term studies?

I've been working on functionally imaging for a while, so I could resist showing you one functional imaging – but this is actually data from Diane – we had the opportunity to do the multi-center functional connectivity analysis – and this is encouraging to me that it might be an early marker and that it's feasible to do across centers.

So I'll end with this urgency slide. I love Dan's quote on this that we have 10,000 baby boomers turning age 65 every day, and I will argue again that right now – even though I hope we'll find therapies – we're running trials at the end-stage of disease that's been going on for 20 or 30 years, and we need multiple shots to unfold to really defeat this formidable and complex disease.

So I think we're going to have to bite the bullet – another war-mongering thing – and be brave and actually start these combination therapies as early as we can do it safely. Of course we need to watch these individuals who are not yet patients very closely, but we have to do it because I think this is the way we're going to win.

So thank you very much.

[Applause]

Dan Perry: Thank you Reisa. I'm so glad that we could work you into the program because you really grasp the key questions about what are the different elements of this disease that could be approached by different therapies in combination.

And by the way, depending on what budget priorities look like after the smoke clears, your having chose a Department of Defense type term for you trial may be very farsighted, so I congratulate you on that.

Now is the time for some Q&A for our morning speakers. I'd ask you to first direct your questions to Mike Krams because we're sharing Mike with another conference and he needs to get to that one pretty quick. So if there's questions for Mike Krams let's lead off with those.

Phyllis.

Audience: I'd like to make a statement if I may. I'm the CEO of the Society for Women's Health Research and we've been running inter-disciplinary research networks for ten years on a smaller scale, obviously, than you were talking about. They've been incredibly successful. Obviously our focus has been sex differences and we're trying to start one in sex differences in Alzheimer's.

We've done the scientific roundtable and briefing on Capital Hill. The problem that we're having is that nobody wants to fund multi-year programs. And the way they run is they go for five years, the

scientists come together four or five times a year, we fly them in, they spend two days together, they work in each other's labs and they exchange information, et cetera, and then they get money for pilot projects, et cetera.

So it's a small example, but a good example of how successful that can be when you're bringing in people who are interested in the same area but from different viewpoints coming together. But it's impossible to convince companies to fund these long-multi-year programs; they want to do a quick thing and be gone.

So that's one of the issues that we struggle with is how we can continue doing this?

Mike Krams: That's a great point. Let's definitely exchange more discussion afterwards. But I've learned that it's worth taking baby steps. You know, when we first talked about this Framingham study on steroids, of course it sounded absolutely crazy.

The _____ project isn't the right thing, but it's a huge investment that's going in the right direction a little bit. But here's the real trick; if we and others can work together and align behind the principle that we have to get rid of our myopic perspective; that will be step number one.

Step number two is at the very get-go, at the design stage, to agree what the right biomarkers are that we need to build on because we need to have that from the get-go.

So with that I'm going to just make a quick comment on these biomarker things. Of course we haven't got a clue but some things we know. And some things we can use as necessary conditions. For instance, in the development of a base-inhibitor, it's going to be of some interest to check whether A-beta _____ lowering occurs, and guess what; it's going to occur quickly.

And so maybe there is an issue around area-E that's going to occur sort of quickly. So there is partial information that we can use as necessary conditions that can be built in, and we can give a user requirement to the engineers; give us biomarkers that read out very quickly – within an hour, if we can.

I've argued for ages that we take a _____, a __ _____ and do the following study. We sample CSF on an ongoing basis over two years; I want to know when is the first time point at which _____ goes down. We know it goes down but we don't know what the

earliest time point is. We haven't asked that research question and we could.

And so that's the way we have to go about the engineering piece. If we know what the user requirements are and we work together; I think we have a totally different way of approaching the problem.

And just one more point on the network. Just as we talked with Down, we had a great discussion two days ago with experts who have the mitochondrial disease network; we're doing the exact same thing there. And the more this becomes an aligned position, that many people work together, the easier it's going to be.

Reisa Sperling: So I absolutely agree with you. And I do think that we have biomarkers on target engagement that are very encouraging. I'm struggling, and I'm hoping you're going to say – how do we, in the absence of a clear, clinical signal with some things, say, "What's their agnostic?" I think that's the piece where I'm struggling because of the disassociation.

Mike Krams: I'm going to break the rules – and folks who work with me at JI; don't listen, okay? Look, there are things we can't talk about here.

Reisa Sperling: Why not?

Mike Krams: Here's what I want to say. What we need to do is to invest just as much time as we did in conducting the experiment in really understanding it. And modeling and simulation approaches are going to make the way forward. What's currently being presented is like the pre-specified test. I have to leave it there.

But the point is it may not be just quite as negative as you think.

Audience: So I just want to comment on this topic of biomarkers and synaptic activity and challenge everyone to look beyond in the areas such as pain and autism and schizophrenia where functional markers and synaptic function – you know, the challenge with biomarkers in this area is that it's taken us so long with the favorite biomarkers to get the standardization/harmonization right.

So in the functional world, and your work, is so compelling yet we're still finding challenges around the harmonization/standardization. So can we think beyond going into disease areas like pain or psychiatry to help us tackle some of those challenges to get those biomarkers much more implemented in all studies so that we get farther?

Reisa Sperling: So I definitely can say – at least on resting state functional MRI – it is imbedded in the Diane study, the Alzheimer's Prevention Initiative, and A-4, and we have a harmonization group; so it's collected exactly the same way across this, so we'll have 40,000 resting state _____ scans to play with.

I don't know if that's going to be good enough. I think FDG-PET needs some more work. I don't know why that hasn't shown more promise because it should be a good marker. But I just think this is a place where there's still a black box. We've got target engagement, we've got clinical outcomes, but it's put – telling us how do we predict whether there's actually a positive clinical affect in the brain; we need something to fill in that black box.

Mike Krams: I will just make one more comment and that is about the develop – how do we fund? Let's make some report of all the dollars that have gone into drug development programs; it will be many billions.

Now let's ask how many billions we've spent on apnea-like treatments – on apnea-like – understanding the disease. So that's the problem. And so we need to shift that balance; we can't possibly run clinical trials if we don't know what the right biomarker end point is.

We need to reverse the balance of investment into methodological studies first, which establish how to identify subjects and how to observe them. Once we've done that we can put players in that modulate that path. But how can we build a _____ game where we try to pull ourselves out of our own hair if we don't fully understand the operating characteristics of the end points?

Reisa Sperling: So I just want to make one argument on that, which is I think I'm not sure I agree with you that we need to do one first and then the other. Only because what we've seen are that the biomarker – what happens in natural history is not what happens in studies.

And so I actually think we have to do them in parallel. We have large placebo groups where we can model natural history biomarkers, but I think we need these biomarkers in large-scale earlier intervention trials to see what happens simultaneously.

And I think our – where cancer, frequently – they've learned about their biomarkers in the setting of these therapeutic disease. We've tried to do it separately. And we do these tiny-weenie biomarker studies in clinical trials and then _____-like studies – I think that's

a mistake. I think we should do them in parallel, do as much as we can and learn from the placebo group.

Mike Krams: Agree, as long as I can have 50 percent of the budget for biomarker work.

Reisa Sperling: Well, 150 percent.

Don Berry: Reisa, it's very interesting you say that because I was going to object to something that you said in your talk and make exactly the point you just made.

You said you weren't clear on the biomarkers and whether they were predictive and you might have made a mistake. With apologies to Donald Rumsfeld; we know what we don't know. And we model the uncertainty but we do it in parallel. So we're learning – and you know, and biomarkers may be so-called prognostic that is predictive of how well you're doing, but they may be predictive as well and specific to certain therapies.

And if you have a biomarker that decreases – for example, in cancer, in tumor reduction, there's some therapies that reduce the tumor burden but have no effect on any clinical outcome, and others that it's the opposite.

So we can model that – and if it turns out that there is no predictive benefit; we'll learn that. But we're not going to bet the farm on the biomarker until we get some validation – as you point out – potentially within the trial itself.

Audience: Steve Saloway from Brown. Mike thanks so much. It sounds like proposing a long-term Manhattan-type project – because Manhattan had a specific goal like the Empire State Building – but obviously this is going to be a little bit more challenging, and so long-term – so I think that sounds fabulous.

And I know this is a forward-thinking meeting, and one part that we haven't touched on today is the stage-zero preclinical Alzheimer's disease using Reese's model and the biomarkers for that. Because I think that's where we're going to have our greatest impact down the road is finding out who's at risk for Alzheimer's disease – like cardiovascular disease with cholesterol and hypertension and diabetes – and we don't have those biomarkers yet to identify people at risk; we're waiting to see if there's pathology because that's what we can measure right now.

Mike Krams: Yeah, I totally agree.

Dan Perry: Michael, we need another microphone here and then we'll go to Ian.

Audience: I have a question. Kind of what's been presented are clinical-development plans, and when I look at it it seems like the underlying assumption is that when you start a –

[End of Audio]

Mike Krams: More of it will have to be ____ in our round table. With what should we treat? Definitely with more than one thing. It's absolutely obvious that there is no such thing as a pure amyloid pathology. It would be a rare thing, I believe. We can learn a lot from cancer, from HIV, and there are cooperative approaches now where academics, regulators, and health industry work together to establish appropriate targets, all the way to proof of concept in a precompetitive open space. Chas Bountra and others are spearheading this. I won't talk about that. You all know about it more, but the conjecture is it might be necessary to combine more than one thing. How can we actually do this?

Now, how do we observe potential treatment effect? I would argue we haven't got a clue as yet. A4, of course is helping, others are helping, but we still don't really know. What I argued a year ago is –

[End of Audio]

Mike Krams: – and then, once we have built that, we have one of the tools required to go into a clinical trial intervention. Now, how do we get there? The familial Alzheimer's efforts are very active in this field. I think we should do the same in sporadic Alzheimer's. An update report is that the European Union has put together some, in excess of, I think, 24 million Euros to sponsor a project which is called IMI EMIF, and the idea is to take available cohort studies and pool them together, and morph them together with electronic health records.

Is it what I want here? No, but it's a first step in the right direction. When we were in Chicago, I asked, "How can we put this down longitudinal study together?" but the real dream is built an ADNI-like, Framingham-like study on steroids – really big with the right biomarker endpoints, and do a really longitudinal observation.

When should we initiate the treatment intervention? All I'm going to say is it's an open research question. There's a nice review paper that Eric Karran has produced, where he points out that what we have tested so far is the idea that amyloid might be a driver, but we haven't tested whether there is a threshold or whether it's actually a trigger. These things require early intervention.

So the flavor of the month right now is to think of early intervention, but what does that mean? How early is early enough? I would argue we shouldn't just say, "This is the right time point." I think we need to look at the entire spectrum. Great opportunity with familial Alzheimer's, but equally great opportunity if only we can think big and work cooperatively in sporadic Alzheimer's.

How can we efficiently prove to the world that it works? That is what Don Berry will talk about. It will be the idea of taking the problem as the center of the universe – dementia, I would argue; not just Alzheimer's – and then deconstruct it, think about the targets that live around it, compounds that we can populate this solar system with, and then think about how can we combine different aspects of this to create knowledge on how to help patients.

I won't go through these slides because Don will talk about them, but I will summarize my main points. I think there are so many open questions and there is such a great opportunity, if only we could extend this meeting for a week. If we were to close these people in some sort of Vatican-like, white smoke/black smoke thing, I really think we would get somewhere.

Whom should we treat? We would have good ideas about that. With what should we treat? There would be appropriate first steps around what that should be. How do we observe a potential treatment effect? Great stuff already happening, but how can we be even more focused on building the Empire State Building? What's the right endpoint? When should we initiate the treatment, and how can we efficiently prove it?

My big idea and hope is that we will be able to launch these very large longitudinal natural history studies that are an ongoing project, a little bit like the Framingham, only bigger, with the right endpoints from the get-go, which are going to siphon off sentinel cohorts that will become pharmacological intervention trials, where we now understand how a subject has behaved before and after intervention. It's going to be very different from the type of

thing where we, as an industry, say, "Here is Compound X. I take a baseline measure and then I look afterwards."

Let's move from the title slide to the actual title, and thank you very much for inviting me back. This was not much about combination. Combination is one aspect of it. This is all about us working together. Thank you.

Dan Perry: A very open format, so if there's a question for Mike Crams, we would be happy to take it now. Tony.

Audience: How many subjects?

Mike Krams: We're talking to different groups. We're talking anywhere from 1,000 to 130,000 patients. Of course, you will call this crazy, the 130,000 number, but if we are not allowing ourselves to dream, nothing will ever come there. Look, ADNI, 30 years ago – who would have predicted that this would become one of the most creative, productive, sources of knowledge in this field?

Dan Perry: Thank you very much. I was just told that we're not taking questions, so you got one in, Tony. Consider yourself lucky. As for the suggestion that we find some hermetically sealed room where we could go for a week, I have to ask, have you seen Dr. Katz's schedule? I don't think a week is going to happen, but still, I think the idea of moving beyond the normal way we do things, and begin to think of some way that we can really think of this in a different way is very much in order.

I've said that we were going to talk and learn from what's happened in other disease areas, and that's why we've asked Don Berry to speak to us about the experience in breast cancer and in oncology broadly. Dr. Berry is a professor at the University of Texas in the MD Anderson Cancer Center, but he is best known for developing the Bayesian adaptive trial design in breast cancer, which has allowed us to get more information out of a smaller sample.

In the spirit of Mike Krams talking about reengineering things, if there anything that needs to be reengineered it's our big, clunky clinical trials that require too many people, take too long, and, in the end, as we have seen, through sad experience, the information we're getting out of all of that is not ringing the bell in the final moment when we need it. So we're going to learn from Don Berry about how to do it smarter, better, faster, and thank you very much for being here, Don.

Don Berry: Thank you, Dan, for that nice introduction, and I agree wholeheartedly with what you say about clunkiness and getting rid of it, and thanks to Mike for some introduction. My financial disclosures include a cooperative group. I work with something called the NETT, Neurology Emergency Treatment Trials network in designing adaptive trials, including some combinations for in the emergency setting, and addressing the barriers associated with them.

This is to dispel, to a certain extent, something that Mike said about oncology. We all too frequently in oncology go into Phase 3, not knowing what we're doing, and rolling the dice. Not too dissimilar from what happens in many cases in AD, you'll see that we're actually worse in oncology than in neurology, 34 percent success rate in Phase 3 in oncology.

At the Alexandria Summit in neurology this year, many neurologists were speaking of cancer envy, so you guys in cancer have the biomarkers, the B-Raf inhibitors, and the like. But even that story, although it's really quite amazing, has a not-so-great ending, in terms of the patient's survival. Of course, as you know, even though neurology looks pretty good, Alzheimer's doesn't look so good.

Dr. Woodcock, a few years ago, at the time that the Critical Path Initiative was getting rolling, suggested, in lamenting the sorry state of Phase 3 clinical trials, that perhaps improved utilization of adaptive and Bayesian methods could help resolve the low success rate and expense. In the last ten or so years, we've designed over 300 trials at my home institution, MD Anderson, taking this perspective, most of them in the early phase setting, and along the lines of what Dan was suggesting, getting better information with fewer patients.

Because we do something really revolutionary in medical research, we actually look at the data. Medical device companies, follow the 1997 FDAMA, the FDA Modernization Act, which used the term "least burdensome," had a Bayesian initiative which they interpreted to be Bayesian, and there have been quite a number of successes in that area, and virtually every drug company is at least dabbling with the subject.

Why do we do this? Smaller, usually, sometimes bigger. Sometimes when you're looking at the data, you see you don't have the answer. I don't mean you don't have the answer you

want. You don't know what you're going to do next. You're sitting on the cusp, so in that unique circumstance, you need more information. More accurate conclusions, and along the lines of combination therapy, you address more question, address questions like, "What about these drugs together? How do they work? Let's learn about that," so I'll discuss some of that.

Depending on the circumstances, you can focus on, such as getting better treatment for patients in the trial, which is then attractive to patients and certainly to patient advocates, which is a major thing in cancer, especially breast cancer, as you probably know. Combination cancer trials. We do combination trials to some extent in cancer. It's still not very great. I'll tell you about that.

But in the early history, it was horrible. I mean, everybody knows in cancer, as in Alzheimer's, that you've got to use combinations with cancer. We've got these pathways. You can hit this pathway, but cancer is a very creative beast, and it finds another pathway, so you have to hit lots of things. Everybody knows that. So in a typical trial, in the early days, back in 1980, for example, CALGB did a trial – Cancer and Leukemia Group B, a cooperative group – of Stage II breast cancer, about 800 patients, and they randomized combination therapy, CMFVP versus VATH.

Nine drugs, you see the V may be in common but is not. It's vincristine versus vinblastine. We had no idea what contributed to CMFVP. None. It was just, well, let's put these together. So this is one combination therapy versus another combination therapy. It happened, if you're interested, that VATH won the battle, and we sort of feel now that it was because of the A, the doxorubicin, Adriamycin, that caused the win, but it was a lousy trial.

In 1993, I designed a trial for the CALGB, using factorial design. It was a very difficult trial to get rolling because there was a great deal of reluctance to do a factorial design, and we had to build it so that it would fall apart if patients didn't accrue. It happened that we accrued more than the totality of all of the cooperative groups previously, so it was successful from a patient perspective, and patients like the idea of contributing in more than one way, answering more than one question.

Allan Fox last night, I heard him across the table mention Taxol. This was the study that gave rise to the sNDA for Taxol in node-positive breast cancer, and it addressed two questions. One was, suppose we increase the dose of doxorubicin from what we knew was an appropriate dose, that we were getting benefit at 60

milligrams. In those days, you may recall, there was a lot of interest in higher and higher dose, so bone marrow transplant, for example, as a support mechanism to deliver higher doses. So could we increase dose of 60 up to 75 and 90, given with G-CSF, and get additional benefit? We wanted to address that question.

We also wanted to address the question of Taxol, after four cycles of AC, in a 3x2 design, so that there are – and I don't like the term – arms, six arms, six different schedules, and it was successful in two ways. One is this issue of Taxol, and the other is it nailed the question of dose. There was absolutely no benefit to increasing dose about 60, and that was part of the whole aura of getting rid of this notion that more dose is better. There's a limit.

In 2010, there were lots of people complaining about the cooperative group system in cancer, and the Institute of Medicine addressed the question of what are we going to do about the cooperative groups. David Dilts was member. This is probably the thing that you read about that, was it recommended consolidating cooperative groups, but it had chapter on design, and this is a piece from that chapter.

This is a particular scheme for an adaptive factorial design, to address Drug A, Drug B, combination, and control, and to look at the data, over time, doing interim analyses, aggressive interim analyses, asking, "Should we stop the trial completely because we've learned that everything is futile?" or "Is Drug A doing something good that we should be considering? How about Drug B and the combination?"

We could be adaptively randomizing, but we might drop one of these completely, at any of these points. Here, just as an example, we dropped Drug A, continued with Drug B and the combination, and at some point we decided to drop the combination and go on with Drug B because the combination wasn't doing as much. You can imagine this with a much bigger setting, with more types of combinations, a 2x2x2x2.

Endpoints is the huge issue in AD, as you know better than I, and there may be different mechanisms that lead to different biomarker effects in the longitudinal setting, and these may be measurable, and it may be that the different drugs have hit different endpoints that you can measure, and that they come together in the end. We lived happily ever after with a combination therapy that was actually synergistic, and this can be modeled.

It may be that for some patients, Drug B is effective, and in other patients you need a combination, and you want to have a clinical trial that will address that. Toward that end, in 2006, the Critical Path Initiative said that they uncovered consensus that two most important areas, improved medical product development or biomarker development, streamlining clinical trials.

In 2010, Dr. Woodcock and others at the FDA wrote a perspective on combination therapies, and they highlighted a trial called I-SPY 2, which they indicated was groundbreaking in breast cancer to predict drug responsiveness based on the presence or absence of genetic and biological markers. In 2011, the FDA's Driving Medical Innovation document highlighted this trial, and you can get my slides to read what they said.

I-SPY 2 is highly hyped, perhaps somewhat overhyped, but take my word for it, it's going to be very successful. I know some things I can't tell you about what's going on with the data, and it's really going to change the way we think about things, if it hasn't already.

This is a *Wall Street Journal* article on the study, and contained a graph that I like very well. Of course, I made it. It says genetic profiles to highlight biomarker differences among patients and to match drugs to patients with biomarkers that predict a benefit. This the old days, and in cancer, we design trials with thousands of patients. It's because, in cancer, we overtreat most patients – I mean, I hate to tell you – and we've got to identify who are benefitting and, of course, the corollary is who is not benefitting and not putting them through this horror. The goal is in the blue – I'm a blue-stater.

This is the design. I'll tell you a little bit more about the design, but this is to highlight that we do MRIs along the way. This is neoadjuvant breast cancer, where you leave the tumor in, deliver systemic therapy, and hope to do away with the tumor. That's the endpoint. If, at six months, roughly, after pummeling the tumor, you got rid of it, that's a success. But that's a long time, even for us, to wait to adapt, so we build in modeling, using MRI volume, to assess what's happening to the tumor and how likely is it that this is going to, whatever the reduction is, that that's going to translate into a pat-cr.

MRI is not an endpoint. It's a marker that we correlate with the endpoint. If it turns out that MRI is not effective, we'll learn that. Think about some of the things in AD. You model things. We

were talking to Reisa last night about this. Put them in the model. If they turn out not to be predictive, you'll learn that. It's one of the great things about being adaptive. If it turns out to be predictive, you'll learn that. You like the latter, but in the former case, you fall back to what you would've done anyway.

This is a cartoon, showing the trial. There are several big things about this, but one is the patient population. The usual setting is that you have a heterogeneous population; you regard them to be heterogeneous. We specifically modeled their heterogeneity, and the possibility that different therapies are going to be effective for different subsets, so we adaptively randomize within subset. What that means is if a drug is doing better within a patient subset, it gets a higher probability of being assigned, and that means that the drugs that are effective move through faster. This is like a Phase 2 screening process.

You see, in this example, five experimental arms. We actually have five experimental arms in the trial now, and two others that are coming along. On the precompetitive note, these drugs come from different companies. They're experimental drugs coming from different companies. Pfizer/Puma, Abbott, Amgen, Merck, Genentech, playing in the same sandbox, and the IND is held by the Foundation for the NIH, which is a public/private consortium.

It's a new world. I mean, it isn't completely new. There still are vestiges of the old days, but ten years ago I tried to do this study and I got pushback from companies saying, "No, I don't want to play in the same sandbox with Pfizer." Today, especially at the higher levels of pharmaceutical companies, there's a great deal of interest in playing together, and this is an example.

So it may be that Arm 2 graduates in a small-focused Phase 3 trial. It may be that Arm 3 drops for futility, Arm 5 graduates to another subset, and there are holes you see here. As we go, we add arms, so we add the experimental Arm 6, et cetera. In terms of combinations, we can embed a factorial design within I-SPY 2. You see this is A plus standard of care, B plus, et cetera. The C, the D, the C plus D, and the control is a factorial design, nested within I-SPY 2, and as we go, we adaptively randomize and it turns out that C is not adding much. We drop C but we might end up doing adaptively comparing C plus D with standard of care, and with the other arms, whatever they are.

So the goal is an 85 percent success in Phase 3, specifically driving the trial. Looking forward, what is the predictive probability of

success? Effects of I-SPY 2 approaches matched therapies with biomarker signatures. There's a savings from a common control, so before you do anything clever, the fact that you've got five or so arms, with a single control, in a controlled setting of the clinical trial, comparable across the various drugs – if you've got six arms in a trial versus five two-armed trials, that's automatically a 40 percent savings in terms of sample size.

Better therapies move through faster, and there's offspring of I-SPY 2 in colorectal cancer, melanoma, lymphoma, HIV, acute heart failure, pandemic flus and treatment thereof. You may think with something like heart failure, you know everything there is to know. It turns out not. We don't know how to use vasodilators and diuretics. We don't know what patient subpopulations benefit from which combination therapy. So the idea is an I-SPY 2, where instead of biomarkers it's things like severity of dyspnea, renal function, blood pressure, et cetera. I'll stop there. Thank you.

Dan Perry: You have to love a presenter who says of his own project "it's overhyped." That's a level of humility that I respect. Thank you very much, Don. Dr. Reisa Sperling, neurology at Harvard Medical School, is well-known to certainly everyone in this room. She's been part of these ACT-AD Allies meetings for the past many years. She was one of the stand-outs on our dream team that published a consensus on neuroimaging and CSF protein biomarkers in the *Neurology of Aging* publication a year ago, from right now.

At the meeting in Monaco, Reisa, once again, was one of the talked-about presenters. She came up to me afterwards and said, "You're going to be talking about combination therapies at your next Allies meeting. I really want to talk about that," so we've made room for Reisa, as we always will. So, Reisa Sperling of Harvard.

