Dan Perry: This is a one-minute warning. We're about to get started. If everyone would like to take their seats. What a responsive group. It's not even a minute.

Good morning everyone. I'm Dan Perry. I'm the president of the not-for-profit Alliance for Aging Research, and also privileged to serve as chair of the ACT-AD Coalition; the umbrella group of multiple patient organizations, organizations that represent the interests of family caregivers, senior citizens organizations, women's health organizations and consumer groups and many others that is the sponsoring organization for the retreat today.

ACT-AD is actually an acronym. It stands for Accelerate, Cure and Treatments for Alzheimer's Disease. And isn't that indeed what we all are here to try to do?

The retreat that we are now engaged in – beginning – sort of at the top of the diving board for the next two-and-a-half days – is a follow on what itself was remarkable meeting of the auspices of the AD Coalition – ACT-AD Coalition – just last November. Because at that meeting we engaged the Alzheimer's community, industry, other stakeholders, government agencies on the question 'Is Alzheimer's disease, research and clinical development ready to take the plunge into combination therapy?' An approach that we know has shown great promise in other diseases, but the idea of submitting to FDA for approval one or more experimental drugs, unapproved, working in combination hitting more than one target in the disease was a rather daunting and challenging prospect.

And in the course of that two-thirds of a day meeting I was personally struck when I heard Dr. Rusty Katz of FDA and Bob Temple and others saying, "Look, this is going to take not only a scientific challenge, but a challenge to industry and developers because most companies do not have two or three compounds that they're ready to test in combination; so it almost, by definition, becomes a multi-company, multi-stakeholder challenge, and are they ready for it?

And if so, we – speaking on behalf of Dr. Katz and Dr. Temple and other FDA-ers – we would be willing to come together, be locked up in a hermetically-sealed room – and maybe we didn't quite get this hermetically sealed but we are a half-mile down from downtown DC, so this is the best that we can do.

And we would give you – what do you want? A day? Two days? Two-and-a-half days? How many of us have been able to lay claim to Dr. Katz's time for that kind of a commitment? But we now have it and here we are.

So this is an exciting, portentous meeting that has tremendous promise for advancing where we are with this terrible disease for which we've been very frustrated in recent months and years by the lack of progress coming from monotherapy.

Let me identify some of the founding members of the ACT-AD coalition who are here: Gail Hunt, who is the CEO of the National Alliance for care giving; Christine Carter, who's here representing The Society for Women's Health Research; Mark Limm, from Faster Cures; and the newest member of our coalition, the Cure Alzheimer's Fund, will be represented over the next few days by Phil Cronin and Tim Armor.

So our coalition has been brought together in 2006, and we found that the most affective way to engage the scientific community, industry, patient advocates and the FDA, is to engage in productive exchanges on areas that seem particularly ripe for discussion and possibly for adaptation.

And we have chosen these topics almost a year in advance. We chose one on clinical meaningfulness: what's the definition? How does it now apply to Alzheimer's drug development? Risk and benefit tradeoffs. We're trying to be a bridge through this coalition to the next generation of Alzheimer's therapies, and the best way to do this is not by chaining ourselves to a fence out in Rockville, but to bring the FDA together with the best clinical research leaders, with people from industry, under the umbrella of the patient community in order to get greater clarity on biomarkers and clinical meaningfulness.

And it was almost a year ago that Dr. Katz himself suggested that the topic for the fall 2012 would be precisely in this area: Are we ready to regulate and to develop new treatments for Alzheimer's disease using one or more unapproved, experimental drugs in combination. And we reached out in order to host that meeting to our colleagues in the Critical Path Institute.

Now, combination therapies have been done for many years. They've been traditionally done by taking a standard-of-care drug and adding something new to it to see if you can get an

improvement and whether it be more effective or safer or easier to use than the standard treatment. And in recent years this has branched out into unapproved drugs – experimental drugs – in combination, but not in Alzheimer's disease.

And in fact in 2012 the FDA issued a guidance that would define at a high level co-development of new drugs intended to be used together, not simply as an add-on to standard treatment.

Now, the guidance was developed primarily with oncology and anti-infective drugs in mind where the primary goals were using combined therapies in order to overcome toxicity and resistance. And at our meeting in November of last year, Dr. Temple reviewed that draft guidance for all of us and the context of potential application to Alzheimer's disease.

And we heard from both Dr. Temple and Dr. Katz that the agency is willing to be flexible in considering combination trials for Alzheimer's disease using two or more experimental drugs in a preclinical stage.

They also encouraged further dialogue with the stakeholders, recognizing the need for perhaps an unprecedented level of legal and corporate cooperation.

So the regulatory path seems open to combination therapy; however, questions remain about the scientific rationale for pursuing multiple targets. Questions also continue to arise as to the need to develop novel trial designs in order to implement, in early-stage Alzheimer's disease, that would accommodate