Reisa Sperling: Thanks very much, and it's true. I actually did beg to come, partly because Rusty had told me about this meeting, and because when I was trying to recover from my Phase 3 depression about the results, I certainly moved towards trying to think about combinations. Here are my disclosures, in working with many of you in the room.

I am not going to use the engineering analogy, but rather the Mother Nature fury analogy, and, of course, here's the tsunami, the original picture of a tsunami that I think is facing us in Alzheimer's

disease, and I'm really going to argue that we're going to have to move to combination therapy very quickly.

The rationale has already been talked about a little bit, but I'm going to get a little more granular, and yes, I am going to talk about amyloid and tau. I guess this makes me a grandfather, again. It's already been pointed out that Alzheimer's disease is complex and that we're going to have to go after this from multiple mechanisms, and I absolutely agree that, ultimately, we're going to have to go after both amyloid and neurodegeneration, not just tau, because there are other things that kill neurons.

But I'm also going to say even within the amyloid world and the amyloid hypothesis, I think we have to consider a greater amyloid reduction, which likely will require combination therapy there as well, because I think we've seen evidence that we may be limited in dosing anti-amyloid compounds of several different types, due to adverse events, and maybe in combination we can get greater amyloid-lowering without having as much adverse events.

Also, I think we have to acknowledge, even if you're in the amyloid camp, that we have no idea, really, which form of amyloid we need to be going after, so I think we want to be a little ecumenical and think about multiple targets within the amyloid. And although I absolutely agree, Michael, that it's an open question when you need to intervene, I'm more and more convinced that you need to intervene on the early side, because the pathophysiologic process begins decades, and not just amyloid. I think we've seen, in the familial ID, that many of these things change prior to symptoms, so I think we're going to have to use combination therapy even if we go earlier.

This was some work that Cliff Jack, Paul Azen, and I worked on a couple of years ago, mostly arguing that we had to move earlier, but also, in this paper, we said, wow, we need to move to combination therapy, so I'm so excited that we're really, I think, on the cusp of that. And again, this is really just to point out, at the shows, that even though I do believe we should work on combination therapy for later stages of Alzheimer's disease, before you even get to the stage we recognize as MCI, there's evidence that all of these markers are abnormal, so definite neurodegeneration, lots of amyloid, and already subtle cognitive symptoms, so I think we have to keep thinking about moving left.

However, I think there are some major challenges in how we get there, and these relate back to some of the things Michael brought

up, and I'll get a little more granular on this. I think one of the biggest problems is how do we actually assess synergistic effects of combination therapy in the earlier stages, in particular, because I think biomarkers at the moment are a little bit behind what we hoped they would be, in terms of predicting therapy, and I say this as a biomarker person.

I think that dissociations of the biomarkers in the clinical outcomes in Phase 3 have to make us wonder about what we're going to adapt on in these studies. Again, this best opportunity may be to intervene earlier, but the earlier we go in the disease, the harder it will be to adapt on the clinical measure, whether it's cognitive of functional.

I'll just bring this up because it's already been brought up, that there may be ethnical concerns, and I keep hearing, "Why would you possibly think about combination therapy in normal people, or near-normal people, because there may be additive risks?" But again, if it is the case that these combinations would work best early on, then I saw that's the ethical place to test them, because these individuals are at such high risk for moving forward.

I'm going to take heat for this slide again, "Biomarker, schmiomarkers, what good are they?" I think we have to address that they've had some limitations and try to understand what they're telling us. I think the data so far suggests that they do help us select participants, potentially, especially if we're going after a specific mechanistic target, and particularly as we move earlier, we're going to have to use these for selection. Maybe they have some utility in helping us know whether we're hitting our targets mechanistically. I think there's some positive evidence there.

But at the moment, I'm not clear which biomarkers, if any of them, really have what we'll call theragnostic utility, that actually track the clinical response, and even better, predict a clinical response, and I'm going to make an argument here that we still need better markers of synaptic function – and I'll come back to this, because I think that's fundamentally what Alzheimer's disease, and dementia, is.

Then I'll just spend a couple of seconds talking about what do the biomarkers and the dissociations that we just saw in Phase 3 tell us in terms of how we would move earlier, and in using combination therapy. I think everyone in this room is well aware of this, but I really thought of it as a double dissociation a bit, in terms of the Phase 3 results, that we had bapineuzumab, and modest evidence

of target engagement and effects on both A-beta and some markers of neurodegeneration, and yet we didn't see that translate into clinical benefit.

Solanezumab had some modest but consistent evidence of clinical effect with slowing, particularly in the mildest group, some target engagement on biomarkers, but we didn't see evidence on the biomarkers we expected for neurodegeneration, that typically track with clinical. So what does this mean?

I think, before we give up on biomarkers, and certainly before we give up on the amyloid hypothesis, we have to come back to this too-little-too-late question. Although we did see, on some biomarkers, that we decrease the amount of fibrillar amyloid, that we slow the rate of increase, there really were not robust decreases from baseline levels, and this said to me, I think, before we give up, we need to see if we can get more amyloid reduction to really alter the clinical course. So the question is, how much do we need to reduce? Do we have to go to 40 percent since birth, which is what I'd say the genetic data suggests, and what forms of A-beta do we have to drop down?

Again, this question of stage of intervention. I think dementia, particularly moderate dementia, more and more evidence from the biomarkers that that may be too late to actually move the clinical course as well.

So, how do we move forward? This is not just theoretical. We're actually trying to plan a trial. The only thing we have so far is the acronym. It's going to be called the COMBAT trial, and as a pacifist at heart, I have to admit that I came up with this acronym but I don't like it because it's so war-mongering, but this actually is a war against Alzheimer's disease, and we are losing, so we're going to have to get more serious.

Here are the things we've been thinking about again, mechanistically, and I'll talk a little bit about the issues of how we might design this. One, again, staying in the A-beta space, because that's where we've got the most drug development so far, is maybe we need to simultaneous decrease A-beta production and increase clearance such as a secretase inhibitor plus immunotherapy. I think this is potentially ready to start over the next few months.

Maybe we need to increase clearance of multiple forms of A-beta, and I would say some day we might see multiple antibodies given together, going after different forms of A-beta, because we don't

really know which is toxic, and maybe they're all toxic at different stages of the disease.

Ideally, we want to decrease A-beta and neurodegeneration, and anti-beta anti-tau. I'd love to build the Combat trial to be Combat 2 and Combat 3, so that we could stick in these arms when these drugs become available. And, of course, any of these plus a neuroprotective agent, inflammation would be great, although I'm not sure whether inflammation is a good thing or a bad thing, based on the *Nature of Medicine* article that came yesterday.

But there are some real challenges, and I did have a great opportunity to talk to Don Berry last night, because I think, as we think about adaptive trial design in Alzheimer's disease, and particularly in early stages of Alzheimer's disease, there really are some issues that we have to address. One is what do we adapt on?

Again, I've already trashed biomarkers, which I don't mean to, because I absolutely think we need them, but it's not clear to me which change on a biomarker right now is really going to predict clinical response. I would say that we built in adaptive futility design in the A4 study we're doing, and I realize that we probably would've made some mistakes, based on that adaptive futility analysis, based on the Phase 3, because so far they haven't been very predictive.

Especially as we move earlier, what clinical or cognitive outcome could we actually use in 6, 12, 18, and even 24 months, in these very early populations, that's going to tell us what's going to happen clinically, because these people are not impaired at baseline, and they're changing very, very closely. So we have the horns of a dilemma. We have to go earlier, but it's going to be harder to see short-term change in this group.

A 2x2 factorial, a more traditional design, although I love the idea of putting them together. The drugs that we're talking about are at very different stages of development, so some in Phase 3, some Phase 1 going into Phase 2. How do we combine these easily in a 2x2 factorial when the needs for safety monitoring are different? I'm hoping to get some input from the FDA on how we could do this better. Of course, how do we blind the placebo groups well if these drugs have different routes of administration and different needs for safety monitoring?

Here are some solutions. Not many. One is we need more biomarkers, not just in small subsets of subjects. We need them in

everybody in these early intervention trials, so we can track them together, and say which go with which, and ultimately, hopefully, when we have a therapy that really works very clearly, how do we predict that with these biomarkers?

Again, I'm going to come back to this. We need biomarkers that tell us whether the brain is working better, that is not just a mechanism but actually, again, if suck all the amyloid out of the brain and you prevent tau, do you actually make it work better, more acutely, so we can see this? We need to pick these leveraged populations.

I hate to use the term "on the cliff," especially in Washington these days, but people who are just at the precipice of dropping, I think, is a very good place to look for individuals, that's early enough to still be able to rescue their neurons but individuals who are likely to decline over two to three years in these studies. And we still need better cognitive measures to detect these subtle changes, especially in earlier stages of AD.

So here again is this idea of a cliff, although it's more of a hill here. Right now we're doing our trials at this cliff, and I think, unfortunately, they're already falling. I think we need to move back to this cliff, and I think we need to move there with combination therapy. Ultimately, it may be that we need to be over here, absolutely, but I think it may be tough right now to design combination therapies for that group.

Again, improving trial efficiency, especially will get us, I think, closer to the combination therapy designs that would allow us to use an adaptive design such as I-SPY, so we're working on computerized cognitive batteries, more challenging episodic memory measures, CSF markers that are of neurodegeneration but may not just be tau and phospho-tau, which may not be as dynamic as we thought in that range. And again, functional imaging methods that maybe get us to synaptic integrity a little closer.

One issue in this design is how, again, could we embed safety monitoring in these 2x2 factorial designs or adaptive designs, in the middle of this cohort. So how can we do this in a short term that allows us to continue long-term studies. I have been working on functional imaging for a while, so I couldn't resist showing you one functional imaging, but this is actually data from Diane. We had the opportunity to do the multicenter functional connectivity analyses, and this is encouraging to me that it might be an early marker and that it's feasible to do across centers.

I'll end with this urgency slide. I love Dan's quote on this, that we have 10,000 Baby Boomers turning age 65 every day. I will argue, again, that right now, even though I hope we'll find therapies, we're running trials at the end stage of a disease that's been going on for 20 or 30 years, and we need multiple shots on goal, to really defeat this formidable and complex disease.

So I think we're going to have to bite the bullet – another war-mongering thing – and be brave, and actually start these combination therapies as early as we can do it safely. Of course, we need to watch these individuals, who are not yet patients, very closely, but we have to do it, because I think this is the way we're going to win. Thank you very much.

Dan Perry: Thank you, Reisa. I'm so glad that we could work you into the program, because you really grasp the key questions about what are the different elements of this disease that could be approached by different therapies in combination. By the way, depending on what budget priorities look like after the smoke clears, your having chosen a Department of Defense-like term for your trial may be very farsighted, so I congratulate you on that.

Now is the time for some Q&A for our morning speakers. I'd ask you to first direct your questions to Mike Krams, because we're sharing Mike with another conference and he needs to get to that one pretty quick. So if there are questions for Mike Krams, let's lead off with those. Phyllis.

Audience: I'd like to make a comment if I may. I'm the CEO of the Society for Women's Health Research and we've been running interdisciplinary research networks for ten years, on a smaller scale, obviously, than you were talking about. They've been incredibly successful. Obviously, our focus has been sex differences and we're trying to start one in sex differences in Alzheimer's. We've done a scientific roundtable and briefing on Capitol Hill.

The problem we're having is that nobody wants to fund multi-year programs, and the way they run is they go for five years, the scientists come together four or five times a year. We fly them in and they spend two days together. They work in each other's labs and the exchange information, et cetera, and then they get money for pilot projects, et cetera.

So it's a small example, but a good example of how successful that can be when you're bringing in people who are interested in the same area but from different viewpoints, coming together. But it's impossible to convince companies to fund these long, multi-year programs. They want to do a quick thing and be gone. That's one of the issues that we struggle with, is how we can continue doing this.

Mike Krams: That's a great point. Let's definitely exchange more discussion afterwards. What I've learned is that it's worth taking baby steps. When we first talked about this Framingham study on steroids, of course it sounded absolutely crazy. The IMI EMIF project isn't the right thing, but it's a huge investment that's going in the right direction a little bit.

But here's the real trick. If we and others can work together and align behind the principle that we have to get rid of our myopic perspective, that will be step number one. Step number two is, at the very get-go, at the design stage, to agree what the right biomarkers are that we need to build on, because we need to have that from the get-go.

Reisa, I'm going to just make a quick comment on these biomarker things. Of course, we haven't got a clue, but some things we know, and some things we can use as necessary conditions. For instance, in the development of base inhibitor, it's going to be of some interest to check whether A-beta for true lowering occurs, and guess what, it's going to occur quickly. Maybe there is an issue around REIE. That's going to occur sort of quickly. So there is partial information that we can use as necessary conditions that can be built in, and we can give user requirements to the engineers. Give us biomarkers that read out very quickly, within an hour if we can.

I've argued for ages that we take bapineuzumab or solanezumab and do the following the study. We sample CSF on an ongoing basis over two years. I want to know when is the first time point at which phospho-tau goes down. We know it goes down, but we don't know what the earliest time point is. We haven't asked that research question and we could. That's the way we have to go about the engineering piece. If we know what the user requirements are, we work together, I think we have a totally different way of approaching the problem.

And just one more point on the network. Just as we talk with Down, we had a great discussion two days ago with experts who

have the mitochondrial disease network, doing the exact same thing there. The more this becomes an aligned position that many people work together, the easier it's going to be.

Reisa Sperling: Can I comment? I absolutely agree with you, and I do think that we have biomarkers on target engagement that are very encouraging. I'm struggling, and I'm hoping you're going to say, how do we, in the absence of a clear clinical signal with some things, say what's theragnostic? I think that's the piece where I'm struggling, because of the dissociation.

Mike Krams: Look, I'm going to break the rules, and folks who work with me at JI, don't listen, okay? There are things we can't talk about here.

Reisa Sperling: Why not?

Mike Krams: Here's what I want to say. What we need to do is to invest just as much time as we did in conducting the experiment in really understanding it, and modeling and simulations approaches are going to ___ forward. What's currently being presented like the prespecified, and I have to leave it there. But the point is, it may not be just quite as negative as you think.

Audience: I just want to comment on the topic of biomarkers and synaptic activity, and challenge everyone to look beyond Alzheimer's in areas such as pain and autism and _____ where functional markers of synaptic function – the challenge of biomarkers in this area is it's taken us so long with the favorite biomarkers to get the standardization and harmonization right.

So in the functional world, in your work, is so compelling and yet we're still finding challenges around the harmonization and standardization. Can we think beyond going into disease areas like pain and neuropsychiatry to help us tackle some of those challenges, to get those biomarkers much more implemented in all studies, so that we get farther?

Reisa Sperling: I definitely can say, at least on resting state functional MRI it is embedded in the Diane study, the Alzheimer's Prevention Initiative, and A4, and we have a harmonization group so it's collected exactly the same way across this, so we'll have 40,000 resting state fMRI scans to play with. I don't know if that's going to be good enough. I think FDG-PET needs some more work. I don't know why that hasn't shown more promise, because it should be a good marker. But I just think this is a place where there's still a black box. We've got target engagement, we've got

clinical outcomes, but this telling us how do we predict whether there's actually a positive clinical effect in the brain, we need something to fill in that black box.

Mike Krams: Can I just make one more comment, and that is about how do we fund? Let's make a summary plot of all of the dollars that have gone into drug development programs. It will be many billions. Now, let's ask how many billions we've spent on ADNI-like, understanding the disease. That's the problem, so we need to shift that balance. We can't possibly run clinical trials if we don't know what the right biomarker endpoint is.

We need to reverse the balance of investment into methodological studies first, which establish how to identify subjects and how to observe them. Once we've done that, we can put players in that modulated path, but how can we build a Munchausen game, where we try to pull ourselves out of our own hair, if we don't fully understand the operating ____ ____ ___ of the endpoints.

Reisa Sperling: I just want to make one argument on that. I'm not sure I agree with you that we need to do one first and then the other, only because what we've seen is what happens in natural history is not what happens in studies. I actually think we have to do them in parallel. We have large placebo groups where we can model natural history biomarkers, but I think we need these biomarkers in large-scale, earlier intervention trials to see what happens simultaneously.

Cancer has learned about their biomarkers in the setting of these therapeutic diseases. We've tried to do it separately, and we do these teeny weeny biomarker studies in clinical trials and then ADNI-like studies. I think that's a mistake. I think we should do them in parallel, do as much as we can, and learn from the placebo group.

Mike Krams: I agree as long as I can have 50 percent of the budget for biomarker work.

Reisa Sperling: Well, 150 percent.

Male: Can I comment on that? Reisa, it's very interesting you say that, because I was going to object to something that you said in your talk, and make exactly the point that you just made. You said you weren't clear on the biomarkers and whether they were predictive and you might have made a mistake. With apologies to Donald Rumsfeld, we know what we don't know, and we model the

uncertainty, but we do it in parallel, so we're learning. Biomarkers may be so-called prognostic, that is predictive of how well you're doing, but they may be predictive as well, and specific to certain therapies.

For example, in cancer, in tumor reduction, there are some therapies that reduce the tumor burden but have no effect on any clinical outcome, and others that see opposite. So we can model that, and if it turns out that there is no predictive benefit, we'll learn that, but we're not going to bet the farm on the biomarker until we get some validation, and as you point out, potentially within the trial itself.

Dan Perry: Steven.

Audience: Steve Salloway from Brown. Mike, thanks so much. It sounds like you're proposing a long-term Manhattan-type project, because Manhattan had a specific goal like the Empire State Building, but obviously this is going to be a little more challenging on the long term, so I think that sounds fabulous. I know this is a forward-thinking meeting, and one part we haven't touched on today is the Stage 0 preclinical Alzheimer's disease, using Reisa's model, the biomarkers for that.

I think that's where we're going to have our greatest impact down the road, is finding out who's at risk for Alzheimer's disease, like cardiovascular disease with cholesterol and hypertension and diabetes, and we don't have those biomarkers yet to identify people at risk, and we're waiting to see when there's pathology, because that's what we can measure right now.

Mike Krams: I totally agree.

Dan Perry: Michael. Another microphone here, and then we'll go to Ian.

Audience: I have a question. Kind of what's been presented are clinical development plans, and when I look at it, it seems that the underlying assumption is that when you start developing the drug in a Phase 2 – I'm interpreting what was shown earlier – that you start with exploring combination treatments. I guess I'm not clear. Are you suggesting that there are some drugs that won't work on their own but will work in combination, or is it that they won't have enough of an effect to be measurable, in which that's a different problem? And how do those assumptions affect what you see as the ultimate development plan?

Mike Krams: The best way to get the answer is to do the experiment, isn't it, so I'm arguing with preclinical folks to immediately put base inhibitors and clearance mechanisms together, as opposed to wait until one drug is developed and then perhaps we think as some biop option. I want to know the answer to that question from the get-go.

Reisa Sperling: Right, and I was trying to argue that particularly in earlier stages of disease, where it's actually going to take us a while to know whether this really affects a long-term clinical outcome, we can't wait and do each one and then say, ah, well, this had some effect but we need 50 percent lowering, or 90 percent lowering if we're in the A-beta space. Again, this issue of stage with neurodegeneration – does it matter when you start the neurodegeneration, and is that an issue of whether there's combination therapy?

So I think our model in Alzheimer's disease, where it's just taking so long to do these studies, to do one at a time is no longer tenable. I think we have to find ways of starting very early – even though I know it's risky – and doing them together from the beginning, if we're going after early disease, early targets.

Don Berry: There's an example of this. In breast cancer, sort of a miracle drug is Herceptin, trastuzumab. It is ineffective by itself. You have to give it in combination, and in combination, it's changing a huge segment of breast cancer, HER2+ breast cancer. It's a good characteristic to have HER2 because you've got Herceptin that's going to treat it.

Dan Perry: Ian.

Audience: Ian Kremer from the LEAD Coalition. Thank you, first of all, for making this material accessible for the handful of us in the room that have no science training, which I will perhaps demonstrate with my question. In terms of the idea of a Framingham-style approach to this, with a population of, as you said, 100 to 130,000 participants, can that population be multinational and can the funding sources for it – government, private philanthropic, industry – can that also be international, and if so, what does it cost and what complications does the multinational or international aspect add to this equation, that we have to persuade American policymakers to support?

Mike Krams: Well, this is, of course, a megalomaniac proposal, but I think the way to go about it is to look at the bookends. Dr. Buckholz said,

the ADNI experiment has totally changed our insights into Alzheimer's, and I tell you, I was involved at the time when we negotiated how can one company put monies together with another. At the time, people said it's never going to work, and guess what it's doing now? That's a very small study, a couple of hundred patients. It was very expensive – many, many millions of dollars.

Is it at all doable? Of course it is, because here's the problem. I just mentioned this u-funding. I don't belittle it, but it would be so much nicer if the engineering roundtable had happened before we invest that money. Here's a pot of money. Maybe there's a little bit of money coming from the U.S. government, et cetera, but the roadmap is done first. So what we do instead is a bit of something here, something there, and then we think about how can we put them together.

It should be the other way around. You don't build Empire State Buildings like that. So it's not a good answer to your question, but the hope is that by having the architect's plan articulated clearly first, we can actually have a concrete answer to your question, then go around to the different governments and say, "Here's the real thing. Please help us pull it off."

Reisa Sperling: I would say that's already happening, so again, in that A4 study which has a Stage 0 natural history arm, we're already exploring with Canada, Australia, and other places how do we co-fund this piece. Even though the NIH may have one important part of it, we're going to need more, and it would really be a mistake, again, to have seven different prevention trials where we do them with all different outcome measures. So this collaboration for Alzheimer's prevention, every outcome measure, we're trying to harmonize up front, and that will be a multinational study and absolutely partnerships from industry, academia, and hopefully other governments.

Dan Perry: Thank you. Another question. I think maybe we have time for one more. Neil?

Audience: With respect to what Michael said, I think there are two different issues. One is this kind of large study, but I think the critical issue to me is the other issue that you mentioned, and it's really critical to this whole idea of adaptive trials, to find biomarkers that change in a reasonable period of time. I think what you said before, in terms of putting in either individual drugs or even combinations, but finding out, over the short term, what those do to the various

biomarkers is critical to being able to do an adaptive trial, and finding the kinds of biomarkers that actually move in a reasonable period of time, and have the measurement precision to be able to see a change if one is there, is the critical thing.

So you could actually do smaller studies, looking at these combinations or single drugs over short periods of time, to see which ones actually move. That, to me, is the critical issue, to be able to do these kinds of studies.

Michael Krams: I couldn't agree more, and we have all the tools. We have compounds that we know move biomarkers. All we need to do is to put them into an incomplete block design, and with a little bit of effort we can learn about this. An anecdote. I'm a stroke neurologist. Neuroprotection in stroke is dead, but it's not disproven. It's just been killed by the people who invested probably 80,000 patients without knowing what we were doing.

About a week ago, I finished the manuscript on a robot-arm measure. Ten years after the field is dead, I'm now finished qualifying the biomarker. I'm telling you this story because it really breaks my heart. My heart is with doing something about stroke patients, and I'm ten frickin' years late. I don't want us to go down the same route, so we need to take that Empire State Building, and what you said, terribly, terribly serious.

Audience: I'd just like to make a quick comment. I worked with Mike years ago in stroke, and I share your passion towards this, but the kind of innovation that may have not manifested in successful neuroprotective drugs and stroke, look where we are with prevention with stroke. The kind of biomarkers that look for effects on functional outcome in stroke, those measurements that we can now apply from the learning from stroke to Alzheimer's disease, because there are tremendous advances that happened that helped us have successful approaches to prevention of stroke, and I think we have a lot to learn.

Dan Perry: I think this morning's speakers deserve our appreciation.

Dan Perry: This really teed up the rest of the discussion. In the second phase we're going to go much more into how do industries work in a pre-competitive space. We need about 90 seconds to set up the slides for the next panel, so this would be a good time for a second-inning stretch. Don't go too far because we're going to get right back into it quickly, but take a minute, check your iPhones, and say hello to your neighbors.

[End of Audio]

David Dilts: The military decided that they would teach a computer what to shoot at, so they built what's called a neural network to figure out what to shoot at. They got pictures of our stuff, and they taught it, "Don't shoot at that." Then they got pictures of their stuff and said, "Shoot the hell out of it." And it worked, beautifully. Then they took it out to Aberdeen Proving Grounds and they turned it on, and during the day it didn't shoot at anything, and at night it blew the heck out of everything.

They went back and looked at the pictures. All the pictures of our stuff – the really pretty, shiny pictures they gave to Congress – all the pictures of their stuff were grainy, dark pictures taken with little itty-bitty cameras. What did the thing learn? Anything that's dark is bad. I know it's that ____ marker, but what are you getting out of this stuff?

I'm going to talk very fast because I only have 900 slides and I've got 5 minutes to do it. Why should we change it all? What do we want to change to? What are our beliefs about why we don't change? What's the value of cooptition, working together? Now, those of you in industry, I'm going to give you real, live, honest-to-God industry examples as to why it's good. You just don't do it in the pharma industry. Well, I shouldn't say that. You don't do it nearly as much as I think you should do it in the pharma industry.

Has anybody got one of these things? It's called a USB. What distinctive competitive advantage is having a USB to any maker of computers? Zip. Nothing. But boy, everybody got together and said, "If we don't have a way that everybody can share stuff, we're all in trouble." This is a pre-competitive consortium called a cooptition because competitors are cooperating on a similar problem, and that's what I'm going to talk about.

I'm not a cancer researcher. I fell into cancer research purely by accident. I give a talk to cancer centers where I say, "You look just like General Motors to me," and they're like, "What?" I say, "You're all going broke and you just don't know it." Let me talk about why you should change. Number one, we're doing clinical research because we're faster, better, or cheaper. Well, guess what? We're not faster than Italy. That's embarrassing. Italy runs trials faster than we do in America.

And, by the way, in pharmaceutical industries, your new product development is going exactly the wrong way compared to the rest of the planet. Anybody got an I-anything, like an iPhone, an iPad, an I-what-the-heck? Guess what? Every year I'm going to have a new one, and by gosh, that new one better have really, really cool stuff. You know what? We've been taught so well that millions of people will buy it, never having seen it before. And you guys are, "Well, no, product development is now going to take 95 years to do." What? Going back to the engineering example, yours is so much harder to do than Apple? You aren't harder to do than Apple, but really? It should be taking that long?

Okay. So your development time is going up and everybody else's is going down, and, by the way, it's getting worse. You're collecting all kinds of stuff that people are like, "I don't know what you're doing" but you keep collecting it. You remind me so much of old manufacturers. We used to keep all kinds of garbage, just because we could – not because we were going to do anything with it, but it's really cool to have.

Now, are we better? This is a study that came out in 2012 that studied the quality of data, internationally. "Thus, a comparative assessment of query rates suggest the quality of clinical trials conducted in emerging countries is consistent with those conducted in developing regions." Oops. We were supposed to be better. Well, that didn't work. And we're cheaper.

You all know that we're so inexpensive in this country to do any clinical research, so I don't have to go there. And, by the way, it's getting more expensive, and it's getting longer, and it's getting, it's getting, it's getting, because you're doing all the same old stuff again, and again, and again, and again, and you're getting the same old results. You have to stop that.

I'm going to talk to you about what's called the knowing-doing gap that Jeff Pfeffer at Stanford developed. Just because you know what the problem is doesn't mean you know what you can do about it. Now, this is my very favorite illusion. See the parallel lines up there? Except they're not parallel.

You see the non-parallel lines up there – except that, wait a minute, they really are parallel. You're blinding the part that says, "Wait a minute, this is incorrect." And, by the way, that's how people like David Copperfield make a gazillion dollars. He works on that particular problem.

I'm going to talk to you about a precompetitive space, not the space that this is the drug we're taking to market, but we really need the FDA to agree on endpoints. We really need to have standard laboratory processes to get consistent biomarkers. We need to do something general for the industry, not specifically for us. As I mentioned, that's also called cooptition, where industries that compete also cooperate – and I've been part of lots of these kinds of guys.

This is a well-known thing in engineering. I used to work with companies that were vicious competitors in the marketplace, but they all had a problem with steel. Believe it or not, steel is too heavy. They wanted to have the same strength, but lighter. That's a generic problem. That's not going to give anybody a competitive advantage. And they worked together, and spent millions of doing it.

Where should you work? On places you're going to share with your competitors, the non-strategic areas, areas where it's difficult to differentiate yourself, or areas where growth in size of the pie is greater than growth in size of the slice of the pie. Basically, let me talk about automotive industry. The automotive guys really never understood this. I used to do a lot of work with General Motors, and General Motors spent so much time competing with each other, they didn't realize the Japanese were cleaning their clock, and they still don't.

They took going broke before anything happened, and even then they still don't. The guys at Pontiac would much rather fight with the guys at Buick than they would rather fight with Toyota, which is like, "You're fighting the wrong battle, guys, because consumers really don't care." So it's a different kind of battle, different kind of problem.

Well, they decided they're going to do a cooperative, and they set up a thing called Covisint, and that's all the suppliers are all going to get together and they're all going to share information and everything is going to be wonderful and cozy – and it didn't work. It didn't work for a very specific reason. They built this for low cost, not for strategic advantage, but knowing who a key supplier is is a strategic advantage in the automotive industry. So they said, "We'll all get together and we'll all share, except we won't share." That didn't work.

One that actually did work is Sematech. Sematech said, "The Japanese are cleaning our clock," – and, by the way, to give you a

statistic that was marvelous, Hewlett-Packard did a study. The very best American-made computer chip was worse than the very worst Japanese computer chip. If that's not a death knell for your industry, nothing is. Well, they woke up and they said, "We need to get together and figure this out," and they actually got together and built a new industry. It's a different way of looking at it. So when looking how to cooperate, just cooperating alone might not be successful.

Here are some more examples. Any time you use the World Wide Web, that's a precompetitive consortium. They all got together and said, "Building a standard for how we talk, it's not important. What we say is really what's important." So every time you do it, that's what it's all about. There's a thing called Genevieve.

The automotive industry said, "We don't know anything about all this computer stuff. Let's all get together and find out how to fit Bluetooth in our cars. Let's just get together and do that." Very, very, very common in other industries. I showed you the USB Implementers Forum, which is why we've now got USB 3.0, because they keep making it better and better.

Should you choose a larger share of a small market or expand the market? That's one of the things to think about. Most organizations think, "I want my share of my market. I'm going to protect this," as opposed to, if we did pre-competitive stuff and laid benchmark foundations, we could dramatically expand the size of the market.

Some of you are mature like I am. Do you remember before there was the Internet, where everybody competed like crazy and my software won't talk to your software, and you've got to physically come here to do everything. Think about it today. Think about how easy it is to share and work and communicate with each other, because people decided to cooperate, not on strategic of things, but communication. Strictly communication, and I'll show you how much it costs it we're not communicating with other industries in a minute.

Let me talk about why people don't do it. We're too big to fail. We have a better mousetrap. We have a gold rush. Or Ford-ism. There's a term you won't hear anymore. Henry Ford was really bright about what he did. There's no perceived need or there's little value for working together. So I'm too big to fail. I'm assuming you all went out and stocked up on your Twinkies, right?

Twinkies have something in them that will cure Alzheimer's. That's why we all have to keep them.

Every single one of these products was the number one market leader at one point in time. Every single one of these dominated their industry, and every single one of them is out of business. Every single one. So just because we're so big now, has no relationship to tomorrow.

Now, I can build a better mousetrap. I deal a lot with engineers who build mousetraps. When you go back and look at the quotes, "If a man can write a better book, preach a better sermon, or make a better mousetrap, then his neighbor, though he build his house in the woods, the world will make a beaten path to his door." It's like, oh God, that's really what's truth.

Well, guess what? How many kinds of mousetraps can you think of? When was the best-selling mousetrap invented? And how many mousetrap patents have there been since 1975? Well, guess what? There have been others. There's spring, glue, humane. This little mousetrap right here, 1924. There's going to be 147 better mousetraps. Bull. It doesn't happen. Or the one I particularly like is this. Interestingly, they haven't changed the design in over 100 years, and in a moment I'll show you why.

Okay. So I've got a better mousetrap and I don't want to play with anybody. That's going to be a problem. So, there's gold in them there hills. There's a gold rush, if I just give the magic thing for cancer. Well, I actually looked it up for Alzheimer's. This I just found. When you look at Alzheimer's, the number of drugs in development per 10,000 deaths, it's about 12.4. Here's the really big gold rush, is in skin cancer, where there's 92.9 drugs. Everyone is running for the gold, because if I make it, I make like a gazillion dollars.

Well, I look at history. You know what? Who made the money in the gold rush? Actually, you want a better example? Who made the money in the Powerball last night. Somebody did. Actually, two somebodies did. How much money did the Powerball guys get, because everybody put in their money? It was phenomenal. They made several hundred million dollars, because everybody's waiting in line, saying, "Yes, it might be my ticket." That's a gold rush. Who made the money? The infrastructure people. The people who run the Powerball make a fortune. By the way, that's why Las Vegas is successful.

Who made the money? This guy who's a store owner who published a newspaper saying, "Hey, you know what? Fred found gold." Oh God, I've got to read that paper. He also ran a boarding house, where he made a lot of money. Do you know who made a fortune? Wagon train leaders. Why don't we take all these suckers out? Hey, go find gold. Give me money and to get there. Steamship lines made a ton of money.

Levi Strauss, who we still wear today, was a gold miner who said, "This ain't going to work. I'm going to make these really tough jeans that work in the gold mines." How many gold miners today are still there? But Levi Strauss, we know. This was a short-term effort. In ten years, technology shifted as such that individuals can do it and you don't need a company. Very different perspective.

Now, Ford-ism. Henry Ford is what a lot of companies are still doing. Henry Ford was an absolute genius jackass. He was a mean – and if I knew you better, I would use more colorful language – individual, let's say. Just a rotten human being. Henry Ford said, "I'm going to sit down and you're my supplier. If you make a dime, that's a dime I could've made, and I'm going to keep it all myself." That's called Ford-ism.

How many companies keep all this knowledge for property, just in case? I'm a university professor, for God's sake. My university is so interested in protecting my IP, we haven't commercialized a damn thing. I get 100 percent of nothing, thank you. It's a strange world.

He really did it. He made it work. He reduced time and ____ to make a car from 118 minutes to 2.3 minutes, a 99.5 percent reduction without a moving assembly line. That's what he's most well-known for. He did a major shift in this. He also then reduced it to 1.19 minutes, and then Toyota today has only got about 50 seconds _____. He beat it up in ____, but he didn't figure out that the world is changing. He never figured that part out.

You will never see a headline like this again. "Will Success Spoil General Motors?" By the way, those of you who think Kodak was out to lunch in the digital age – this is 1983. Embattled Kodak enters the electronic age. Kodak had the first electronic camera, and you know what? Nobody bought it. They were the wrong time.

You know who had the first electric vehicle in America? General Motors, called the EV1. They didn't sell them and had to pull

them back. And now everybody goes, "Oh, they don't do that stuff." Actually, they did it but they missed the window of opportunity, and that's the other thing to think about in our precompetitive consortium – is this the right time? It sounds like it is the right time, but you've got to be careful, because if it's wrong, you're going to lose.

I showed you this. Why should we work together? I love giving talks in this town, because in Baltimore, Baltimore burnt to the ground. Fifteen hundred buildings burned in 1904, because of lack of standard fire hose couplings. When firefighters from Washington and as far away as New York City arrived to help douse the fire, few of their hoses would fit the hydrants. When they counted them, the National Bureau of Standards collected more than 600 sizes and variations of fire hoses.

How many variations of biomarkers do you have? How many variations of how people develop biomarkers do you have, and what happens when you try to share? They don't fit together. This is 1904. Oh, we're beyond that now. We've learned our lesson from that. Well, let's stay with manufacturing. During the first Iraq war, this was great.

The Army vehicles had a different sized nozzle than the Marine vehicles. They couldn't fuel each other. You know what they did? They put them in 5-gallon tanks to pour them in. That's called a World War II solution. Their radios couldn't talk to the Army's. They couldn't communicate. Nobody every thought they'd actually want to talk to each other.

This one, even if you think you're doing it well in your company, this is a beautiful one. Airbus decided they're going to make part of their airplane in Germany and part of it in France, and they ship the two pieces together and plug it in. Guess what? They didn't fit. Three hundred miles of wire and 40,000 connectors didn't connect. That's like, oh, damn.

And they called each other and said, "We're all doing digital design." "Yes, we're doing digital." We're all using CATIA." "Yes, we're all using CATIA." "We're all using CATIA Version 6.0." "Oh, no. I'm using CATIA Version 5.0." "You're kidding. Really? You guys never tried to plug it together before you built them?" "No. We built them, sent them, plugged them in. They don't fit."

By the way, a $6 billion charge later, a new CEO, a new CFO, a new project manager, new chief engineer are all in Airbus. The only one that survived the debacle is the chief of marketing. Everybody else got fired, for not even thinking about how to put this stuff together. A precompetitive consortium is how to put it together. What you plug in is what your competitive advantage is, but plugging it, that should be everybody's business.

How much does it cost because you can't plug it together? In 2004, the National Institute of Standards said to do capital facilities – in other words, build an Empire State Building – cost that industry $15.8 billion a year. The automotive industry, conservatively, is over $1 billion, and pharmaceutical clinical trials have been researched, and it's $8 billion to $9 billion a year, just because you don't communicate.

You should pick up this brand new report that just came out from GE. "Connecting industrial operations to the Internet could lead to significant gains in productivity, potentially worth trillions." Nobody anymore talks about billions. Now it's got to be trillions before anybody cares. Do you know what this is? The machine phones home when it needs help. That's it. That's the whole thing. You know who already does that? Caterpillar.

Caterpillar can tell you the status of every single thing they've ever made, in their history, and exactly where it is, on the planet, and when it's going to break. These guys have digital signatures that will listen to the sound of the engine and can tell it's about to break. It's not a biomarker but it's a hell of a good marker. Do you know why they do that? Because they guarantee shipment of their product. They will give you any part in their inventory, for anything they have ever made, anywhere on the planet, in 48 hours.

Some of their stuff it takes two years to make, so how do you ship stuff in 48 hours that takes two years to make? Because they have an insane amount of data analytics to predict when something is going to go wrong. They collect data after data after data. One thing about consortiums and data, data is cheap. If you can get together and figure out how to share data, data is cheap that you can mine for all kinds of ____ benefits, and that's something you think about.

By the way, railroads. Once again, I'm going back to "When I was a youth and got on a train." Railroads were grand things, novel distribution system, all kinds of fun things. Before they had

railroads, do you know why Lewis and Clark kept looking for the Northwest Passage? Because it was incredibly expensive to ship anything over land. It was cheap to ship it over water. They kept looking for a river that went east to west, and they couldn't find one. Thomas Jefferson was really ticked, because he didn't find one.

Well, railroads said they could do that. Andrew Jackson took a month to travel from Nashville to Washington. This one I love. "Potholes were so large in the Great North Road in England in the 18th century, that men and horses are known to have drowned in them." I've seen some of those kinds of places here in Washington. Everybody is like, "Don't be on the Beltway."

Okay. And shipping a ton of goods by boat, 400 miles, could easily quadruple the price. Really expensive. Well, they decided that, you know what? We're going to build railroads, and railroads were the gold rush of their day. They made a fortune, but they only went from city to city. So I would go from Nashville to Murphysville, and then somebody else would pick up from Murphysville to another place. They were only point-to-point connectors. No infrastructure.

Two-thirds of the issues on the New York Stock Exchange were railroad stocks. Made a freaking fortune until the bubble burst. When the bubble burst, there's a guy by the name of Vanderbilt, at a school I used to teach at – which, by the way, he never visited. They could start one but they couldn't run them. Two-thirds of them went broke.

Cornelius Vanderbilt was no schmuck. He went in and he bought rail lines, the only contiguous rail line from New York City to Chicago, so he had the only point-to-point solution that went from a major port to a major port. He died the Warren Buffett plus Bill Gates of his day. He's known as a railroad baron, and he never built a railroad in his life. All of his was network connections and knowing how to connect the right things together, how to put the infrastructure together to make money.

There's all kinds of other things that came about. By the way, Morse code lines. Do you know where the Morse code lines went They went right down the railroad tracks, so that's why we have communications today. Why did Carnegie make so much money on steel? Because the railroads needed steel.

By the way, before the railroads, every little hick town had a blacksmith, and after the railroads, they didn't, because they didn't need to have one. The infrastructure changed society dramatically. Think about building the infrastructure that can change the world. That's what precompetitive consortiums are all about.

Are you building a solar system? I appreciate it, but it's the wrong analogy. You know what? I really don't care what happens on Mars. If there's a storm on Mars, it really doesn't affect me. We really need to build more of a network, where things are interconnected and shared. It's not on a single note – everybody shares and works together.

So what's the value of doing this and how do you justify it? Let's talk about the cost of doing it alone. You all know about drug development costs. They're rising. You know the biomarkers are coming like crazy. Technology is developing a gazillion new tests that you've got all to adjust for, hence, it's getting more and more expensive, and most importantly, it's taking more time. Guess what? People who work together do better than people who don't, and in the electronics industry, they do three times better than the people who don't.

My analogy – which is not perfect – have you ever seen five-year-olds play soccer? I call it pack soccer – while the goalie is picking flowers. "Oh, there's the ball." What happens as they get older? They start saying, "Great. You know, if I don't run around a lot, I'm a lot more effective. If we actually played positions, we can be really, really much more efficient. Hey, let's not do this. Let's build a structure where people know their roles."

The roles, by the way, are very flexible. My daughter is a goalie. She would score goals. I have no idea how she would do it, but she could do it. That wasn't her job but she could do it, so that's the kind of structure you want to build, rather than a pack mentality of everybody running around for the same thing.

Let me give you one other thing – and, by the way, this is only my opinion, because people get pissed when I say it – I had absolutely no idea that cancer research was a fashion industry. I had no idea. Oh, everybody bevacizumab – that's a real drug, right? And, oh, everybody loves this one. And everybody is like, "Oh, there was a trial presented at ASCO," and everybody runs to that trial, and at the next ASCO meeting somebody says, "Hey, I've discovered this," and everybody runs to that trial. And you're watching this thing and it's a fashion industry.

I do work on how long it takes to open clinical trials, and whether they're actually successful, with success meaning do they accrue. Do you know what happens? If it takes too long, nobody shows up. You spend an enormous amount of effort building a trial and nobody gets screwed for it. Because you know what? It's not fashionable any more.

If you approach pharmaceutical industries as a fashion business, that's a totally different perspective, a completely different way of viewing things. You better be time-dependent. You better be fast. You better be accurate, but you better be there, quickly. In my business, that's called fast, frugal failures. Get in, get out, quick. Try it small and see what happens. If it doesn't work, you didn't spend a gazillion dollars.

There's a multiplier effect. I used to run one of these things. It was fun. I would go to industry and I would say, "Hi, Sue. How you doing? I need $100,000 to study this problem," and she'd go, "Oh, that's an important problem. Here's $100,000." "Hey, Steven, I need $100,000 to study this problem." It's the same problem. "Hey, Deborah, I need $100,000."

You know what I sold them? For every $1.00 you gave me, I'm giving you $3.00 worth of research. You all gave me $100,000, and I've got 10 companies, I'll give you $1 million of research for $100,000. That's a really good return on investment. They loved me for that, and then they did something else that I found really, really bizarre.

None of the stuff we did worked. I mean, none of it worked. I said, "Sue, you're a brilliant, smart person. None of the stuff we've ever built ever works. I don't understand, and I've got an MBA, for God's sakes." Sue was really smart. Sue would go, "You really don't understand," and I said, "Obviously."

"I gave you $100,000. I got $1 million worth of research. I was about to build a $2 billion plant on that theory, and you just proved it was wrong. So thank you very much. You saved me $1 billion of cost, and I spent $100,000." And I went, "Oh, that's cool. I'm going to go fail more." They give a consortium as a low entry fee, fast, frugal way of testing things. Not doing the big Phase 3 studies, and doing it after design is beautiful, but it's a different problem.

Now, this is how Caterpillar does it, and once again, I deal with heavy things. I love this. You know you're a weird company. Caterpillar was going to put a base on the moon to send back all the data that all their equipment was transmitting, because they got more transmission of data than any telephone system could handle. That is a big-thinking problem. Yeah, I'm going to send a bulldozer up to the moon. No, I'm not going to do that.

First they put all the projects together. Then they said, "There's something that's critical, that we're going to do, no matter what." Pharmaceutical companies do that. They evaluate the risk, they evaluate the opportunities, they say, "This is the thing we're going to have," and they're going to do it. But there are other things, you've got a pay line. There's going to be a hurdle raid. You've got to be so much of a return – this kind of stuff. And every single company does that.

You know what? As you all know, there's lots of projects underneath that, that would be really good to do. Well, that's where you get a consortium. That's where you say, "I'm going to share my data." And ____ ____ _____ linkages to what you do. Hardening. Hardening is a really big issue in steel. Let's get together a hardening consortium.

Have any of you heard of the Advanced Battery Consortium, ABC? Advanced Battery Consortium is enormously important to every single thing we play with, and their entire mandate is to make better batteries, theoretically better batteries. Not actually make them. By the way, one of the things they developed – and I love this – the case itself is the battery. That is so cool, if they can ever actually make it work. And then, you do it until people or money runs out. So don't think of it that it just didn't hit the hurdle right and we need to get rid of it. There are other things you can do.

Now, this is what I think you ought to look at. This is way too important to be left to what I call a craft industry, onesies and twosies. It's way too much money, way too expensive. You need to look at throughout. I spend a lot of time talking to government folks, saying, "I really don't care how many papers you published, because I really care about drugs to people, standard of care."

And, you know, if you publish a lot of papers, that's very good but that's not really the metric. I gave a talk before the TJSA and I said, "I really don't care how prestigious you are if you've never

actually developed anything that makes any difference to standard of care." They don't invite me back.

Look at the things that enter the system for standardized information, standardized processes, and leaving the system, pre-approved endpoints. There are things that are not competitive advantage to your company that would be enormously valuable to Alzheimer's patients. That's what you need to work on, and, by the way, literally locked in a room like this – I used to do this in manufacturing – it takes about a week, and you will lay out a roadmap.

By the way, the other thing a roadmap will get you, that's really interesting, is all the places that you're not funding. We did this for a governmental agency and they all went, "Oh, this is all so incredibly important. We have to do blah-blah-blah." And we said, "Yes, you do this, you do this, but you never fund this, so nobody can get to this."

You couldn't get throughput because they didn't fund the right things. A colleague of mine, by the name of Joe Gray, says you don't get a working cyclotron by funding 1,000 R01 grants, and that's exactly true. That's not mission-driven, which is a different kind of problem.

The most critical factor is the will to do it. This is not an easy thing to do. It's something you have to say you're committed to do, it's important, it's a change in the future. That is, by far, the most difficult thing to do. Then there are all kinds of issues you get into. It's the technology, how do we coordinate, IP, regulations – there's a ton of stuff.

My message to you is, it's a well-known path. Other industries know how to do this, know how to deal with honest brokers, and have solved this problem, and they solved it 30 years ago. Follow their footsteps, learn their lessons learned, and it will save you so much time and so much effort. You can't wait. This is an important problem you need to work on.

One reason for the knowing-doing gap is people confuse talking about something, as I'm doing – and, by the way, sorry; I am pontificating. What aspects can we do this with target, and what are the barriers you perceive, and when will we start? If you learn anything from me, I want you to learn this quote: Unless a decision has degenerated into work, it is not a decision. It is, at

best, a good intention. If this is a good intention meeting, I'm out of here. You've got to get to the work part. Thank you.

Dan Perry: David Dilts, another boring Alzheimer's speaker. Don't you just hate these long, slogging, scientific meetings, with a lot of boring data? How would you like to be the person to follow David Dilts to speak? Well, that job is going to fall to Debra Hanna, who is Associate Director of the Critical Path Institute.

Debra is going to show us how what we have learned and what they've accomplished in identifying key targets in tuberculosis can actually carry over and show us some of the path forward for Alzheimer's. Who would've thought there was anything you could learn from an infectious disease like TB that would be able to pave the way to Alzheimer's, but she's going to show us how, so we look forward to hearing from you.

Debra Hanna: Thank you so much for having me. That is a very hard act to follow, but I'm going to do my best, and I think this is a great example of how we've put really good intention to work, as he said. I want to share the similarities, and believe it or not, there are quite a few, between the disease area we work in and Alzheimer's, and hopefully we'll find ways that maybe we can coordinate efforts even in the future.

I'll start by saying I'm here to talk to you about the Critical Path to TB Drug Regimen Initiative. This consortium was born in 2010, really around the absolute determination to deal with one of the world's largest unmet medical needs, which, believe it or not, in 2012 is still tuberculosis. A third of the world's population is infected with this organism. We have 1.8 million people that die every year from this disease. I think a lot of people think we've eradicated this from the globe fifty years ago, when streptomycin was introduced, but that is absolutely not the case.

What's even scarier, for those of us in the field, and should be for all of you in the room, is that the incidence of multi-drug resistant and extensively drug-resistant TB are absolutely skyrocketing around the globe, and with the ease of travel, what we think is just a problem for the impoverished world is really going to become a problem for us. This is a great example of where, because we thought we'd tick the box and have the solution for this disease.

We quit innovating. Drug companies didn't work in this field, so we didn't have a pipeline available with drug-resistant forms emerged, so we are really playing a massive catch-up game. It's

because of the Bill & Melinda Gates Foundation, and their commitment to treating this disease that we have this consortium that I'm going to talk to you about today.

If you'll allow me just a slide or two to tell you a little bit about TB, I think that sets the stage for the problems that we're trying to solve. I think you'll see some of the similarities. A major similarity is the need for combination drug therapy. For Alzheimer's disease, it's clear that you're thinking that this is going to be an important strategy for solving it. It is an absolute requirement for the treatment of TB, because of drug resistance so the World Health Organization mandates that we use multiple drugs in combination.

Currently, for this disease, when it is drug susceptible, we have four first-line medicines that are used in combination, with the hopes of treating those patients and preventing even further resistance emergence. But there are a lot of problems with using those very old medicines. They were never developed to be used together. They were never designed, originally, actually, to be used for TB. They were designed to be used for other infectious diseases.

So you have an awful lot of significant drug-drug interactions that happen when you combine those four agents, serious adverse events that happen in effects that range from skin problems to breathing problems to kidney problems to stomach problems – but we have to use them, because that's what we have.

When you have all these adverse effects, and you don't feel good when you take these medications, it leads to noncompliance. You have to take these medicines for six to nine months, four pills a day, four times a day. You get tired and you don't feel good so you quit taking them and you end up with drug-resistant TB.

Many of the TB patients are actually co-infected with HIV, and for that disease, many patients are taking up to seven medications, just for the HIV. You add four pills, three to four times a day for six to nine months on top of that, we're talking about a very complicated disease state, which I think is clearly what you're facing, also, in Alzheimer's, from a complex disease form perspective.

We know that new drug development tools are urgently needed, and they're really needed because there have been no new TB treatments approved in the past 40 years, and that looks to be changing. I'll tell you a little bit about the vidapoline advisory

panel meeting that Martha and I attended yesterday – really good news for the field.

Despite the increase in MDR, we just don't have a lot of agents in the pipeline. We absolutely have to go with the multi-target approach, just like with Alzheimer's disease. Because of the complexity of the disease, as I mentioned – this is a disease where these bacteria sit in the deepest part of your lung, form major cavities. They are walled-off by your immune system, so it's very hard to get drug, even if it works in a Petri dish, into the part of the body that has the infection.

Another challenge that we face in TB is the prevalence is highest in the emerging parts of the world, and it really impacts the poorest patients. What this means for industry investment is that the return on investment for acute therapies is always going to be lower than for chronic treatment, but the return on investment is even lower in this area because we're talking about the poorest of the poor, who can't pay premium prices for a new medication, so innovation is even more stagnant in this field. Where there have been innovations in other therapeutic areas, or even for other antibiotics being developed, those technologies and advancements have not been applied to TB drug therapy, so we are playing a major catch-up game.

We also have barriers that are related to regulatory pathways. During the development of new drugs, we have lengthy regulatory approval times, even when you're talking about a single agent, but we also have to consider the fact that these drugs then have to be approved and implemented in other parts of the globe, and that slows the process, and it slows the access that patients have to new therapies. So we are taking, in this consortium, a multi-pronged approach, trying to deal with all of these scientific innovation issues, the economic hurdles, as well as the regulatory hurdles, to bringing a new TB drug regimen forward.

This is just a picture to depict the challenge that we're really facing. If we implement the current regulatory strategy for developing a new drug combination, and what we're really seeking to do is combine multiple novel target approaches in one brand new regimen. If we follow the current strategy of taking each new drug from discovery to approval, and sequentially approving those therapies, and then combining them at the very end, we're talking decades before we have a new regimen, and if you're one of those patients that is suffering from MDR disease today, that is

completely unacceptable, so we're trying to take this holistic approach to completely shift the regulatory paradigm as well.

This is the design of our consortium. The initiative is a unique public-private partnership that brings together drug developers, academic scientists, global regulatory authorities, and civil society organizations and patient advocacy groups in order to effect the change that I've talked to you about. And we have one very clear, but one very massive mission in front of us, which is to accelerate the development of a new, safer, more effective regimen that can be taken for a shorter duration than the six-to-nine-month course of therapy that I described, by enabling the early testing of drug combinations.

For us, we have the advantage of having a really nice biomarker, very early on, preclinically, which is what does a new drug do a bug in a Petri dish? I understand that you don't have those same types of technologies, but I'll talk to you about the advancements we've made in this area, to really look at preclinical PK/PD relationships, so that we can choose best combinations early, and that's one of the major initiatives within our consortium.

This is really a talk about precompetitive data-sharing and why this is important, so I thought I would share with you the members of our current consortium, all of whom have signed on to the legal agreement that say they are willing and prepared to share data in a safe manner within this consortium. It absolutely can be done, and it's certainly done within CPTR.

Our industry members represent all major companies that have a molecule or molecules somewhere in the drug development space, spanning preclinical to clinical phases, because there are a few in the pipeline, many of which are repurposed from other infectious disease areas. I'll share that with you in a moment. Partnering also with nonprofit organizations, as I mentioned, as well as government and regulatory agencies with groups like FDA/EMA, CDC and World Health Organization being very, very important to the work that we do.

I mentioned that there has been a lot of innovation in this field, and for a very long time there were absolutely no drugs in the pipeline for TB. Fortunately, we're in a very different space today. Yesterday a few of us participated in the FDA advisory hearing for Janssen's bedaquiline compound. This is the first new drug that would propose to be used for multi-drug-resistant patients. The advisory committee recommended that FDA approve this under the

accelerated paradigm yesterday, which is a great advancement for the field.

But what we're trying to do in CPTR is move away from, again, moving a single agent all the way through approval, and then taking that wonderful new agent and piling it on top of three or four old, bad drugs, and moving forward in an entirely new regimen, and that's what we're trying to do. This just gives you a spectrum of the work that we've undertaken in this consortium, and just a couple of points that I want to make, based on what we heard earlier today.

This is a little bit about, as Dr. Krams introduced in the morning, the importance of organizing the chaos. We have a lot of very important goals. We have a lot of wonderful groups and scientists and researchers spanning academicians and industry, world health groups that have great ideas and great innovations ongoing within their silos, but the idea is, how do we coordinate all of that information and all point in the same direction, so that at the end of the day, we get not only this new regimen that we've advanced very quickly, but we know that it's safe and effective and we can get it to patients as quickly as possible.

In our field, we have to be working and thinking about things like clinical trial infrastructure to evaluate these new drug combinations. We have to think about advancing and streamlining global regulatory pathways, such that when this new regimen is developed, it's being distributed to patients quickly in the parts of the world where it's most needed. We have to think an awful lot about access and appropriate use, because we're talking about introducing new medicines into the developing part of the world. So we have to deal with all of these huge policy and regulatory type issues, but we don't want that to slow our progress on the science side, so we're addressing all of these things in parallel.

Under another part of the consortium, we're dealing with pre-competitive data sharing, really around advancing the science. We have a data standards and integration team – and I'll talk to you about why that data standard is so important when we're talking about data-sharing. We have a clinical endpoint group that's really focused on innovating in the biomarker space, so that we get very early readouts of efficacy during clinical trials, much more quickly than the current microbiological standard.

We have preclinical clinical sciences teams who are thinking about outcome measures in clinical trials, that are thinking about how do

we assess drug safety for these very complex drug regimens very early, so that we weed out the loser quickly and move the winners forward as quickly as possible as well – and I'll give some examples of some of these advancements in just a moment.

I do want to very briefly mention – I talked about the precompetitive legal framework. We actually have another group within this consortium that has developed a competitive data-sharing legal framework, that actually allows companies who have joined this agreement to share competitive clinical trial data if they wish, to help each other understand what's going on during their trials and maybe how they might want to work together in the future.

This legal agreement has dealt with serious issues like antitrust. I'm not going to spend a lot of time on that today, because this is not the part of the consortium that I lead, but I do want to let you know it is possible. We say that lawyers and legal works get in the way. It can be done, so if you'd like more information about that, we can talk about that offline.

I'm going to talk mostly today about what we're doing in the regulatory sciences arm of this particular consortium, and our goals are really to accelerate this drug development and approval process in the following ways. How do we identify tools and methods to accelerate the process? How do we pick the winners early, fail inexpensively and cheaply, as was mentioned in the previous talk?

How do we build scientific consensus in a very complex field, break down the silos, talk about what we've learned within our own company or organization? How do we share information and data? And then, how do we proceed to regulatory qualification for those tools when it is appropriate?

There have been two guidances put forth by FDA that have really enabled the work that we do in CPTR, and I'm just going to briefly tell you about each of them. I know Dr. Temple will probably speak to the combination drug development guidance in his talk, which is shortly following.

The first, as I mentioned, is the guidance for drug combination. This is really intended to assist sponsors in developing two or more novel drugs to be used to treat very serious, life-threatening diseases, which is absolutely the case in tuberculosis. And again, we're talking about not combining one new drug with old, well-studied drugs. We want to bring forth three, and if possible, four,

novel, chemical agents with novel mechanisms of action within an early clinical trial, so this has been very enabling.

FDA believes that co-development should be reserved for, as I mentioned, serious diseases where you have compelling biological rationale for that combination, where you have preclinical data and/or biomarkers that tell you that there is going to be some additive activity and durable response to use of that particular combination, and that there's a compelling reason why you can't be developing these compounds individually, and why there's a real benefit to patients.

The second guidance document that we leverage at the Critical Path Institute, and certainly within CPTR, is the qualification process for drug development tools. That's a pretty nebulous term, so what does FDA mean by drug development tools? It can include things like biomarkers and also patient-reported outcomes, but certainly it isn't limited to those two things.

Really, what does qualification mean? It's a conclusion that within a stated context of use for a specific biomarker or tool, that the results of assessments with that particular tool can be relied upon to have a specific interpretation and application in the drug development decision-making process, and within regulatory decision-making.

So if FDA has qualified a tool or a biomarker for use, the advantage to industry is they know that they can rely on using those tools to make good decisions on the data that comes out of them, and it will speed, in theory, the review process of that particular therapy moving forward, which is very important when we use a term like "accelerate" all the time. We're really trying to accelerate this process of combination drug development.

I'll talk to you about a couple of the milestones that we've reached within our consortium, that I think are relevant to the group here today. The first was the launch of an approved data standard, which for us is incredibly important. What is a data standard? A clinical data standard that's been approved by seedict is used and preferred by FDA review divisions. What it allows you to do is when you collect clinical data using these standards, and using these standardized terms, it allows organizations, should they choose, to share those data, and it allows you to aggregate those data and query the data very efficiently.

We're talking about qualifying biomarkers. We're talking about making decisions on drug development tools. You need to leverage really large data sets across multiple clinical trials in order to really learn about these diseases and make good decisions, so the data standard is a really key element to that. When you implement the use of a data standard in the beginning of a clinical trial, you can significantly lower your cost of acquiring data and analyzing them. So when we're talking about a low return on investment area, like tuberculosis, implementing these kinds of innovative tools are incredibly important.

Once we have those data that are brought together through the data standards, and we've agreed to share them in this pre-competitive forum, how do we use the data? Why do we care about querying them? One really good example of tools that we're working very conscientiously to build within CPTR are modeling and simulation tools.

I am a firm believer in modeling and simulation in implementing these tools, spanning the preclinical to clinical space. Even for single agents, you learn to fail early and it helps you make very good decisions. But when you are talking about piling in multiple novel drugs, modeling and simulation, to me, is absolutely critical, so you need to compile as much data as possible in order to build truly validated and informed models.

We are taking this translational pharmacology approach within CPTR. We are building modeling and simulation tools that help us take even in vitro preclinical PK/PD data, where we're evaluating single agent and agents in combinations, to understand how they work together in terms of efficacy. We're taking those data, building PBPK-based models so that we can understand how drugs distribute into the very infected and inflamed lung in TB patients. It's great if combinations work well in a Petri dish.

We've got to know that they're going to get to where they need to get to in the patient. We're also using these clinical trial data to build disease progression models for TB, so that we can effectively simulate clinical trial designs for combination therapies, and we think this, again, is really critical when we're talking about accelerating the drug development process.

I am just going to briefly touch on this slide. Again, the goal is accelerating the drug development and the drug review process. The drug development tool qualification process is what I've outlined here, and I think one of the things that we need to consider

is a group is are these modeling and simulation tools, is it sufficient to simply have these validated tools that we've built off of shared data, so that we know that they are broadly useful and broadly applicable, or should we consider that these, just like other biomarker tools, be put through this qualification process. This is something that regulatory agencies, as well as groups like C-PATH are thinking about for multiple disease areas.

I will end my talk on the opportunity and challenges slide. I think the challenge is, at least for TB, we don't have the option. We have to go to multi-target, multi-novel therapy combination approaches, because of the complexity of the disease and the issue with drug resistance. I think many therapeutic areas are realizing that combination approaches are absolutely mandatory, but we face a lot of challenges when you try and tackle combination therapies.

You have to select the right combination preclinically, and that's where choosing the winners and failing early is very, very important, so we are investing a lot of resource and energy in validating those preclinical tools, both for efficacy and safety, to help us make good decisions. That's where we've chosen to invest a lot of our resource.

Once you've chosen the winners, you don't want to fail because you chose the wrong dose in your clinical trial for people, and this is where developing appropriate modeling and simulation tools that really take into consideration PK/PD parameters is very important, so again, we've invested a lot of energy and time in this area.

We have to share data in order to accomplish points A and B, so we have built our framework around the importance of sharing those data. And then, for us, we need to make sure that we have the appropriate clinical trial design and the infrastructure in the developing world to help study those combination therapies.

Lastly, you can advance the drug development process but you also have to advance the regulatory approval process as well, so we have to focus on potential regulatory review pathways, like adaptive trial design, perhaps, or accelerated licensing, to facilitate a more expeditious review and approval of combination trial efforts, building on the current guidance that I described today.

I really want to leave you with a thought that it's a daunting task, which you've talked about this morning, in Alzheimer's disease. We were certainly in no more privileged a position with tuberculosis, and if we can do this, in the poorest of the poor parts

of the world, I believe that we can do it here for other disease therapies. So if there are any questions about this consortium or our legal agreements, I'm happy to talk to people offline.

Dan Perry: Thank you very, very much, Debra. We gave you a tough slot on the program, but you more than fulfilled it, especially with that hopeful comment at the end, that if we can do it in TB, we ought to be able to do it in Alzheimer's disease. We've long known that the National Institutes of Health is a world treasure, a palace of basic science. The rap on NIH, from some quarters, has been that there's not enough of a focus on how we take basic research and translate that into real advances in human health.

It was part of the vision of Dr. Frances Collins, the current director of the NIH, that he wanted to create a center, the National Center for Advancing Translational Science, better known as NCATS. There has been some controversy surrounding this, but we thought it was very appropriate for today's meeting to try to bring that link between basic science and translational science, so we've asked Dr. John McKew, who is the Chief of the Therapeutic Branch of the new NCATS part of NIH. Dr. McKew.

John McKew: Thank you for that kind introduction. What I thought I would do today is talk a little bit about some of the programs that we have at NCATS, give you an introduction to the institute, and then talk about how we're moving away, perhaps, from traditional R01-type funding mechanisms to collaborative processes, both in grant funding as well as in research collaborations.

NCATS came into being on December 23rd of 2011, when President Obama signed the budget bill. We quickly put together what we thought would be a fairly high-reaching mission. It's not very often that you hear government agencies talking about disruptive innovation as part of their mission, but it really is what we feel is needed to make a big impact across this translational science space.

We're basically empowered to catalyze the generation of innovative methods, techniques, and technologies that are going to enhance both diagnostics and therapeutics development across a wide range of human diseases and conditions. There are specific programs within NCATS that are focused on rare diseases or more common diseases, but taken as a whole, this really is our mission.

A quick snapshot about our organization. We were brought together through taking programs from existing institutes and

merging them together under this new focus. The scientific-based groups really fall into three places. The Office of Rare Disease Research, which has been ably run by Steve Groft for a number of years; it used be housed in the office of the director of the NIH. It's been moved into this organization.

The Division of Clinical Innovation is primarily comprised of the CTSA program that was in the old NCRR organization. That's part of our NCATS now. And then the Division of Preclinical Innovation, which is where I work, was a group of programs that was primarily in the National Human Genome Research Institute, and a few other programs that have been brought together to form a collaborative intramural research organization.

Just to highlight some of the programs that we're starting and continuing with in NCATS, I'm going to give you a couple of examples. I'm going to give you some novel ways to give out money and stimulate research in translational science, particularly in therapeutics development, and then I'm going to talk later about collaborative processes that we have within the Division of Preclinical Innovation.

Two grant initiatives that kicked off in the last year, one focused on drug rescue and repurposing, and the other is on building tissue chips for drug screening, both for efficacy and well as for toxicology. The problems these programs are trying to solve are how long it takes to get a lead molecule into the clinic and find out that it doesn't work, and I think the thought was, can we come up with some kind of crowd-sourcing approach that's partially funded by the NIH, to stimulate new uses for some of these molecules that companies have brought to a fairly advanced point in clinical development.

And then the tissue chip is really to collaboratively put together screening tools that could eventually replace in vivo toxicology or efficacy methods, and overall it's going to help us develop tools to enable and speed the development of drugs.

The drug rescue and repurposing project is really a pilot project, so this is the first time it's come together. We were able to get eight pharmaceutical companies to contribute molecules, a total of 58 molecules all together. Some of the key things that we did, I think, will echo some of the things you heard earlier this morning. It was very challenging to get the first person to sign on, the first company to sign on, but once you've had that, it kind of dominoed, and when we finally closed things, we had more people waiting at

the door to add molecules to this, so I think the first company is always challenging.

One of the key things that this collaboration put together were template model agreements that all of the academics and companies had to use, and again, once you got one of the big companies to agree to that, it became the model agreement for all that joined after that.

Essentially, these are 58 compounds across a broad range of targets that had reached a point in their clinical development where the company chose not to pursue it anymore, and it wasn't because of toxicology. It was primarily because of lack of efficacy against the indication that they were originally pursued. Really, the goal here is to go out in a kind of grant approach, crowd-source ideas for how to repurposes these molecules. Extramural researchers, primarily in academic, and some intramural to the NIH, write applications in a short format, kind of a letter of intent format. If they pass that initial cut, then they are brought together to collaborate with the owner of the compound, the pharmaceutical industry.

Then they sign this model agreement that's put together, and then they're able to write a full application, and then if their applications get funded, the reviews happen within the NIH, and then they get the money to really do the preclinical experiments and the in vivo pharmacology to support a new use for this drug. The companies provide their IND packages, their toxicology, all the data they had previously generated, to enable a trial on a new indication.

Where we are in this process right now is the pre-applications have gone in, they've been approved. All these partners, both the companies and the academics, have signed agreements, and the final full applications for that third or so who got approved from the letter of intent are due this month. What we would hope is, by the second quarter of next year, these projects will be kicking off and we'll start to see what some of the results are. It will be interesting to see all the different ways that these molecules have been thought about to be reused.

Again, this is the pilot project. There is only funding for this initial round. I think we can very quickly see how useful this is going to be. I think one of the key things is this template agreements, the model agreements that could be very useful for many other things. They're all on our website if you'd like to take a look at them.

And then, really, the key is, scientifically, do you advance the understanding of what the mechanism of action of these drugs are, and then, finally, you'd like to get some new therapeutics out of this.

The tissue chip is an example of another collaboration to address a very important part of the drug development pathway, which is toxicology. First, it tends to be one of the most expensive late-stage things you have to do before you get into the clinic, and it can take some time to design the correct toxicology experiment, and there's not always great correlation between the toxicology you see in a rodent and a non-rodent species, and what you see in humans.

This was a collaborative grant process between DARPA, the Defense Advance Research Projects Agency, and the NIH, where they each put upwards of $70 million into a pool and challenged people to come up with tissue chips to mimic, first, individual organs, and then an entire body. This will be a multi-stage process. NCATS and DARPA are independently managing these two groups of grantees, but they're highly coordinated, and the goal is to bring them all together.

The timing here was, this program was started out of Building 1 before NCATS was even put together, about a month before the funding announcements were issued, but we're at the point now where 17 awards have gone out, and then there were 2 additional awards, so we exceeded all the money that we had, and other institutes at the NIH put in additional money to enable 2 more awards to be made.

Again, this is a project that we'll be watching over time, over a five-year window, to see if we can actually come together with some tools that will be very helpful. Now, this is very forward-thinking. This will be years before it impacts day-to-day drug discovery, but I think some of the incremental advances that you make in the tissue chip or the engineering to enable this can be used fairly quickly, for efficacy or helping to predict toxicology.

The characteristics of these new grant initiatives really are to address significant bottlenecks in the transitional science area, and I think you'll see that they're highly collaborative across the NIH and outside extramural researchers, and they tend to look at things like crowd-sourcing or collaborative sharing of data. What we hope to do is come up with additional programs that are quick to respond to needs of biomedical researchers.

I'd like to shift gears and talk about a whole other set of programs that we have within the Division of Preclinical Innovation. All of these programs are not grant programs. These are collaborative programs where people from the outside work with intramural scientists at the NIH. We have a number of programs that address every aspect of the drug development pipeline. The only one that extramural investigators cannot access is our RNAi screening facility. That's only available right now, due to funding constraints, to intramural investigators.

But we have an entire program, one of them electro-library screening centers, that does high throughput screening, assay development, miniaturization, and hit-to-lead chemistry. That's open to all researchers who want to apply. We have developed a number of preclinical development programs. One that I run is called the Therapeutics for Rare and Neglected Diseases Program.

Another one that I run is called the Bridges Program. It used to be the former NIH RAID Program. These are programs that take molecules early in lead optimization all the way through to early clinical development. The Bridge Program is a little bit more focused on generating a data package for a clinical candidate to enable an IND filing.

We have a full-blown systems toxicology program that we run with the EPA, the FDA, and the National Toxicology Program, trying to develop in vitro fingerprints that could be predictive of in vivo toxicology. And across the bottom is an underlying theme, of trying to develop new technologies or paradigms to speed this process, lower the attrition, help us be more predictive about the molecules that we're working on.

I thought I would give you one example, in the repurposing space, of how the intramural research group is building somewhat unique consortiums to develop therapeutics. This is a repurposing case study that we did, where we were focused on patients with CLL. We started with a collaborator at the National Heart, Lung, and Blood Institute, who brought to us patient-derived cells from six CLL patients, and we have five normal donors that we used as controls.

The focus here is to quickly come up with an approved drug that might have a use in a different indication. So we've put together, over time, a screening set of about 4,000 approved drugs from the U.S., the EMEA, Japan, and Canada, and we use that routinely to

test primarily rare disease assays. What we like to do is do this in a format just like this, where we've taken primary cells or patient-derived cells, or iPS cells, and use the phenotypic assay to see, are there drugs out there that could have another use.

Really, what we did here, for oncology, these are usually very easy assays to run, because you're looking at a cell viability assay. You're looking at a cell death assay, so you can do very high throughput measurements like an ATP measurement, to determine cell viability. What you're really like out of this whole thing is you'd like differential cell killing. You'd like to kill cells that are derived from CLL patients and leave the normal cell donors alone.

Here's snapshot of the data. At this time our collection was only about 2,500 compounds. We went though 2,500 compounds in this screen, and we came up with 102 compounds that were quite active in the CLL patients – so the red is highly active. Then we went and we looked at the normal donor cells. What we really wanted to do was focus on molecules that are in this space, that are highly active against CLL patients and they are moderate to non-active against the normal donors.

We've also taken this compounds and screened them against a number of other primary patient-derived cell lines in different cancers, and I think what you'll see is this group of molecules is fairly specific to CLL. We found about 30 molecules that we chose between, and we found a molecule called auranofin, which is an old gold salt that's been used for years in RA.

Part of our decision about which molecule to look for was to really go through all this, and even though all these drugs are approved drugs, there are varying data packages for each one of these, depending on what time they went to the FDA, when they got approved, and we kind of did an assessment of efficacy, let's say, in the cell-based assay versus how much effort does it take to get this molecule into a new patient population, and the compound that we chose was auranofin.

I think one of the unique things that we put together, as well, is recognizing that as one part of the NIH, we weren't going to be able to do this alone, so we built something we termed the Learning Collaborative, which is a three-way collaboration between the group at NCATS – we were at NHGRI when this started – where what we brought to this table was our focus on rare and neglected diseases, the high throughput screening capabilities that we have within our organization, many people with years of

pharmaceutical experience, and we married that with some expertise at the KU Institute for Advancing Medical Innovation.

Lots of experience there, bench-to-bedside translation, and a real leading pharmaceutical chemistry and medicinal chemistry group. And even with those two groups, we didn't think we had enough expertise to finalize the development, so we brought in a patient advocacy and research funding group, the Leukemia and Lymphoma Society, who has, over the years, really built a robust research portfolio of funding over 400 active research projects.

But importantly, they also have a worldwide network of experts, much like the groups that you're trying to build here. With the three of those parties brought together, I think we had a very interesting way to try to advance this molecule. Each one of these parties put money into a pot, and we took that money and we moved on to develop this molecule.

Just as a quick snapshot, I think even working with a nonprofit, the federal government, and an academic institution, you can quite quickly go from what you would see in a 1536-well plate, which is how we found these things, to actually dosing this in a patient.

This is a fairly easy example. This is a molecule that's approved orally at the same dose that we were going to use it. But even with that, we very quickly overcame all the hurdles. Most of this time, to be very honest, was developing an agreement between these three parties that everybody could live with. We did that. We developed that, and within a year we had to amend it. But even still, we had a CRTA that was useful for everyone to give the rights to the right party to develop this when we were done generating data.

I want to stop there. I just wanted to highlight novel grant opportunities and novel collaborative drug development mechanisms, because I think there are, perhaps, things that could be formulated along these lines, as well, for Alzheimer's disease. I will make one quick plug. The Bridges Program has a solicitation open. We're happy to accept applications for Alzheimer's research.

If you have a molecule that you think is a clinical candidate, I'd be happy to accept applications. We would gladly fill out your portfolio of data, to enable an IND. You can go to the website right there. The solicitation will open, I think, on Saturday and it will close in February of 2013. With that, I'll take any questions if you'd like.

Dan Perry: Thank you very much, John. This is the plan going forward. We're going to have a Q&A session with Debra and Dave and John, and then we're going to have a closing speaker for this morning, Dr. Bob Temple of the FDA. Then there will be a Q&A for Dr. Temple, and then we'll get our box lunches and we'll have a working lunch, and then we've got a very interesting panel that will be chaired by Allan Fox, that will bring back a lot of the good speakers that you've heard this morning, for some real mixing it up with the audience, and a good amount of time for Q&A then. So let's begin now with any questions for our last three speakers. Any questions?

Well, I have one. John, you described that learning collaborative with an academic institution, a patient advocacy group, and a NCATS. Some of the talk this morning has been about, obviously, multi-industry and patient group and regulatory collaborations, getting people together in a locked room, and all that sort of thing. Do you see NCATS being able to play in that kind of an environment, with multiple industries as well?

John McKew: I think within the TRND Program, Therapeutics for Rare and Neglected Diseases Program, we have 14 active projects going on, and every one of those is a collaboration between NCATS and at least one outside partner. About half of those projects are with small companies, the other half are with academics, and many of them, again, have foundation or advocacy support or participation. Just looking at the amount of interaction that occurred between groups that are now in NCATS and the big pharma industry, to pull together the rescue and repurposing initiative, I think that's a big part of our mission. I think we equally talk to industry as often as we talk to patient advocacy groups and basic researchers.

Dan Perry: I know you have a background in industry. NCATS is sort of this new creature at NIH. How is that fit going? A real emphasis on translational science within a traditionally basic science megalith.

John McKew: I think it was a little bumpy getting up to the point where it started, and I think a lot of it was clarifying the mission of what we're trying to do. Francis Collins put out a really nice article last summer, saying that NCATS was going to be the hub of this translational wheel that was going to drive. We're not going to usurp any existing translational programs that are fantastic, that other institutes have.

There are many really good and fantastic programs. I think as an intramural research group at the NIH, we're very unique in that we don't start any projects ourselves. Everything starts as a collaboration, so that is kind of second nature to us. We're happy to go out and collaborate across the NIH and then with folks outside.

I think, for me, I came here after 18 years of working in industry, and I was truly taken by the mission of helping underserved patient populations, and I think it's very easy to recruit people with the type of pharmaceutical experience that I had, to come and take this mission on. So I think it's going to be a nice mix. I think it's easier to talk to people in industry if you've at least walked in their shoes for some part of your career.

Dan Perry: That's very helpful. Another question? Anyone at all? Question for Dr. Hanna about TB? A question about the California Gold Rush or the Baltimore fire, for David?

Audience: Hi. I have a question for Debra. The beauty, I think, of the CPTR is, in part, your productive partnership with the Bill & Melinda Gates Foundation, and I think that where we find ourselves right now, with consortia like CAMD, there really is no one large donor to support, ongoing, a lot of the efforts that need to be undertaken in the Alzheimer's space.

What can we, as Alzheimer's advocates, do to really urge large foundations to make contributions, so it's not weighing so heavily on the individual companies to fund projects through Critical Path?

Debra Hanna: That's a great question, and I will start by saying we absolutely acknowledge that we are fortunate with the funding that we have, because it wasn't going to come through industry fees for our consortium, because companies weren't investing to begin with. They couldn't afford the drug development programs for these low return on investment therapies for these neglected diseases, so we absolutely needed that.

What I would offer is that where some of these consortia are really starting to make progress, where we really are advancing the field in areas like CPTR, for you to leverage those examples of how this works, in terms of moving forward real products, whether we're talking about data standards or the development of models that are implemented and used, or whether we're talking "I hope, in the next five years" around a new drug combination, and we've advanced it through a group like CPTR. There is no reason you

don't use our example, and I think that once we have some of those wins, people will understand why the investment is important.

John McKew: If I can add something to that, I think what's different is, for the pharmaceutical industry, there's real money to be made in Alzheimer's disease, so a lot of it is de-risking individual approaches to the point where they feel like they can jump in. For the TRND Program, that is the model. We're not going to get anything through to registration.

We're going to de-risk a molecule to the point where somebody else wants to invest in it, and what we've seen is three of the companies that we've worked with, who had no access to private equity because the equity market has pretty much vanished over the last five years, have, after collaborating with us, been able to receive some pretty significant funding, either from venture philanthropy or just straight-up equity markets.

I think it was a lot easier for them to sell their programs after they had some validation that their molecule might work, and it might be de-risked enough for someone to invest in it – and those are all for much smaller patient population therapies than what you're talking about.

David Dilts: I'm going to do a different perspective, because that's what I'm here for.

David Dilts: I look at a cancer research, and a cancer research goes to one company and says, "I need $10 million," and the company says no. Then they go to the next company and say, "I need $10 million," and everybody keeps telling them no. There's a theory, by Jim Collins, in *Good to Great* that's called the Flywheel Effect, which is, if you ask somebody for all the money to do the whole thing, that's really hard. So what you do is you ask for smaller amounts. The first one is always hard. The second one is easier, and then using what's now called crowd-sourcing, nobody wants to be left out. Then it just becomes a virtuous cycle. It gets better and better and better.

And again, that is well-done in engineering because nobody can afford the kinds of stuff, like, to build a space shuttle anymore. So if you ask one company for all of this, the answer is usually going to be no. I'm going to use your data standards. If you take this piece, and that's a deliverable, that's really important. And I'm also a deliverables-driven person. Show me the standard you

developed. Show me an output. Because otherwise, it's just kind of charitable giving.

Audience: I think another challenging case for being in the advocacy community is data standards aren't really sexy, and it's not something that I think groups like ours have been fast to come around and taking up our message of why they're important. I think for a long time it was not as understandable as the traditional way of understanding drug development, so I think the more that we can learn, as advocates, on how to articulate the need for data standards, I think that will make our job a lot easier.

Debra: It's absolutely not sexy, but I think when you understand the power of what you use them for, it's really hard to disagree that they're necessary, so we can certainly help you build that case.

David Dilts: And today, every business is on data analytics. I enter the baseline data to get the information. Think of how much information there is about Alzheimer's that's just sitting in somebody's file cabinet, that nobody else can get access to. But if you're able to mind that data, imagine how much progress you could make – and it's not getting new data. All the research I do in cancer, I do not collect primary data. All I do is take data that already exists, then massage it and hand it back to them. So think of how you could jump-start the knowledge that already exists, if you had some way to share it.

Dan Perry: Thank you. Another question or two? Neil?

Audience: There are initiatives like that going on. The Alzheimer's Neuroimaging Initiative, for example, has gotten, in the first five years, $20 million to $25 million from industry, and ____ too, also, with that same idea. The idea is that everybody is not putting in $20 million, but each of the companies is putting in a smaller amount but everybody gets access to the data. That's one model.

And also, the Alzheimer's Association has an initiative called GAIIN, in which they are starting to work on getting data from new investigators to put into one source of information, so everybody can have access to the data that have already been collected. So there are some ongoing initiatives like that already. Obviously, we need more of them.

One difference I should point out, though, I think, with Dr. McKew and the intramural program, is these are done through a different mechanism. These are done through CRTAs where the

intramural program is working with external sources. We're talking more about extramural investigators working with companies. I think both are very critical and necessary, but that's a different model from the one we're working with, in terms of extramural sources of funding.

Dan Perry: Good distinction. Anyone else have a comment? Diane.

Audience: Just on the same theme. I work with Debra, and the Coalition Against Major Diseases has a lot of the similar missions as CPTR. For Alzheimer's disease, we have the therapeutic area-specific standard for Alzheimer's disease that we just received funding from the FDA to create a version 1.1 that focused on pre-dementia, and we also created this first unified clinical trial database from 22 clinical trials with placebo arms.

I would say the biggest challenge is we were fortunate enough to have pooled this data to this unified clinical standard, but what we see is that as we go forward to try to expand the pre-competitive space, including biomarkers, there is a concern of risk, and that has been harder and harder to get the companies to contribute biomarker data, and as Reisa pointed out this morning, the tremendous learnings of biomarker performance in ADNI may not be the same as we're finding from clinical trials.

So I think as we go forward, there are ongoing initiatives that we all work together on. It's many of the same members and organizations that collaborate on these initiatives, but we need to make the value proposition to try to expand the pre-competitive space so that people understand when they're being asked to share data, what will emerge from that and what won't happen if we don't share the data.

Dan Perry: Diane is going to be on the panel following the luncheon, in which we're going to hear some new voices as well as some of the people that have already spoken precisely on this question of what are the barriers to sharing pre-competitive data, to collaboration between industries, letting down some of the guards. Are they real, the barriers, or not? So that's going to be taken up again. Yes.

Martha Brunfield: Thank you. I'm Martha Brunfield from Critical Path Institute. I just wanted to add a comment and perhaps a thought about this element of de-risking. When it comes to sharing data and having data compiled in a large database, where other researchers may have access to, I think one of the concerns the industry has – and having spent my career in industry, in regulatory, I fully

understand this, and it gets to the data-mining phrase that was just referenced.

Industry considers that their liability never ends, so if a patient has been exposed to something, and even five or ten years later you find out that the biomarker was used inappropriately or led to some conclusion that would've impacted treatment, had we know that at the time, it just puts industry in a very defensive position. So if there could be some discussion around a safe harbor environment, so that there would not be so much liability for the owners of data, that would seem to be held to going forward, I think we could make a lot of progress.

And I don't have the answer for how that could happen, but I do think it's something that it doesn't get discussed a lot, because it's not a pleasant topic, but it is a reality of what a regulated industry, particularly one that's prone to the U.S. litigation system, something that has to be dealt with.

Dan Perry: That's a great observation, and we may hear more about that later today, too. Any final comments from the panel? If not, let's show our appreciation to this morning's speakers. Thank you. Our final speaker for the morning session, before we indulge in sumptuous box lunches – Dr. Bob Temple really doesn't need an introduction. For many, many years, he has been considered the dean of drug development and drug review at the FDA. He's had many positions, and some changes within Cedar just this year, and I'm not going to attempt to get his title exactly right, because I probably won't.

It's been sort of a Washington game, and within the entire drug development world for a long time, to try to guess where Bob Temple is going to come down on something, so we are very pleased that we could work with his challenging schedule to bring him here this morning. He'll speak, and then we'll have questions directly for Dr. Temple. He will not be here for the afternoon session, as I understand it, so this will be your one shot. Thank you for being here.

Bob Temple: Okay. Thank you. I'm going to talk particularly about a new guidance we put out on combination development, that was designed to make it at least potentially easier to develop a combination of two drugs that hadn't been previously approved. As I was looking at this, I realized maybe not everybody knows what our overall combination rule is.

Just briefly, we have a very short regulation that's been in place since the '70s, that basically says if you put two drugs together in a fixed combination, you have to show that each one of them makes a contribution to the claimed effect. That's basically the effectiveness requirement as applied to a combination. In the '60s, when we looked at all the combinations that existed, we found that a large number of them didn't not work. They did work but they had extra stuff that didn't contribute.

The ordinary way that people show that is they do what's called a factorial study. They compare the combination with each of the components, maybe a placebo, maybe not, and they show that the combination is better than either of the components. We have dozens, probably hundreds, of antihypertensive combinations that have been developed that way, lots of antibiotic combinations, and once you leave those, not so many in too many other places.

But we began to hear from people, especially in the oncology and anti-infective field, with more and more information about pathways and things. They were often coming up with several drugs that really seemed to hit a different part of the process, and probably made sense to put together, and they were disturbed, or wondered whether the usual amount of information you'd have about a new combination was still needed. So we wrote this to try to say, well, not necessarily.

But it's worth remembering that in those two areas, you have very good biomarkers. If you have an anti-infective drugs, and you see that you killed the bug in the test tube, that gives you a big head start on whether it's going to work, and if two drugs together kill it better, you have a very good idea of what's going to be happening. Maybe you don't need so much clinical data.

Similarly, in cancer, if you shrink the tumor, that's a good start towards showing that you're going to be able to do something useful to survival and things like that. In other areas, I'm not as sure we have other kinds of information that are going to be that persuasive, and the people in this room probably know more about that than I do.

I'm going to tell you a little bit about what's in this new guidance. I think it's still a draft guidance. It doesn't change the basic principles. There are potential exceptions to this, too, but you have to have reasons to believe that each component is making some contribution. Otherwise, you're just getting the risk of side effects for no benefit.

But as I said, we were asked by people developing, particularly tuberculosis combinations, where you always give multiple drugs together to prevent the emergence of resistant organisms, and combination oncologic drugs, which is sort of the standard of care – most tumors are treated with multiple drugs – where neither drug was already marketed, what would be needed to support the combination?

Unlike a combination of two drugs that have bee marketed for a long time, you don't have a whole lot of information on the single drugs. You don't know what their safety is. You may or may not know much about what their dose response is, all of which is potentially problematic when you're trying to make a combination. On the other hand, if the drugs have added effects in a bad disease, there is a certain urgency to making the development of a combination as efficient as possible, because it's of potentially enormous value.

We have a certain sense, still to be proved in a variety of settings, that our increased understanding of pathophysiology may stimulate approaches that use combinations that are directed at multiple targets – several places along a pathway, or something that wipes out the emerging resistant cells or resistant organisms – and that there ought to be an efficient way to gain that advantage. So a lot depends on having reasonably well understood mechanisms, whether in most neurological diseases, or Alzheimer's that's true, remains to be seen, I think.

In December of 2010, we proposed a draft guidance called "Co-development of Two or More Unmarketed Investigational Drugs For Use in Combinations." It's very explicitly described as a high-level documents. That means there's not a lot of detail in it, not a lot of examples, and we're going to work it out. It's very clearly sort of an invitation to come and talk and think about this without a lot of information, especially beyond the anti-infective and cancer areas of exactly how to do this.

It does two things. It talks about trying to decide whether co-development makes sense, co-development with at least somewhat less data than usual, and then how to go about attaining the necessary data, and it gives some illustrations of how to go about doing that. Because there will, inevitably, be less information about each individual drug and its safety and effectiveness – and you don't like to discover bad news five years later – the idea is

that this should be reserved for cases where it's important and plausible, and there are five criteria that are suggested.

One is that it's for a bad disease. The second is that there's a compelling biologic rationale for the combination. For example, the agents inhibit distinct targets in the same molecular pathway, so there's good reason to believe they'll have an additive effect or super-additive effective. Or one target is a primary and the other target is the compensation, so that you don't develop a resistant organism and having wiped out the usual organism.

Maybe there are only four. Three, a preclinical model should exist, or maybe short-term clinical data, on some established marker that makes you believe that the combination has substantial activity and provides greater than additive activity or more durable response. It's interesting. I hadn't noticed this before. This almost calls for synergy. It's not very common to find, in combinations, true synergy.

Additivity is pretty nice, too, and we don't really insist on synergy. That's what you dream about but you don't have to have that to have a useful combination. Antihypertensive drugs pretty much have additive effects. Some cancer treatments, though, really do have synergy, improved survival well beyond what each drug does alone. Anyway, we would generally say if the total effect is greater than either drug alone, that's probably pretty good, too.

Four, there should be some reason why the drugs can't be developed individually as monotherapy, for example, because monotherapy leads to non insistence but resistance, or has little useful activity, some reason to think that the usual method won't make sense. The guidance then talks about what to do with the animals, what to do in early human studies, and what to do in later studies. It's very focused on oncologic and anti-infective products, because that's where we're asked about it and those are both crushing needs, but there are other needs, too.

What it says is that the biology of these diseases, together with animal findings, can provide a pretty persuasive, plausible biologic rationale for use of the combination. You know, animal data don't always tell you what's going to happen, but they often do, and when what you're dealing with is bacteria or viruses or things like that, the preclinical data may be highly relevant, because you're really not treating the person; you're treating the organism anyway.

How, exactly, this would pertain to a drug intended to modify Alzheimer's disease is certainly not known yet, but there may be people in the room who already have a good idea of how some of these rationales might work. In any case, the expectation is that the non-clinical analysis would be based on the best available and most credible animal models, and you hope a finding of some kind of additive or synergistic effect in that model, and there are animal models of Alzheimer's disease, so that's certainly possible. Whether they're going to be predictive of human results remains to be seen, I guess.

Depending on the persuasiveness of the model, evidence of such an interaction could support the kinds of abbreviated pathways that we're talking about, noting, of course – and this is very important – there will always be clinical data on the effectiveness and safety of the combination. So you may give up a little bit on what the contribution of each component is, but it's definitely going to be a drug that does something good. And the nonclinical toxicology would be sort of as usual, looking at each drug separately.

The early studies, the Phase 1 studies, characterize toxicity, pharmacokinetics of the components, would probably be more or less the way you do it. Usually you'd look at the separate drugs, and you'd certainly want to know whether they interact with each other, and you'd want the usual kinds of information about their kinetics and what affects their excretion, what affects their metabolism, all that kind of stuff. You'd be interested in pharmacogenomic effects, if there are any. Many of those actually could be done using the combination. You can do simultaneous PK using a combination, so that simplifies it a little bit.

There is a thought that you'd want dose response on a relevant pharmacodynamic or short-term clinical endpoint from these early studies. Now, that's easier in antibiotics and cancer than in most neurological diseases, where the endpoints that we most believe in are probably clinical outcome endpoints, and it's not too easy to do that in tiny trials. But maybe there's a good marker that people believe in, and that could be used there. So, again, this is all high-level and we'll see, but those are the possibilities.

The Phase 2 studies that are in this document are called proof of concept studies, and that's certainly something you hope for. What these are are the earliest, well-controlled studies, and it's hoped that these will show the contribution of each component to the extent possible – there's a certain give there – and to the extent

needed, you may already be totally convinced from preclinical and pharmacologic data.

I'm not sure how often that's going to happen, but the documents suggest the possibility, and you'd use these studies to optimize the dose or doses for the Phase 3 trials. Again, that's not easy if it's not a clinical endpoint. If it's some biomarker and you don't really know the relationship between the biomarker and the clinical outcome, this is hard. We would almost always say you should study more than one dose in Phase 3. We always say that; people don't always do it.

Anyway, what needs to be done and what can be done will vary by specific circumstances, and we've put in three scenarios – not my favorite word, but that's what these are. One is there are some cases where the components can't be given individually. This comes up in TB. You can't give something that has a modest effect and study that in a population, because they'll die of their tuberculosis, so you can't do that. A factorial study there, you just can't do, so in that case the concept would be based on a comparison of the combination with standard of care, or a study adding the combination to standard of care, and that's just the best you can do.

My bias would be that in Alzheimer's disease, it would almost always be possible to do the factorial study with an appropriate endpoint. We don't know enough yet to say that a given trial would be unethical. It could turn out that that would be, if some drug looked pretty good.

The second proof of concept is the typical factorial study, AB versus A versus B. Usually, with a placebo, and if there's standard therapy, you add these all to standard of care. If not, you just compare it with placebo. There is no reason why an adapted design couldn't be incorporated into this, so if one component was just doing nothing on the endpoint, you'd drop it. That's okay, too. The endpoints conceivably could be a pharmacodynamic endpoint, if it was convincing and plausible, or it could be an early clinical endpoint.

How reasonable any of these things are in Alzheimer's disease remains to be seen. The short answer is if the effect is very dramatic, all this works fine. If the effect is very modest, it's going to be very hard. Anyway, the thought here is that whatever the evidence of the contribution of each component is should be quite convincing, and if it is, then maybe the Phase 3 study could study

only the combination, and that's the simplification. That's a very big deal.

A study designed to show that a combination is better than placebo is a very small fraction of the size of a study design to show that AB is better than A and AB is better than B. Especially if the difference between one of those is very modest, those can be very difficult, very large studies. In the models where they've been successful, hypertension, it's very easy to study blood pressure. You can measure it very precisely. There's really nothing to do it.

Similarly, you can tell whether you've killed a bacterium and you don't need a vast study to do that. In cancer it can be harder, but in many other areas, it's not easy to pick up a small effect. So if there were some pharmacodynamic endpoint that was very persuasive, and everybody bought it, and you could study just the combination against the placebo, that would be a huge advantage in getting to the endpoint.

And then, of course, there's the special case where one drug hardly has any activity at all. Then you don't need to study that alone. Nobody ever studied carbidopa alone, as a treatment – you didn't need to – or beta lactamase inhibitors. They don't treat the bug so you don't study them alone. If that were the case, for example, where one drug is there to keep a drug from being broken down or to help its absorption, those are easier.

The guidance strongly encourages testing of multiple doses of both components. That's easy to say if there's a good biomarker or an early response, but if you're looking at clinical outcome data, studying a large number of doses of each one becomes daunting, and the fact is we've accepted lots of drugs where the dose response was not terribly well known. If it did something good, you can't really avoid that.

Now, the confirmatory study – this is important – it not really at odd with our current combination rule. Our combination rule says you have to show contribution of each component. It doesn't exactly say how you have to do that. It doesn't say you have to do a factorial study all the time. You may know from other data that one component just doesn't do anything alone and you don't study it. So this is not completely different but it's emphasized.

In the in vivo, in vitro, and/or Phase 2 studies adequately demonstrate the contribution of each component to the combination, the Phase 3 trial can compare the combination to a

placebo or standard of care. This is clearly what the great hope here is, because for reasons that I just gave, that it is a much, much simpler and smaller trial to do. And if the effect size is larger for the combination than either of the components, which it better be if the combination makes sense, you have a much smaller study and enormously increased power.

If the contribution of each has not been shown reasonably well, then you probably need the usual factorial study or at least a three-armed study to show a role for the less clearly effective component, and again, it emphasizes that it's a good idea to study more than one dose.

So you could ask, what's new here? How different is it? I think it's not that different but it shows what flexibility there is in how the combination rule is interpreted. You still don't want to give a drug to people that contributes no useful effect, so you do want evidence of a contribution, but evidence of a contribution can be based on data short of the usual factorial study, AB versus A versus placebo, and we're going to be very eager to look into that. We intend to make all our results known, and there's no question this is going to be a learning experience.

There is one final thought. We're in the process of rewriting our combination rule. It's somewhere in the murky places that rules on their way go. But we've always known. I'm sure nobody in the room remembers Marion Finkel, but she was sort of what John Jenkins is now, a long time ago. She wrote a memo saying if a combination does something fantastic, improves survival, what are you going to do – not approve it because we don't know which drug contributed? You'd have to put people in a trial to see whether the removal of one component kills them.

I don't want to be in that trial, and it's not going to happen, and we wouldn't. We've contemplated this for 30 years, to my knowledge, and more. If a combination does something wonderful, it's going to be approved. You think of the early combinations for treating leukemia. Now, they weren't fixed combinations so the rule doesn't apply. But I remember, as an intern, we'd give people with acute leukemias a drug and it would go away; three months later it was back and they died. Then people developed combinations, and all of a sudden it didn't come back.

Did everybody know which drug exactly did what? No, but you didn't need to. You knew the combination made them all better.

It's pretty clear that if you get results like that, we're not going to worry that much about the contribution of each component, because how can you? You can't do the factorial study anymore, and you don't want to lose a survival advantage, so it's worth thinking about that.

But nonetheless, if people are developing something intelligently and want to learn, these are some rules that will help them do it, we hope, a little more efficiently. All through this document it says whatever you're doing, be sure and talk to the division, talk to Rusty about it, because we need to all be on the same page on these things.

Dan Perry: Thank you very much for sharing all of that. All right. Here's your opportunity. Have at it. Reisa, I was hoping so. Reisa, in one of your slides, you actually sort of gave us a hypothetical drug for Alzheimer's that would hit tau and amyloid and inflammation and other things, so go at it.

Audience: My question is not that profound. It's about the fourth of the criteria, which was about the reason why they can't be developed individually as a criteria, and whether that's an issue. You brought this up, Rob, a little bit, and again, at least one argument I tried to make was that the problem is how long the trials take, especially in earlier stages of Alzheimer's disease, as the compelling reason not to wait to do each one individually. So the question is whether the FDA would consider that a compelling enough reason for why they can't be developed individually, and particularly because the combination might work best in this very early group.

Bob Temple: I would say all those things would be on our mind. You mentioned duration. It also has to do with effect size. After all, if each of these is contributing a little, then the study has to be way bigger to show that difference. In that sort of case, I guess maybe you had two things that affected something that you thought was likely to be valuable. Well, you don't know if it's going to be valuable until you do the study.

On the other hand, you do know that each of them contributes to this marker, so if the marker then proves to be useful, when you've studied the combination, that probably could be persuasive. So I think we're very open to thinking about these things, and, of course, there is no track record because we don't have anything that works yet.

Dan Perry: I think that term "we are very open" is always a welcome to hear. There's a question over here.

Bob Temple: Yeah, because we think it's a really bad disease, especially as we get older.

Audience: A related question. One of the scientific rationale is to have some potential for more than additive effect. We can easily draw a grasp where tau effect and amyloid will be synergistic, but the requirement of more than additive effect could cause a problem, because we really don't have much evidence from preclinical models or biomarker models that you achieve that. How do you view that requirement in the scope of developing combination drugs?

Bob Temple: As I said, I don't agree with it. Additive is good enough. I am sure we'll get around to revising that. I mean, synergy is dreamed about all the time, but how many really good examples of synergy do we have? We have some. I mean, Sinemet is sort of synergistic, because one of the drugs doesn't have any effect on the disease. But for two drugs that actually have an effect, can you really show synergy?

It's very hard to show synergy. None of the antihypertensive combinations have more than the additive effect, to the best of my knowledge. So I don't think that's going to be critical. A good additive effect ought to do it, and that's always been true for the interpretation of the combination rule. You didn't have to display synergy.

Dan Perry: Another question back here.

Audience: Thank you. Thanks for clarifying the synergy, because that's been troubling us, actually. From a theoretical standpoint, if you have, say, a biomarker that you're using to kind of judge your additive or synergistic effect, but that biomarker is questionably linked to the progression of the disease – so this is easy to talk about for Alzheimer's – so you do this proof of concept trial, where you've got drug A and drug B, and you do a nice factorial design, and you show that A and B change the biomarker to a greater degree than A or B, but A and B are both changing the biomarker.

That Phase 3 that has to look at the cognition outcome is a question of, do you still keep the factorial design for A, B, and AB together, for the primary outcome? That's one question. And then the other question is how does that factorial design, if A works and B works,

but A and B don't quite work as well as AB, how does that affect the approval of B or A, particularly if there are some advantages for one or the other?

A good example, and I'm sure Reisa's been thinking about this, is you have an IV drugs that's antibodies, very expensive. It might not be desired by some people. It may even be slightly more effective, let's say, than a small molecule drug, which has some modest effect on the combination of slightly better than either of them.

So you have some various advantages of the drugs, and some might be a little bit better, and so forth. How would the FDA look at the approval in, say, Phase 3, where AB is better than A or B. Would B not get approved, or A, or vice versa?

Bob Temple: This document is about approving the combination. It doesn't specifically address the single entities, but I'll get back to that. On the first question, that's what I was trying to address. Let's say you have an effect on a biomarker that's considered plausible enough, but you don't know whether the biomarker corresponds to outcome.

The combination study answers that question. If both drugs affect the same biomarker, they do give you the answer to that question. Again, all this has to be taken up with the review division and thought about, but I think the idea here is that the study of the combination might very well be persuasive because, after all, it does validate the biomarker, and just to say what I said before, a factorial study has to be a huge multiple of the size of what a single entity would be.

Whether these studies would support the approval of the single entities is another question. We would certainly want any combination to cover the range of doses that could be used – whether there needs to be data on each dose is another question; maybe it's a tolerability question. I think before you'd market the single drug, you'd have to know that it's useful by itself. But again, this needs to be worked out in detail.

I don't know that this approach would necessarily support separate marketing of the two entities, but even that remains to be seen a little bit. And, of course, once the combination worked, it might inspire someone to actually look at a single entity, although the trial would be larger. But I don't think per se it gets you the single entities. Others might have different thoughts about that.

Audience: If the components of a combination and the combination itself are shown to be safe, does that change the efficacy requirements for the individual components, the need to show contribution?

Bob Temple: So the combination looks good.

Audience: Well, safe, and the combination works.

Bob Temple: And the combination works. We accept the idea that we will have less data on the individual components and their safety, but, of course, you do have the safety of the overall combination. Now, if something troublesome comes out in the course of the Phase 3 study, in the combination, you won't necessarily know which drug did it, and that could be a problem. If that was so bad that you're worried about it, it might defeat the ability to approve the combination, and you'd always wonder whether a lower dose of one of the components would've avoided that.

There is a certain risk to doing this, because some surprise might come up and you won't be able to explain it. Again, a major effect in Alzheimer's is going to overcome a vast amount of safety problems. So it depends on the disease you're looking at, and we're talking about bad diseases here.

Audience: Let's say you test two drugs that individually have a modest effect, let's say a monoclonal antibody against a beta and secretase inhibitor, neither of which could clearly lead to approval on its own. And then together they do better, which could lead to approval. Would the agency consider that approval, and would a second confirmatory trial be required?

Bob Temple: What you're basically saying is you'd have to do a study so enormous that it's unfeasible to show the contribution of each, because it's small. Presumably, there is a contribution, and if you made your study big enough, you could probably show it. But the point of this, I think, was to say that's not necessarily in the interest of everybody, because for these kinds of diseases, where there is no treatment, if the combination does something good, even if you have great difficulty showing each one – especially if they're synergistic, then you really don't have a shot – that's probably what we would be looking for.

I forgot the second half of your question.

Audience: *[Inaudible comment.]*

Bob Temple: The usual rules apply to whether you need a confirmatory trial. If the earlier evidence in the Phase 2 studies was very helpful, that could be the confirmatory evidence that's called for. In FDAMA, if the P value is very small, that helps usual rules on one versus two. *[Crosstalk]* to some extent what your endpoints are and what you've shown.

Dan Perry: Dr. Katz had a comment.

Audience: It's a question that I meant to ask you back at the office but I forgot.

Bob Temple: We're going to have some new drugs that are going to take care of that.

Audience: You had mentioned that the document says that the non-clinical tox requirements are more or less the same as for the individual drugs together. As I read it, in the document, there is a sentence that says if two drugs are intended to be given together, forever and always, in effect, that the tox studies can be done just with the combination. At least that's the way I read it. Do you have any view on that?

Bob Temple: I'll have to read it again. That was not my read. Of course, if you do the tox studies and nothing shows up, then neither component is doing anything bad. It does make the case that you want tox studies on both the single entities and the combination, in case they have some adverse interaction. I would have to look and see what that point says.

Audience: Again, as I read it, it sort of breaks it down into if you have two late-stage entities, they call them, or one late-stage, one entity where we have a lot of experience and maybe both where you have a lot. But ____ ____ for two early drugs, in early development, where you tend to just give the combination and not the individual components, you can do the tox with the combination.

Bob Temple: I think there are probably some cases where that would be acceptable, but you sort of what to know before you get into it what the nasty stuff is that each drug does. It's going to help you choose the dose and things like that. So at least part of it says – and maybe I didn't look at it closely enough – at least one part of it says you more or less work them up as usual.

Could you get away with doing them both together? Maybe, but it's complicated. You'd have to study multiple doses, and the dose of each one would vary. To me, as a practical matter, it seems like the usual approach is safer, but I'd have to look at it again and see what it says.

Dan Perry: Allan Fox and then Reisa.

Allan Fox: The subject of the meeting is co-development, but, as we got into it this morning and we'll get further into this afternoon, part of the reason for the meeting is to figure out what are the barriers – scientifically, legally, regulatory-wise – to actually get to goal here. We really want to accomplish dealing effectively with the disease, or series of diseases. One of the things that you missed was when we were talking about how companies can share data, work together, so it's not just one company pursuing one drug, or two companies in combination.

So as we get into this, I think your discussion now just sort of brings up – and I was talking to Rusty about this as well – how does the agency work collegially with a coalition of a Manhattan Project, to actually work together to figure this out?

Bob Temple: We're enthusiastic about all those things, but companies control their data, and historically have not been the most sharing of people. I think the mood there is changing a little bit. A number of companies have said "We're going to do it." We know the AIDS circumstance, where everybody shared like crazy. We can't reveal privileged information, but we talk to people all the time, and the fact is our experience does get shared. We don't name it or say where it comes from, but you can't help conveying what you know.

So we are advising people on study designs all the time, and the reality is it's, of course, based on our experience. Maybe I shouldn't say that. But you can't help doing it. All of what wisdom we have about how to design studies comes from people's malfeasance or success. That's how you learn. As everybody knows, we're looking at lots of cardiovascular outcome trials, where the failure to follow people up is 10 and 12 and 13 percent. Well, we're trying to figure out how to do something about that. It's everybody's problem.

Audience: Well, just to make it explicit. We talked briefly and the suggestion made this morning by Mike Krams said you ought to get a group of people, lock them in a room for a week, and just try to come to

some agreement on some of these things, or at least try to identify what the problems are. There's no reason we can't be a part of that kind of thing.

Bob Temple: And we would meet. If multiple companies want to come into the room together, that's fine, and they can bring other smart people with them, and that's fine. We'd do all that, but they're in control of those matters.

Dan Perry: Thank you for that comment. Reisa?

Audience: That's great. I think we should find a room. I have a specific question about the multiple doses, and this relates to, again, the scenario we're in right now in Alzheimer's disease. We have some things that are in early development, some things that are in late, where the dose finding has already been done. Would you think it would be a reasonable strategy, where you did multiple doses of the lesser-known compound with a fixed dose of where more information is known, say, through Phase 3, or would you really want multiple doses of each, with the idea that somehow you could get away with a lower dose in a synergistic or additive, because that would, I think, make it a little more difficult for some of these compound combinations.

Bob Temple: There's a difference between what's optimal and what's practical. After all, you may know a drug very well, but you don't know yet how it interacts with drug B. So the more of that stuff you can get in, the better. The thought is that if there is a reasonably likely biomarker – and those are much easier to look at than IQ or ADASCOG or something – that you can do a fair amount of that in Phase 2, and nothing says you can't drop a group that isn't doing very well.

We like adaptive designs in these early settings. The more of that you do, I think everybody would say the more likely it is you're going to find the best dose and win. But there are practical limitations to those things. In a big Phase 3 trial, it's not easy to have too many doses. I mean, you can see this all through. Almost every antidepressant trial has two doses these days, or three sometimes. Every antihypertensive trial has three or four doses, because you don't have to have a very big trial to show that you lower blood pressure.

If you're now looking at outcomes, well, some Alzheimer's drugs have had multiple doses, too, and you can do that. If it's a factorial trial and you're trying to show a small additive effect, it can get

very big, so I think you just have to have practical limitations. You hate to have a dose that's so large it does harm, because that screws the drug, and you hate to have a dose that's lower than it could've been to get a bigger effect.

So the more you can do in a Phase 2 is credible, fine, but even there, we've always thought it's worth spending the extra to make sure you've covered the dose range well. You know, there are some notable cardiovascular examples. Dabigatran at 150 mg had effects that 110 didn't come close to having. Well, those doses are almost the same, most people would say, but it made a huge difference in what the outcome was.

Dan Perry: Steven, again. Brown University, for the record.

Audience: This is a forward-thinking meeting, and just given what Don presented from the cancer world, it looks like multiple drugs have been tested together, more than two in cancer. The agency, I would assume, would have no objection, at some point, when we're ready to testing more than two drugs, because we could easily come up with rational targets – let's say two in A beta and one in tau, for example – for AD in an adaptive design.

Bob Temple: We just approved an AIDS combination with four drugs in it. The cancer combinations, they're not technically fixed-dose combinations, so those kinds of rules don't clearly apply. There's another reality that nobody pays attention to. Most new therapies in fields are done by showing that when you add the new therapy to the previous therapy, you get a benefit. Well, those trials don't tell you anything about whether you still needed the thing you added it to.

In heart failure, you start with a diuretic, which we're pretty sure works. Then you add an ACE inhibitor. Nobody knows whether you still need the diuretic. That's not how the trials were done. It was ACE inhibitor versus placebo, each added to the diuretic. Then you add a beta blocker. We don't know if you still need the ACE inhibitor. Nobody's ever looked. Then you add spironolactone. We don't know whether you need those other drugs – nobody's ever looked – but you had a survival effect from adding it. Who wants to look?

In oncology that's frequently what you do. You take the baseline therapy and then you add something to it and you get a survival advantage. You have no choice but to use it. We've actually had arguments with companies that were added to. This came up from

– maybe I shouldn't say. Anyway, a certain drug was added to other drugs and showed a survival advantage, and the label said you've got to add it to these other drugs.

The people who had the drugs it was to be added to wanted to put it in their labeling, and we said, "Hell, no. We don't know if you do anything." But still, you learned something important and valuable anyway.

Dan Perry: Reminiscent of what Bismarck said about making sausages and legislation. Now it's drug development. Who else? Anyone at all? Golden opportunity. Thank you, Dr. Temple, very much. We're going to give you your biggest break of the day – fifteen whole minutes. In that time, avail yourself of the lunch selections, and come back in at 12:15, and we'll begin our panel discussion on industry collaborations. Thank you.

[End of Audio]

Dan Perry: If I could have your attention again for just a minute. Hello? Everyone. Welcome back from your extravagant lunch and please feel free to continue just chew quietly. For the next hour, we're going to indulge ourselves in listening to viewpoints that will enhance our grasp of the challenges of combination therapy and also collaborative and pre-collaborative research between companies, interest groups, regulators. And the person that's going to moderate this session is Allan Fox. Allan is full disclosure, chairman of the board of directors of the Alliance of Aging Research, a long-time friend. He is the founding partner of the Fox Kiser Firm in Washington, D.C.

Those of you in the biomedical space know the Fox Kaiser Firm as a place of great ideas and generation of collaborative efforts in biomedicine, and law, and public policy. Allan and I have known each other since we both worked on Capitol Hill. He worked for two of the really titans of the history of the United States senate: Jacob Javitz of New York and Edward Kennedy of Massachusetts. In both cases, either of chief council, chief legislative assistant, or chief council. So, it's a great honor and pleasure to have Allan at this Allie's meeting and I'll turn the panel for the next hour over to him, and then you'll have another half hour to pepper him with your questions before we close. Thank you.

Allan Fox: Thank you. You didn't tell him who you were *[laughter]*. You worked for a giant.

[Inaudible comment]

Allan Fox: Huh? You don't care. We won't mention it then. We'll talk about it later. Great. It's a pleasure to be here. I'm not sure if I'm supposed to stand, be at the podium, or sit and talk, so I'll start here. Right? Okay. I wanted to participate in this because as was discussed this morning intentions are wonderful, but actions critical. And so my involvement in this meeting – Dan and I talked about this awhile back and I don't want to be involved in anything that's not really real where we're making decisions and we're moving to action.

And so that's why I'm participating in this. I would like very much – to has this meeting ends. It just leads into further activity that will move towards cooperation and overcoming a lot of barriers that we have discussed and that we will be discussing. Some of those are scientific, which are obviously the most critical, but in the context we're going to get into there are legal and other business realities that prevent communication sharing and getting to goal, and we need to go through them and figure out how to solve them. And all of you that are doing fabulous work in the scientific research area need to be doing that in the context of a business and legal environment that accelerates and supports what you're doing and throw barriers and constantly making it more and more difficult. And patients have to benefit from this and families, and that's what this is about.

And so this is a great pleasure for me to be here and to what extent I can help I would love to do that. I'd like to introduce the panel. Some of whom you've already met. The first person – they all sat out of order and moved their name tags around *[laughter]*, so they're not going to be in order. You met David Dilts this morning. He was quite boring and unentertaining *[laughter]*. Some of us had dinner last night, and I sat next to him, and it was just a hoot. It was just a great, great meal. And as you know David is the director of strategy alignment at Knight Cancer Center and no one knows what that title means *[laughter]*. And he's a great guy.

You have not met Owen Fields. And Owen will be leading off when I finish speaking. Owen Fields is vice president of regulatory strategy for Worldwide R and D at Pfizer. He received his Ph.D. from Berkley. He worked at FDA Center for Food Safety where he helped develop US policy towards food biotechnology. Following that he worked with Wyeth, and Wyeth merged with Pfizer, and he found himself at Pfizer*[laughter]*

where he became responsible for regulatory strategy for the biopharmaceutical group and their research assets. Since then he has expanded his responsibilities and is now as I mentioned before in charge of worldwide strategies regulatory strategy.

Next to him is Dr. Russell Katz, who we all refer to affectionately as "Rusty". Rusty was going to speak earlier today, but Bob showed up *[laughter]* and knocked him off. It would have been a lot better if Rusty had spoken. We would have learned more *[laughter]*, but we have to tolerate Bob. We've known him a long time.

[Inaudible comment]

Allan Fox: Right. Rusty is the director of the division of neurology products at FDA Center for Drug Evaluation and Research. Joined the FDA in 1983 and you may be able to tell from his accent he's from New York. Next is Johan Luthman, who is at Merck. He is the program leader early development neurosciences. He came to Merck in 2009 to lead translational neuroscience and prior to that time he was at Serono where he headed the neuroscience and neurology units there, and then also at Merck Serono.

He joined AstraZeneca in 1991 working as a project leader and director of research in translational sciences there. And we're very pleased to have him here as well. And I've left out Diane who you also met earlier. She's the executive for The Coalition Against Major Diseases at the Critical Path Institute and is instrumental in this whole meeting. And we want to thank her very, very much. So, Owen if you would come up and take over. And you're free to use –

Owen Fields: Slides.

Allan Fox: You can use this or you can use –

Owen Fields: I'll use that.

Allan Fox: Okay. So, I'll shut this off.

Owen Fields: So, these are all going to be very familiar themes after our discussion this morning. And just to give you some background on the presentation, the first part I put together fairly quickly. Shall I move this closer? The first part I put together fairly quickly after we had our preparation for the panel discussion kind of to crystalize my thoughts. The second part I actually wrote years ago

just before the draft at the eight dodence on combo products was published. I actually worked on that for internal purposes that was focused on combination of biologics, which raise a little different flavors, but not fundamentally different.

So, as I go through this, if I see something that we have talked about and I have nothing to add, I'm simply going to go through it very quickly. Alright. So, I have the usual disclaimer statements that our lawyers require. The one that I'll actually comment on is that these comments are specific to novel drug development. Add on therapy as was discussed in the morning is really subject to well-established paradigms from a regulatory development perspective. Alright. So, overview. What are the possible negative industry perceptions specific to novel, novel combinations? Well, first of all, there are some IP concerns as I will say in a few minutes. I think these are addressable.

There are also concerns over complex and time-consuming early development requirements that could extend into phase three if you haven't done your factorial showing. What I call a factorial showing adequately before phase three. I think many of these are addressable with regulatory science. You heard earlier how flexible the guidance is in some cases and I think that flexibility makes a lot of sense. There do remain some questions with this disease especially in a disease modification context, but I say that as someone who's fairly ignorant of this particular disease. Alright. So, two types of IP are relevant here to industry.

The first is confidential data information and what's called "know how". In other words, I know something that you don't and this is of value to me. There are a range of industry perceptions. I think they are getting better over time. They certainly have been in my time. I think they are largely addressable by industry consortia. The NCATS model, which Pfizer was involved in very early is another, I think, very good example. And I think these can address this concern. Also, Transcelerate. It's a new non-profit company that was founded by a number of us larger pharma companies and The Critical Path Institute have actually addressed this for clinical conduct, clinical data standards, and data sharing matters. In my mind, there is no fundamental difference between co-development of new drugs for Alzheimer's, or any other disease, or even pre-competitive consortia as long as the data can be blinded and your legal rights can be protected.

So, it seems to me there are means for addressing this particular concern. The second is obviously patents. And industry can't

really survive without patents. The industry is primarily over which party owns IP related to the novel, novel combinations. And having spoken to some patent attorneys all I know is that I don't understand this area *[laughter],* but they assure me it's extremely complex. However, they also assured me this is addressed on a regular basis in the form of alliances, and licensing activities, joint ventures, et cetera. So, they tell me it can be very complex, but it's quite doable. There are models for this and in fact, we do this all the time, for example, with drug device. I worked on a couple drug device combinations where we were actually working with a device company – has a very different culture, and we managed to work it out, and those products are both approved now.

Alright. So, regulatory process concerns. Are there actually regulatory process concerns about the actual filing, et cetera. Well, there are questions of two IMD's versus one. There's concern over providing all of your IMD content to another company. Also, there's an inability of FDA to communicate with a non-owner of regulatory files, so you might think would be complicated. It can get that way in some cases, but I really don't see this as an issue 'cause there are mechanisms for addressing this. For example, you can give another company a so called "right to reference" your IMD or you can follow the direct master file and give them a right to reference. This makes it completely available to FDA reviewers and completely invisible to the other company.

FDA's now accepting single IMD's for two compounds. That cuts down on procedural complexity. You can address some of this complexity with joint development teams and we actually do this now regularly as I said previously. Even with device companies who have very different procedures, and standards, and cultures. So, again, I think there's no really killer issues there. So, the rest of the slides are actually recycled from something I put together years ago. You'll see the same scenarios that are in the draft guidance there in a different order and they are flavored a little differently.

Mostly because I'm too lazy to go back and re-do my own work. But, you'll see there exactly the same scenarios. And I actually came down in the analysis I did for internal purposes very similarly to what the FDA guidance did. So, I started this with what do agencies need industry to show fundamentally. Well, each active element needs to do something useful without bringing baggage that overbalances the added benefit. So, that's probably a simpler way of getting at the additive versus synergistic. So, you

have to balance risk benefit. Fixed combination has to be rational and relevant. And of course each stage of development is stepwise. In especially early development you have to add one element at a time.

This is not fundamentally different between multi-molecule development and single molecule development. Elements can be at increased level of exposure, duration, number of exposed, or a new entity. So, the thing to this novel is that for novel, novels a general requirement would be to one at a time then to both and you have to do some dose ranging as well. And of course any biomarkers have to be adequate for their purpose. Alright. So, the early clinical concepts – and so this slide did adapt a little from the FDA guidance that was reviewed before.

The main thing is if there are truly two brand new molecules that haven't been in the clinic or your early single a sending dose studies: A1, A2, and then concurrently B1 up to high those B, and then and only then do you get into the high dose combination or in some cases can you do a simultaneous dose escalation. Now, that makes an enormous difference on the context and the context of early development. It can make a large difference in the time required. The expense not so much, but time is money in essence. And then the question is do you have to repeat the exercise in multiple ascending dose settings? So, do you have to then re-do that stepwise dose escalation in a multi-dose setting?

In my mind it's going to depend on the mechanism precedence. Some of these molecules have already been in phase two or even phase three already. And I actually believe simultaneous dose escalation should be feasible in a case by case basis. One is already well-characterized and I think in some cases a biological combinations because I think biologicals with almost no exceptions I'm aware of do not hit off target, do not have off target toxicity. That's just my view however. In terms of phase two, the general requirements were reviewed before. I don't need to go over them again. I will bring up the concept of response bio markers, which we've talked about before.

And note, with a large number of cohorts that could be required they could be even more critical than when engaging one target and in some scenarios I think it can be essential. And I'll talk about more specific context, which reflect the scenarios we reviewed earlier just in a different order. So, instead of scenarios I call these "fact patterns". Maybe FDA wants to adopt that nomenclature if they don't like scenarios. The first one would

seem to be the most simple that it may not be. This is a scenario in which both have expected activity alone. In that case, a factorial showing of some kind plus some cohorts to explore the dose range of the two molecules in combination.

Now, if you've ever done this – and I've worked in asthma and inflammatory disease – this can very quickly add up to a huge number of cohorts, so then the question for Alzheimer's is can we practically do this for symptomatic combinations given the insensitivity of the end points? And I may be wrong saying it's insensitive; it may simply be a noising point, which in my mind is the same thing. Can we do this for disease combination, disease modification combinations given the slope progression? And then finally, are there response bio markers or target engagement markers that can support a factorial finding and help you set your dose in ratio finding in either the symptoms or the disease modification setting?

And here I want to point out that when I refer to use of bio markers or target engagement markers, I'm not talking about them standing in for the showing that's required for approval; I'm talking about them helping to define the ration and the dose range, which in my mind requires that you meet a lesser standard. Fact pattern two. A is expected active isolation. B is inactive and isolation. I can tell you many cases in my career where this has been shown to be convincingly true based on the biology. Again, a factorial and, again, as the FDA guidance lays out, it's a logical assumption that you wouldn't need to dose range B in the scenario alone at least once you've shown early clinical development safety.

So, probably modify the factorial dose ranging to focus your dose ranging on A and the presence of B. And I think the same might also apply if one element is fairly well-characterized. Let's say it's been through phase one or even phase three and the other one's starting development. You can probably then focus your dose range on the less known element. And, again, I ask the same questions as I did on the last slide. Fact pattern three. Both drugs are in isolation due to either redundancy or homeostasis. And I can tell you there's some extremely good examples in autoimmune setting and in signal transduction pathway. And of course, the brain is all about signal transduction of this phenomenon.

And there are several cases I've been involved with where we figured out that the drug failed because there's some homeostatic adaptation or there is some biological redundancy. In this case, one entity will simply not do the job. And in this case, that is one

answer to the question of why we need to do combination development. 'Cause one entity given the biology will simply not do the job. So, the sort of phase two design and dose ranging designs that you need to use are uncertain. If you read the FDA guidance closely you'll see that there are actually some scenarios based on practicality disease context where your phase two or later studies are really not that different than developing a single drug.

So, there are scenarios under which the clinical development if you can make the case on a case by case basis is actually not going to be any more complicated. How to dose range in this setting? Is it even needed? The guidance gets that a little indirectly and a large range of cohorts; practical, if they are needed. And then the same question about response bio markers and target engagement bio markers. And then this I believe has been discussed already. The value of adaptive trials.

You have a situation where you have a large range of cohorts. You need to minimize exposure of patients to drugs that don't work. So, adapt tutorials are very well-suited for this setting. Okay. Thank you.

Allan Fox: I want to thank you very much. So, we've been assigned a certain procedure that we're supposed to be following, but I'm not sure we're going to be able to follow the procedure we've assigned. So, forgive us. We're going to do our own thing. Alright *[laughter]*. Okay. It's okay. Get nervous.

[Inaudible comment]

Male: Okay. If we're too off base. So, what I'm going to do is I'm going to ask members of the panel to respond to Owen had just discussed. Any comments on what Owen has just discussed? Anybody want to say anything?

Male: Again, I'll just say that there was some detail about different scenarios, and what the studies ought to look like in phase two and phase three, and I just reiterate what Bob Temple said and which the guidance says, which is that everything depends on the details and what's known about the specific drugs that we were contemplating putting into combination. So, you really have to talk to the division. Every case is going to be different. We have little to no experience with this.

We have sub general principles that guide us and we're willing to have those conversations. We are very much interested in the

development of combinations for Alzheimer's. And I don't think it's a one size fits all. We know a lot about this drug; we don't know a lot about this drug. What's the right design? I think it's going to depend. It always depends as you've often heard me say. But, in this case particularly, we're happy to have those conversations for the individual programs that you're interested in.

Male: The other thing I noticed in internal anyway is that the number of times where the drugs are exactly at the same point in development is pretty rare actually. Often if you've taken one, you've got extensive safety, pharmacogenetic, pharmacodynamic information, but you're missing something, and then you're kind of back filling with another one, which is why it is so incredibly case by case. How known is a known entity and what do you know about that known entity?

Male: And maybe a lot of the subsequent questions we will be asked to address will cover this, but about IP issues, which I think have the potential to be large. And you always hear this anyway; that these are issues. I don't know anything about it, but I'm struck by one thing that Dr. McKew said, which is that he thought it was pretty rapid that they were taking a marketed drug, and moving it into a different population, and it took two years, and that was pretty good. And most of the time apparently was related to trying to get everybody to agree to everything, sort of the legal agreement aspect of it.

That seems like amongst the many things we need to be thinking out of the box about. It seems to me trying to address sort of the typical or the largest IP issues in some sort of generic way and coming up with a process, a template. I realize I'm being very coarse about this, but some sort of a template that we can use to address this 'cause I assume it's more or less the same types of issues from company to company, drug to drug. Some sort of template that people could use to solve these problems at the beginning for any particular combination of drugs. And I have to take a year and a half to work out those sorts of agreements.

Male: I think that's a very insightful comment. And I note that one of the elements of the drug re-purposing program at end cats was they came up with a model agreement and you either signed on to it or you didn't. So, you had your choice of getting in, or getting out, or staying out as I understand. Now, we were in very early on that one, but my understanding is there was a flood of companies as was said earlier. So, that model agreement was key to that.

And I think a lot of the regulatory paradigms I talked about are going to apply to that as well. We have a large range of compounds in that program as nominated compounds. Some of them we never had an IMD; some of them we had an IMD and its inactive or withdrawn. But, there are ways of filing a drug master file, giving them a right to reference it. So, there are ways of dealing with them. And so some of those concepts I think will come into play as well.

Allan Fox: Johan, did you want to say –

Johan Luthman: Yeah. Sorry. Well, the IP thing is definitely a big challenge and the legal procedure to sort it out. We have gone through this – all of us – in different settings. I'm looking at Diane *[laughter]*. Even when you have a standard contract and 16 companies have signed, it's still 17th company like to discuss the contract. I think if we should look someone into the room, it should be the lawyers of the different companies *[laughter]* because we could go very far to have a template contract that we have say the old, big farm has agreeing upon. But, there are two very different kind of situations. The IP problem is generally a problem when you have a competitive consortium or you like to void to have a competitive aspect in the pre-competitive consortia.

So, we basically need two different kinds of templates. One for the pre-competitive, non-IP kind of work. The legal structure for that. That could be very dynamic across the world I would say. And then, of course, for the competitive partnerships where you come together, and then all of the commercial entity together. That needs a more standard partnership agreement.

Female: Great. And on those themes it's how one defines pre-competitive. So, we see the pre-competitive space as being somewhat wide. And I want to go to this example of end cats. I don't know if John's still here, but the success of advancing combinations is going to be a complete understanding of as much data as possible about those individual drugs. And within those companies that had so much foresight to share those re-purpose compounds evidently there's a lot of limitation as to how those drugs can be used and how much information is provided.

So, for advancing combinations, these companies might have a lot of genomic data, and signatures, and signal transduction pathways. That information could really help with those selections and trying to do some of these modeling concepts to help frame what dose and what settings you would combine. So, I think how this

framework is positioned in terms of what kind of legal agreement needs to be as broad as possible. The scientists always say yes; it's the attorney's that push back. And we need to understand what is the risk for sharing this information so that we can all benefit.

Male: It's extraordinarily difficult to imagine how combinations can be developed protocols for combination – you're talking about doses and everything else – without everybody knowing everything about these two particular entities. Again, we have no experience with it, so I don't know. But, you can imagine it would extraordinarily difficult to design a trial if the people involved in it don't know. Now, it's possible it can be a third party doing this study or holding the IND and they have access to – and we have some of those, but that's fairly cumbersome from a regulatory point of view. It's potentially doable.

We don't have very many and one's just sort of getting off the ground, so we'll see how that goes. But, it's potentially quite cumbersome. We have access to the data. The investigator has access to the data, but if something happens or some amendment to the protocol has to be made, presumably the investigator has to speak to both companies independently. Can't speak to them together because they're not allowing each other to look at each other's data. And you can imagine there's all sorts of problems that could arise. So, to me I agree.

If we're going to lock people in the room to the extent that IP is an issue, a barrier, an obstacle, I think you have to get the people who are – I wouldn't say the people who are the obstacles, but I would say the people who have the greatest concerns about this *[laughter]* 'cause I'm married to a lawyer *[laughter]*. But, the people who express the concerns, who present what appear to be the obstacles. They're in a room and say, "What actually are the problems?" Identify. We talked about deconstructing the problem. Deconstruct that problem. To the extent that that problem can be solved, I think that would be a huge step. I would assume it would be a huge step.

Male: The door opening to all this is to see the proper risk benefit balance here. If everyone agrees that there is a huge benefit, then you can take bigger risk whether it's IP, or scientific, or regulatory I guess to some extent. We are rarely in the case where we're that informed. And you have a lot of internal debate in companies and organizations. Now, is it true they're going to do this? Is the benefit good enough? Should we do it on our own?

I think if you have a test case that is crystal clear, it is some benefit to do it together and you have seen that in the bio market field. It's really deliberate. But, I think the next step is to bring the drugs to the other room. Maybe drugs and diagnostics together and the benefit is not obvious to do it in sort of a pre-competitive or even a bigger partnership competitive space. I think we have to find a test case to drive forward.

Allan Fox: David, you've been quiet, unusually quiet.

David Dilts: Because nobody's going to like what I'm going to say *[laughter]*. Okay. This is an observation and I know nothing about Alzheimer's. Okay. The reason I got into cancer research is because the cancer doctors kept saying; "We can't get anything from the IRB. The damn IRB is the biggest holdup we've ever had. You've got to come in here and make this IRB the most efficient you have ever seen." And I said, "Okay." Let me map out the time it takes from the time you have an idea until you actually close a trial. And I'm a ____ scientist, so I laid it all out, and then I timed it. Guess what? It's not the IRB. You know what it was? Getting it through legal. And by the way, whenever I do that –

Male: Getting it to legal and getting it from legal.

David Dilts: No. Hang on *[laughter]*. I would go to the investigators and I'd say, "What do you think the biggest holdup is?" And they would say, "Well, it's the IRB." I'd say, "No, it isn't." They would say, "Well, what was it?" I said, "It's the lawyers." "I knew that *[laughter]*." It's like I spent a year then everyone knew. So, I said, "Okay." And I picked on lawyers and I apologize.

Owen Fields: No. That's fine.

David Dilts: I picked on lawyers for a year, and then one of my students said, "We should really investigate this little piece more." And you know what we found out? It wasn't the lawyers. The lawyers couldn't approve something until the budget was done. The major problem in cancer research is getting the budget finished that then leads to everything else. So, I'm not saying intellectual property with the lawyers is not an issue, but I'm saying be very careful of assuming it is the issue until you really know. Okay. Again, I'm personnel, so you can –

Allan Fox: So, just as we go through these issues just pretend we're researchers for a second *[laughter]*. We have to do research to

find out what are the real barriers because what appears to be a barrier may not actually be the whole barrier and so we have to really figure it out to make it work. And I agree. I think that's terrific.

David Dilts: Yeah. Well, I used to spend a lot of time with organizations who pointed out the problem that you then – by the way, remember; my entire thing is throughput. It fit doesn't help things get through the door, it really doesn't matter. And the automotive industry used to give me a lot of money to solve point problems that really didn't make any difference upon getting more cars out the door. So, I did what a good friend of mine calls "good clean fun". It was fun. It was exciting. It was great. And it really didn't make any difference. And know that I'm old, and gray-haired, and wisen I've learned a little bit more to say, "Let's focus on what the major issues are." I'm not saying it's not the lawyers 'cause it could be, but you're theoretically a data-driven industry. Show me the data. Show me the data it's the lawyers. Okay.

Male: I will.

David Dilts: *[Laughter]* I have a volunteer.

Female: So, when you say show me the data, one thing Johan mentioned is it's not clear that doing this in a pre-competitive space is essential. What incentives are there for companies to go forward and do this combination with another company because the science suggests that we're all saying that we think Alzheimer's disease is going to require a combinatorial approach, but do we know that yet? And have people bought into that as they are in other diseases? Or is there still this hope within companies just like that article that I read from Wall Street Journal? It's like okay. This guy's going to have it. Phase three, tower x drug is going to be it. How do we get consensus that is going to get everyone to agree that we are going to have to take a combinatorial approach to have an effective approach to treating this disease?

Female: Reisa.

Reisa: Maybe the history of the past two decades *[laughter]*. And one other thing, again, for arguing the value added from I Spy Two is my impression, is it's not just the lawyers and the budget. It's also the time it takes to enroll patients for each study and particularly, again, if we're talking about earlier disease and finding the people in that right sweet spot, that takes tremendous amount of time. So, trying to find a way for companies to work together on a patient or

participant 'cause they may not be patients yet population who's ready to go and bring this in. I can't imagine that that would not be helpful to every company here.

Johan Luthman: Actually, thank you for raising this. This is one of my favorite topics. Where really companies compete is in how to execute trials in their element. This is sort of a holy space. And the speed of finishing a trial, competing for good trial size, that's really at the heart of competition in the industry in the ____ side. If you could find the _____ where we could collaborate, of course there are centers. Sort of in academic research arena we have all these cooperative networks. At the old ____ we sort of compete. If you could find a ____ where we were not so afraid about losing speed and still collaborate on enrollment because enrollment is the number one component in getting those drugs tested and hopefully out to the market.

Allan Fox: But, I think I heard both Don and Mike talk about I Spy and other techniques to really re-engineer or re-invent the clinical trials so you don't have to have 1800 people for 18 months. That it could be fewer people getting more information faster. Could this consortium buy into that and get past the clunky problems of the old clinical trials?

Johan Luthman: Certainly. There are two approaches. One that you described. The other one is volume. Basically have internet enrollment. Have everyone be very loose in your inclusion criteria. That's the other one. It has to be by volume, which is probably not the best company. I'm very hesitant because you like to have quality trials basically. But, no. There are a lot of new instruments being done to recruit patients, but at the end of the day we're talking about people that are ____ _____ _____ that have a caregiver. It's a lot of time. You really have to give them all incentives and support to come into the trials because it's a burden for the patient and the caregiver. It's just extra time and if they don't really see the potential side for themselves it's really hard to motivate.

Male: One thing – and I think one of the speakers this morning mentioned – certainly adaptive designs is we don't make enough use of. Certainly not in the early stages, or phase two, whatever you want to call it. National registry of patients somehow would be very useful. The other thing is there are many, many data points collected in clinical trials. There's lots of study visits, this sort of thing. We need to be thinking about decreasing that and somebody mentioned it this morning.

Of course, it depends on how much you know about the drugs or the individual components, but you don't have to collect reams, and reams, and reams of data necessarily. You don't necessarily perhaps have to have people come in to be evaluated. So, thinking about creative ways to minimize the burden to patients and their families in clinical trials – certainly shorter trials will help. But, we have to be thinking about what are we actually doing. What data are we collecting? Is it really necessary? We tend to be reactive. So, folks propose protocols to us and they have all kinds of things in them, all kinds of data collection, inclusion criteria, exclusion criteria.

We don't always say, "Look, you have 12 visits. Maybe you can get by with 6 visits." So, people should be thinking about designing trials that are less burdensome. There may be cases where that's inappropriate, but there may be many cases where it's perfectly appropriate.

Allan Fox: We have been given a series of questions. I'm not sure everyone knows the questions we've been given, but we're not following our questions very well *[laughter]*. But, we are answering the quest – it's like and essay *[laughter]*. It's a collective essay. David, did you want to share something.

David Dilts: Well, you guys have been talking about roadmaps, so I thought I'd show you what some actually look like, which I've been busily playing around on my computer. I'm sure you've been paying attention.

Allan Fox: I'm sorry. I moved that podium.

David Dilts: That's okay.

Allan Fox: You don't use podiums anyway.

David Dilts: I don't use podiums, but I use one of these. Help *[laughter]*. I know it's universal; it doesn't fit *[laughter]*.

Allan Fox: I moved that back so it wasn't a barrier.

David Dilts: Yeah. I think it's great.

Allan Fox: So, the first question we're supposed to be addressing, – so I get good points on my evaluation *[laughter]*. So, ____ stab. Why is pre-competitive collaboration essential to the development of combination therapy for Alzheimer's disease? So, we answered that?

Female: Yep. The chance that one company owns the molecules essential for a successful combination is pretty minimal.

Allan Fox: Thank you. We answered that question.

Female: Even the largest company *[laughter]*.

[Crosstalk]

Female: Great. Owen. Sorry.

Allan Fox: Second question. What should our shared vision be a pre-competitive collaboration in Alzheimer's disease?

[Inaudible comment]

Allan Fox: I think we answered that question. The third question we're supposed to address is what can we learn from models of pre-competitive collaboration on other diseases and industries? And I think we're going to see that again in a second. Right? Okay. Alright. We have two more questions we're going to go to. Alright. You're up.

David: Okay. This really isn't a consortium. Got this before. This is a roadmap. So, we changed topics. Okay. The Translation Research Working Group from the NCI looked at what does it take to actually do different pathways for development and said, "What's it going to take?" This was the entire issue of clinical cancer research for I think it's 2008. Yeah, it's 2008. They developed these little roadmaps that say, "If we're going to do this, we need to start there. Here's branching points. Here's the various places we can go." And they linked it to whether it was a supporting tactic, or clinical research.

For example, today I heard about when you buy markers, then we need to ____ these for clinical trials. Nobody mentioned follow up, which is an incredibly expensive thing to do with cancer. ____ _____ as far as money goes. It's like how do we put all this stuff together? They did a really nice job when they developed six different roadmaps of what it takes. Okay. Now, this was a very high level effort, a very nice effort. Now, they also said very quickly, "What are we doing and what's not being done by people?" So, you find out gaps. So, for example, one of the gaps would be let's say we don't have the lawyers involved.

But, supposedly magically tomorrow the lawyers say, "Yes. We completely agree. Wouldn't life be good?" No. 'Cause _____ must guarantee the finance people are going to get involved. So, what else do we need to have? What else do we want to put together? So, this is another group I used to work with called the Integrated Manufacturing Technology Roadmap Initiative. We like cool titles too. Like, "I work IMTR and we don't say what that means, but it sounds very cool."

And so what we did here is you look up what is the major function that needs to take place? What are the goals you need to do in the future? What kind of timeline do you need to have as far as getting these things done? What's your current state and future state? And how do you get there? What are the milestones that have to be achieved or you can't make your deliverable? This is a project management kind of idea and this is just one where you did project design, link into the data required, and link into the main function of execution. This is what people use today to build things like airplanes.

So, you have a digital design that actually we sit down and forward the ___ to where they're making money. And, again, what are the major elements? That's the functional. What's the current state assessment? What does it look like now? Where do you wanna be? And what are your goals? And then how do you get there? That's the roadmap. And you break it all the way down to specific tasks that need to take place. I'm going really quickly.

And you get some pretty good idea about what's the current state and where you're going? We did this 16 years ago, so this is what we expect it to be in 2016. You can then do it visually, which is really nice toward a goal. And you can also say, "Why do you do it? What's the benefits? And then what's key to begin this stuff working?" So, you map all the way out, so everyone knows where everything is linked. And how do you do it?

You do as much data gathering as you can. You build a functioning model. You gather as much other data, and then you get it together, and you look at it. What did you call it? The lock room. "If we only sat in a room for a week, we could solve this problem." Well, if you sat in a room for a week, you could get all the data to solve the problem. Then it's going to take another two months to put all the data together, then you need to vet it again as a process. Now, this one of the most interesting outputs that you get. Here were all the goals that needed to take place in order to achieve our vision of a completely integrated organization.

Sorry. Look where the money goes. Everybody's funding this; nobody's funding this. This is called "you can't get there from here *[laughter]"*. Okay. Now, note, again, I'm not saying that's not an important problem, but unless you fund the whole pipeline at least a little bit, it's never going to happen. Okay. So, this is one of the things this kind of activity gives you.

It says, "We're not going to be able to do this." Now, one of the other things of doing a lot of roadmapping and standards is you get this comment very frequently: "How did the new ____ ____ go? Did you convince 83 companies to adopt standards and benefits only as while dooming the entire industry long-run? Or are you a complete failure *[laughter]*?" Okay. And I'm sure that's never happened in your company that I used to be part of the national senior citizen part of the problem. And very specifically everyone intends on building this, which is the Brooklyn Bridge.

I didn't like the empire state building. I like the Brooklyn Bridge because you have a contrary. Some people build this. This is called the Comon Narrow's Bridge. If you've never seen it, you should see it. You will see a bridge that sways, and finally buckles and breaks because they forgot a basic engineering principle. Right? You want to build one of these 'cause these are beautiful. They last forever. And some people because they haven't thought it through build this.

So, my suggestion is this and this comes from also my friend, we didn't get to be this smart because we were this smart. We got to be this smart 'cause we did all the problems and now we need to learn what other people did. I'm trying to be careful. I think that needs to be done. I heard today a lot of point issues: legal, adaptive clinical trial design, bio markers. How do all these things link together? What are the next phases? What are things you need to talk about that might be important?

What are the gaps? And, again, everything you talked about is important. That's not the point. The point is what did you talk about and how did they interrelate together? Okay. And now I'll shut up *[laughter]*. Thank you.

Allan Fox: Thank you very much. Is there any reactions to any of that?

Female: I have a comment. In industry when a compound has a negative result it's very challenging to get resources to go back and look. The company that owns the compound and did the clinical trial

have the best majority of the data. And in industry when you have a negative study – I won't say failed – it's so hard to have the resources to go back and look at that lesson learned. We had a document, where we went back and asked, "Why did it fail?"

But, there's a huge, huge, vast amount of data. Rusty commented, "Companies collect a tremendous amount of data from trials." Yet, I always felt like it was that game chutes and ladders where you go up a little and the chutes become really far. And you don't get the time, and energy, and resources to go back and learn from what were the bio marker results from those studies. What were the outcome measures? How can you define subsets of patients that could benefit from a future study? This is essential for combination therapies because you can't be guessing.

Sometimes it feels like we're guessing, but I think the expansion of the pre-competitive space is to, one, get access to that data and, two, collectively mind that data so that we understand in a complex disease like this how can we learn from what's happened in the past.

Allan Fox: So, we have heard a lot of what has worked, examples of things that have worked. Some of us have been doing a little research in preparation for this meeting to see what has worked and what hasn't worked. And I think the subject is not just pre-competitive collaboration; it's collaboration. I think what is pre-competitive? Let me see. I think somebody wanted to comment on – you did, didn't you? Johan, did you want to get into that?

Johan Luthman: Yeah.

Male: I think it's –

Johan Luthman: I have actually a ____ try to define. But, I'd like to build on what they told. Organization learning is really very hard particularly in a climate where you fire and hire, and your people move around, then you re-organize all the time. So, to keep organization learning you need to build some kind of active instrument to harvest that information that goes beyond what's up here and ____ people. You have to build an active system for it. And you have to also see their internal investments on it. We are living in an industry that fails 92 percent to be exact of the time in development and we're actually in the business of learning from mistakes.

We actually move on. The minute we fail a program, we move to another program and hope to win in that program. So, there's the systematic problem or organization learning in the industry from our failures.

David Dilts: Wow.

Allan Fox: You have a slide that's up there.

David Dilts: Yeah.

Johan Luthman: Wow. Okay.

[Inaudible comment]

Male: So, how many more –

Johan Luthman: Maybe that one should be here. This is more ____ meeting, but I think when you look at combination therapy in Alzheimer's disease, what should you combine? What is out there? What is the scientific rationale or supported data to really consider combination therapies? And what kind of opportunities do you have there? And then there are the components here. We are supposed to sort of marry two things that are not really related: pre-competitive collaboration and combination therapy.

It's not exactly the same thing. But, how do you bring the molecules together? You have the classical one. You have one ___ or you have one company with two compounds. That's fine. It's easy. It's not that easy, but it's at least within the company. Then you have the classical partnership form. You have two different companies coming together and working together on the topic and that's the classical competitive partnership. And it works quite well. We do that all of the time.

About 50 percent of all ____ are partnerships in some manner. And then you have the pre-competitive and that is not easy because pre-competitive is that you are actually avoiding IP issues. And how can you do that when you have a commercial interest to develop a drug? So, there are some novel partnership models that I'd like to touch upon and we have done that today. But, just to touch upon this, what's the scientific rationale to combine? This is a message picture down here. You have to illustrate. No. I have probably something similar.

And you have all these ideas. What may work in Alzheimer's? And we're actually not getting it to the point where we test them often. I would claim that we had not them on a hypothesis yet. It will take some more years until we have the proper tools to do it. So, we haven't really tested what's out there. What we even know less is that it isn't really sufficient support to combine two mechanisms or even two drugs with the same mechanism. If you think you can reach better efficacy by combining two drugs and you cannot do that alone, fine. You may have the rationale.

If you believe you have less side effect problems, fine. You can combine them, but we're not there yet. There's no evidence ready to support that today. And the other thing is do we have any evidence that, for example, inhibiting gamma ___ or beta ____? Do we have a tolerance development? I may have missed that literature, but I haven't really seen in vitro ____ in animal models that you lower your efficacy on ____ effect of those drugs. If we had an issue, if that was a huge issue and you thought it was a reason for trial failure, fine. That's the way to go.

So, I'm looking for really the strong scientific rationale today to do the combination. It shouldn't out of, "Well, monotherapy failed, so now we have to try combination." The other one is of course the additive effect. That was addressed earlier today, so maybe I shouldn't pick on it. But, if one plus should be three, you really have to have a good rationale for it. We now heard that maybe not the requirement, but it's mentioned in the draft guideline. And if you have zero, one that doesn't work, and you add zero and you get two out of it, then you have to have a really strong rationale.

We heard about the breast cancer drug that actually seems to work like that, but I cannot come up with any case today that we really should assume that combination therapy is better than monotherapy. Hopefully, that will come and we have had sort of a _____ model for it. Another thing is the partnerships. You have the classical competitive partnerships, the private one. And with the industry trimming down the usual partnership we have today is actually big company with CRO's, Contract Research Organizations. That's the classical partnership we have now.

And of course with biotech. But, then you have the Public-Private Collaboration Academic Research Group within the industry. We do that all the time. It's competitive again; it's not pre-competitive. It's searching competitive advantage from this. And then you have the classical PPP, Public Private Partnership, which ADNI, CAMD, whatever we have. Those are very successful.

But, they work. They come together with a very clear understanding we're bringing a platform that will serve the whole industry. No one will benefit immensely more than someone else in this effort, so it's sort of a balanced competitive advantage together. That's when you do it together. And then you have the private and this is quite interesting.

You have the non-profit private organizations. Maybe a patient organization coming together with industry. This could be pre-competitive, but in the private space. It could be for the whole benefit, but it's often actually for a competitive reason. And this is with the ____ initiative. There could be some commercial interest; it could not, for example. And then some novel partnership models. We are used now today in forming virtual companies and they are truly competitive. They are not pre-competitive. And virtual companies are basically a bunch of guys that got fired from big pharma *[laughter]* as they like to work, so they come together and they start to work on a molecule that they managed to steal from the company that fired them.

Right *[laughter]*? That's the usual model. But, it actually works well. It's very, very cost effective and they use their ____ basically 100 percent. They don't do anything internally. They may not even have an office. And this is an extremely efficient way of developing drugs and we see more and more of this. But, the next model I'm sure will come – people talk about it and I have some colleagues thinking about how we should do this – is really this open source virtual development. Basically, you place the molecule out there in the open space and anyone can bid on it.

Company, an individual, or whoever is out there can bid for a slot. Raise your hand quickest and you say, "I do regulatory for this program." Another one says, "I do ____." And you build a project team in the virtual world. And you may or may not have the project management also raising their hand. I do the project management. Again, this is a competitive enterprise. You have IP. You have commercial interest and everyone signs with a standard contract. That everyone agrees to sign that contract and you get just percent, royalty on what you put in ____ ____.

If you build a ____ of this, you can actually sustain yourself doing it. And I think this will come more and more in the future. Finally, one word about competitive and non-competitive pre-competitive partnerships. We're actually struggling with this right now, but in a slighter different field. The combination of a drug in a diagnostic. So, we have a lot of pre-competitive efforts trying to

build standardization. CAMD does a wonderful job as does the Alzheimer's Association. The ADNI private industry group is working on this in the working group. Where we come together and actually try to solve common issues. But, this is really when the rubber hits the road.

We're really touching upon a competitive component here 'cause we have diagnostic companies participating and they may or may not benefit individually from this. So, if we already have a test case, how can we do this in a mixed pre-competitive and competitive space? And hopefully this will speed up and allow us to get diagnostic combinations, co-diagnostics, or standalone diagnostics for Alzheimer's disease approved to the market. And this will be a test case probably for when you like to combine drugs in the future.

Allan Fox: Any reactions?

Rusty Katz: Just one reaction about the timing or are we ready to do combinations? Is there evidence for utility of combinations when we don't know if one works yet? I think it's probably true that we haven't adequately tested, let's say, the amyloid hypothesis yet, but you'd have to say more or less that there's no evidence that that's going to work either at least given everything we've seen so far. So, there is evidence that there's lots of things wrong in the brain in Alzheimer's patients.

So, I would say that sort of primafacia evidence that it's at least rational to think about trying to attack those various things assuming we had compounds that were directed at those other things. But, the fact that we haven't adequately tested the amyloid hypothesis, which I think is true, doesn't take into account that it really is not particularly any empirical evidence that that's useful by itself.

Female: On that note, we all want to see a compelling side, underline machanus scientific rationale for why pursue combination strategies. But, I think some of the animal models are pretty revealing in that these bigenic mice where you cross the amyloid mouse, and a tow mouse, and a triple transgenic mouse or now you introduce an inflammatory gene is pretty compelling showing you augment the pathology and potential relevance of the model by having multiple factors. And having one animal model for one target has kind of been the dogma to develop individual targets. It is something that has happened for far too long. So, I think there could be pretty compelling scientific rationale if one were to integrate the data that we have today on what's been done so far.

Johan Luthman: Maybe, if I may. I agree with that. Particularly in the transgenic animal world, there's some evidence. Of course, you put the pathologies together you have additive effects and probably you'd like to have drugs that affect those different components. But, I think the problem here is little bit that companies that do have a drug in development for one mechanism, they're extremely worried to put it together with another drug, and you start to get to see bad stuff, and then you have to disentangle your drug from that bad label. I think that's one of the key problems. So, if you really see the huge benefit of bringing them together, I guess, then you have that situation.

Male: Let me ask. Has that happened? 'Cause that's something we've been talking about a long time. Why not put combinations into animal models assuming you have an appropriate animal model that has multiple pathologies? Have people done that? They may be worried about bad things happening, but not 'till look.

Johan Luthman: Well, some people do it I guess *[laughter]*. Some people like Mark do it, but I think in the end, of course, it's a cleaner situation when you have monotherapy in some manner. It's likely easier to try to understand what you're dealing with, but I think eventually we have to go with the combination, the pathway. Definitely. But, when you look at the drugs that are in development today, I don't really see the strong rationale in combining them until you test them in monotherapy.

Rusty Katz: Yeah. The other thing I was very much struck by Dr. Diltz when he talked about in cancer that it's sort of a fashion business. Somebody's over here, everybody runs here. Okay. Forget that. We're here, you go here. There are people clearly working on pathologies and Alzheimer's other than amyloid and tau. That seems to be the other alternative. If it's not amyloid, it's tau. There's a lot of things. Even though some people may be losing their fondness for amyloid and they may be moving to tau, but there are plenty of other places to look. So, I think that's worth at least bringing up.

Allan Fox: Cynthia.

Cynthia: The other thing I'd add and I think the most important thing I took from Dr. Temple's talk is that it not only has to have the biological rationale, but it also needs to be important. And I think that's something that's getting lost in this conversation – is how important it is to capitalize on the time we're losing in pursuing

monotherapy alone. And I think that's critically important to patients and I think we're getting a clear sign from FDA that they're willing to talk about it. And so I would think if one really good thing comes out of the meeting today is knowing that patients need better options.

They're willing to support you. The FDA is almost clearing a path to make those conversations happen. What more do you need from us to convince you all that the will should be there to do this? And what's to stop us from them putting everyone in a room and as Rusty – "i can be very persistent and persuasive," he said, in getting people into a room. And so we can make the legal challenges potentially less burdensome.

Allan Fox: So, I guess, I'm a student of decision making and that's what I do as a profession. And the first question is who are the decision makers in companies, in agencies, in patient groups, in research centers, in critical path organizations? Who are the decision makers and what are the decisions that have to be made? Perhaps, one of the decisions is to come up with a design similar to David's design and to figure out how do we do this, do we work together, not work together. The lawyers can come in after the decision makers say, "Go forward and do it."

I'll never forget as a little side story, but when I first worked in the senate, and the staff were gathered around at the senate l subcommittee, and Senator Kennedy and all the other senators were there, the staff, and there was a piece of legislation they wanted to move thought the committee and no one on the staff knew about it, which is unusual. Usually the staff, the staff, and the senators. And the senators said, "Okay. We would like to report out a bill on x subject," and they left the room. And the staff were sitting there saying, "What are they talking about?" And we just sat around and said, "Well, I guess we'll have to come up with some bill *[laughter]* that supports this concept that they gave us." Right?

So, we sat around and we drafted a piece of legislation. All we had was, "Get it done." We had no idea what they were talking about, but we sat, and we designed something, and then took it back to the senators. It's sort of the same thing here. We want to accomplish something, but there's a lot of detail. There's a lot of real things that have to be done. But, if real decision makers got around and said, "Okay. We will commit our cooperation. We will commit our resources.

We will instruct the lawyers. We will tell everybody there is a mission. Let's go after that mission. How do we get it done?" Obviously, there's going to be problems, but at least there's some leadership that's moving it forward. And I'd like to throw that out in the few minutes we have left here for us to talk about and get some reactions to it. I know you can't speak for Pfizer. I know that.

Allan Fox: Alright. First thing to consider is anti-trust concerns.

Allan Fox: That's on my list.

Owen Fields: But, there are mechanisms. There's industry organizations. I think CPI. There's Transcelerate. There are mechanisms I gather. Again, that's not my expertise, but there are mechanisms for addressing it, so you'd have to start there. Can you have these discussions in a way that's clean from an anti-trust perspective? And then after that you'd have to have the researchers together and they'd have to have some ability to share what they have, and then turn it over to you because that's more your expertise. Yours actually and yours *[laughter]*.

Male: You first.

Johan Luthman: Well, to go back to combination therapy I think someone mentioned that drugs are rarely aligned. They move forward and that's true.

[Crosstalk]

Johan Luthman: The ultimate combination we're doing already today. We combine a drug and a standard of care. That's being done and that's not the topic of today, so we should avoid that. But, you could have a very advanced compound we understand quite a bit, and then you're both on something else. We also have another situation. We actually have tested mechanists that ____ coax inhibitors didn't work. Maybe they didn't' work because the mechanist was not dry, but maybe they did not work because they were not combined with something else. And maybe those are things that we should revisit in the future. There may be drugs that are out there that are sort of related from the other side that could be bought in basically.

David Dilts: So, because I, again, don't do anything typically – the Manhattan project was mentioned several times today. Okay. The Manhattan project was a whole lot more than just a statement because you had

Openheimer, who didn't really know whether the physics would work or not. They didn't know you were going to actually fly this thing and would it actually fit on an airplane. When they took it off from the Nolengay, they took it off from an island because they were worried the thing was going to crash. Right?

Looking back in history it was all great. Openheimer took care of the scientist who had exactly the opposite problem. They wanted to share everything. And Grove, who was the military guy, said, "Don't share anything." They built some world class management techniques to put two incredibly different cultures together to be productive. Now, one of the things they had was an overarching mission that millions of people will die if we invade Japan. We must do something now. If we don't do it and the Nazi's get it, the game's over.

So, they drove really, really hard, but when they did they created brand new management structures and brand new ways of approaching major problems that – speaking as a management _____ – you should go back and look at. They were incredibly creative at what they did. Did they make a lot of mistakes? Yes. As somebody who lives in Oregon, they just buried a bunch of stuff at the Hanford Nuclear Reservation in Washington and nobody knows what it is *[laughter]*, which is why you don't farm in that part of Oregon. Okay. But, they achieved their objective. Was it the objective they should have achieved?

That's a different question. But, you were faced with a major issue. I always like to say, "Let's find out a person who solved the problem close and what can we take from them? Or even more importantly what do we not want to do that they did?" Okay. Now, I'm going to be really pejorative, so don't hit me. Okay. If you continue to do a single drug at a time knowing that a combination's the only way it's going to be effective, you're General Motors. Okay. You have just said, "Our industry's going to die. We're just not dead yet." Okay.

Because if you know the desired out capacity combination, but you can't get there until you do singles and singles are going to take 15 years, you can't get there from here. Now, again, that takes a different management idea. And I'm not a biologist or scientist. I don't know anything about it, but just a primafacia case, you can't get there from here. Right? You're the Alzheimer's group. Is it acceptable to say it will take 30 years to get a decent Alzheimer's drug?

Female: No.

David Dilts: No. Okay. Well, you know what? If you keep doing one at a time, what's going to happen? Can you get to where you want to be doing what you're doing now?

Allan Fox: So, let me try to operationalize this a little bit back to what Allan said and try to be very practical. Sounded to me like if we could put out an invitation to x number of companies, y number of patient groups, z regulators that we're going to have a gathering. It will go over three days in a locked room. Maybe we'll go to Los Alamos because I understand they have some excess space out there now *[laughter]*.

David Dilts: Just a little.

Allan Fox: It's a nice place this time of year.

David Dilts: If you like a barracks *[laughter]*.

Allan Fox: Barracks. We can see if there is needed any anti-trust protection, some kind of safe harbor so that everyone can go in there without any fears of legal ramifications. If we could kind of spell out what is expected at the end.

David Dilts: If the government invited them.

Allan Fox: And it has to be government roll. If we could define that and deliver that invitation to those that we feel are essential. And as someone said, I think it was David, you don't try to see anybody on the whole thing. You get someone to buy in ten percent and you then you get the second percent, third person. Pretty soon nobody wants to be left out. If you can define what it is that you need at the end of that, that may be the next best step to try to catalyze this. Maybe it's not quite the Manhattan project. Maybe it's the Rockville project or the Los Alamos project, but let's see if we can replicate that.

David Dilts: That'd be great.

Allan Fox: Response?

Female: Debra had a comment.

Debra: So, this is very close to what we did when we launched CPTR. So, there was absolutely that locked room so to speak brainstorming

session. It took folks at the Gates Foundation two years to convince industry partners and other groups that this was the right thing to do, so I hope it doesn't' take you that long. And it sounds like you're going on the right trajectory. But, that's really what we did. And it was three days of bringing all the parties together to talk about what is the mission. You have to start there. What is the objective going to be? For us, it was very clear that we needed to accelerate the development of an entirely novel regimen.

That took an awful lot of discussion to come to that point, but at the end of the day that's what's going to treat these patients that have multiple drug resistant forms of the disease. And that if you want to treat those patients, you not only have to introduce one drug, you have to introduce multiple new drugs so that you protect those agents and make sure that resistance doesn't develop quickly. Now, that was a lot of push back on that because the barriers were too high. Don't we just need one new medicine that works? Wouldn't that be good enough? We haven't had one in 50 years, why can't we settle for one? Because it doesn't work. In our case, because we know that drug would not last for very long. It would be misused, and resistance would form, and you would be back in the same boat five years after it was introduced.

Not good enough. So, that was the scientific rationale for having to have that entirely novel regimen. And then you bring in that locked room all the parties that have to participate to change not only the innovations and the science, but in the clinical trial infrastructure, but also the policy piece. I think Martha's point around safe harbor and changing laws such that industry partners aren't going to be persecuted if people mishandle data. I think that's incredibly important 'cause you're in a return on investment area; we are not.

And that's one of the critical differences between the two different consortia we would be talking about. But, I think to have all those people in the room and to say that, "We collectively think this is the direction that we need to go," you have to get everyone to buy in. But, it's been done.

Male: It has. A precedence.

Male: Well, and there are vehicles to approach some of these problems particularly on the policy side. The national plan to address Alzheimer's Disease calls for essentially transformational change by 2025 and at least as I perceived it, the mood around the room when that decision was reached – not when it was proposed, but

when it was reached – were a lot of folks saying, "Well, that's lovely and visionary, but how in the hell are you going to do that in 12 years." This is part of attempting to answer translating the vision of 12 years into the potential practical reality of 12 years. And we have at least one member of the Federal Advisory Commission in the room.

Maybe more than one if I'm missing anyone, but I see Rusty sort of crouching down *[laughter]*. But, there are others we have access to. And Don Molds will be at part of the lead coalition meeting in a couple of weeks. We have a lot of vehicles to raise this with Don, with other people in the administration, and in Congress to say, "This really needs to be on the radar screen." Now, we don't have all the solutions, but we have identified all of the problems. And to your point, I think you're exactly right. It's partly the science. It's partly the regulation.
It's partly the public and private policy. And Dan, to your point, and I'll end with this, it's who wants to be left behind. If it's going to happen, who doesn't want to be in the room at that point whether the room is locked or not.

Allan Fox: Steven and then Reisa.

Steven: Yeah. I'm going to have to go catch a plane, but I wanted to make a comment on this topic. So, I'm basically in agreement with the whole spirit of the meeting and I think that what's been talked about today fits very well under the national plan. And I think we need a mandate coming from the government. I like Reisa's effort to combat and to put it in defense terms, unlike a tsunami, which is a one-time event, this is coming in a sustained wave and that's the 10,000 a day for the next 15 years. It threatens our livelihood, our quality of life. This is a national emergency; it's not a one day emergency.

It's a sustained emergency. And I like the idea of a retreat and moving forward. It think it's imperative. That's the only way we're going to be successful. And I think that if we are going to be treating Alzheimer's as combination therapy, it's going to take us a little while to get there, but I'm confident that that's what our eventual result will be and today's exercise is very helpful to get us moving in that direction.

Allan Fox: Reisa.

Reisa: So, I very much agree with Steve and I very usually do, but back to this issue of why would we want to and should we wait until we

fully test the amyloid hypothesis. They should happen in parallel. If you have a drug, a single monotherapy for a data that knocks down Alzheimer's disease by 50 percent, great. Then we'll say, "We didn't need this whole consortium thing." But, I think we should start building the other and it's not just the pre-clinical animal data, patients with Alzheimer's Disease – if you have amyloid alone, in general you don' t have dementia. If you have tangles alone, you don't have dementia.

You need all of these we know to cause dementia. And we don't fully understand that, so the idea that we're going to have a single mechanism knock it down I think just doesn't make scientific sense. I very much agree with the who wants to be left behind because I think we should empower this to say, "This is the wave of the future. Get in now or wait and see what happens when you don't have a dog in the game." And I think we should have a retreat. I think it's a great idea, but I've been involved in a lot of task forces work groups recently.

I think there's a little bit recommendation task force fatigue among the academics anyway. So, if you do this, I think there's got to be a really clear piece of this with some money behind it and some real piece to go forward 'cause I think some of the roadmaps been set out in a variety of things – the summit at NIA, a bunch of things – and now the question is how do we actually do it? So, I would just encourage you to have this real action come out of this, not just recapitulate the ideas that we all need to be done.

Female: And, Allan, I just wanted to ask a clarification question 'cause you said if the government invites them then they don't have the anti-trust issue.

Allan Fox: I'd have to double check specifically, but as a general rule the government can invite people in who are competitors. If it's at North Pennington, then they can talk.

Female: Okay. Because my feeling about this is most of the people who are in the Alzheimer's space –

Allan Fox: Some of the AIDS and work that we did was that way.

Female: Okay. Because my feeling about this is that the folks who are in the AIDS space know that the groups in the Alzheimer's space don't play in the sandbox well together. They just don't. And I feel that at the last advisory council meeting Don Molds, who is the acting assistant secretary for planning and evaluation made a

comment that the secretary can convene people, but not necessarily tell people what to do, or direct people, or this, or that. And I feel like this is the perfect thing for the secretary and for the assistant secretary for planning and evaluation to do, so I really want to encourage.

I know that Tony and Neil are here to go back to Dr. Hodes and for Dr. Katz to reach out to Don and say, "If this is going to get done, it's only going to get done through ASPE and it's only going to get done through that process. We'll help with resources, with organizing it, but it's not going to get done any other way." I know for a fact that there's groups involved in the process that are fighting over this right now and you're well passed the deadline for anything to happen. There was supposed to be a meeting in September. We're a couple of months passed that at this point.

The only way is that this is going to happen is for ASPE to convene it. So, I just ask please. I know Dr. Hodes, Dr. Katz are both on the research work group. Please go to ASPE. Please help to make this happen. We'll help pay for it. We'll help get people in the room. I think this could really be transformational.

Allan Fox: I think Johan may have started saying something about not having the right drugs available yet for a combination or you said something. Could you flesh that out a little bit? Maybe you said that it's not clear. For example, like gamma ____ inhibitor by itself – there are a few that have shown the ability to knock down ____ beta in the _____ say with base inhibitors.

It's not clear that putting them together would necessarily be better. That tow drug. There's a tox rx drug that's been alluded to. Whether that's going to effectively attack the tow target is not clear. Is that what you were getting at? Or could you flesh that out a little bit.

Johan Luthman: Yeah. I think locking people into a room and discussing this is probably very good because we have to come up with pretty strong rationale why one would like to test the combination without testing the monotherapy itself. You have to really understand the benefit of it and the benefit could be, of course, basic scientific rationale. You combining tow mechanists with amyloid mechanists, et cetera. But, if you look at drugs in the pipeline, I think they need to generate that understanding of the opportunities we have today.

We could just say, "This is futuristic thing. We're planning for the future. We're building a pathway and once those drugs that attack those mechanists around that they will only be our best ones, then we do it." I think what you seriously have to do to look at a drug mechanists we haven't developed in today – and there aren't so many unfortunately – and see is there a clear rationale to combine those mechanists? And when should we do it?

And how should we decide this? I think some kind of a partnership could actually – whatever. If it is competitive or pre-competitive, I don't really care. It's probably going to be competitive in some manner. But, if you could really join some companies together and maybe even do the monotherapy and add on in a big trial, then you have gained a lot because you gain much more understanding about the separate entities and the combined entities. That's a huge enterprise.

That's a huge trial that no one likes to run, but if you have four or five companies coming together maybe you like to do those kind of exercises and together we like ____ _____. So, I think those are the things we have to solve.

Allan Fox: I think we're winding up. I want to begin my thinking our final panel. I think they were superb and really hit nail and got the discussion ____ *[Response muffled by handclapping]*.

Dan Perry: And it falls to me to offer a few closing comments and that's not going to be easy for a meeting like this.

Allan Fox: Did you ever introduce yourself *[laughter]*?

Dan Perry: I'm a man no one knows.

Allan Fox: It's better that way.

Dan Perry: First of all, I want to start off by thanking all of the participants. I want to offer a special thanks to CPath Institute and Coalition Against Major Diseases for being our co-host and for participating in such an effective way. Special thanks always to you, Dr. Katz, and to the neurological products division of FDA, and all of your colleagues in the room, and those that have been in the room, and to Dr. Temple. Your willingness to come and confer with us, and to show continually your openness, flexibility, shared commitment to try to move the field forward in reasonable ways. I know a lot of this is virgin territory particularly when we're talking about combination therapy, so the phrase "it depends" keeps coming up.

But, it depends is a whole lot better than hell no *[laughter]*, so you really are showing an openness and flexibility and I know that's appreciated by everyone. Very grateful to all of the sponsors of the ACT-AD Coalition, to all of the member groups, to the staff, Cynthia Bens and Sue Peschin, for all of their input. But, my final thoughts are that we had to have the right topic and, again, thanks to Dr. Katz for suggesting combination therapies. Many months before it really started becoming the hot issue – just over the last few issues. But, while we start out with combination therapy as that implies most likely more than one company, so that leads us into multiple companies pre-competitive collaboration, collaboration period between companies.

And out of that came this discussion that I think we owe David Dilts some gratitude for sparking the idea of a super collider, super conductor type project, the Manhattan project. We certainly have the incentives in Alzheimer's disease that we had in World War II. We certainly have that sense legitimately so of urgency and there's lots and lots of precedence from tuberculosis for combination therapy, cancer for an I-Spy, for making clinical trials smarter, faster, better. We've got precedence in AIDS area where Andy Trust was set aside. And Allan, I think, even said for bird flu, the federal government created an exemption in anti-trust. Certainly Alzheimer's disease ought to be able to make that kind of claim. And this idea that is now –

Allan Fox: Baseball.

Allan Fox: In baseball. They're pretty competitive.

Allan Fox: Football.

Allan Fox: Baseball's got a _____.

Dan Perry: And now this idea of a retreat sparked by Dr. Katz saying, "Yes. I would be willing to give that kind of time, and attention, and rough ideas at least of how to create that and see who will come in." I think that brings that to a great ending point, so, Allan, this was about action. It was not just about talk. It is driven by a sense of urgency, Diane, and I'm so grateful for all of you. We'll do another Allies event a year from now. We're going to do a lot of things between now and then to try to move this process along and I consider you all part of the network. I thank you sincerely. Have a wonderful year, and holidays, and be safe on your way home. Thank you.

[Applause]

[End of Audio]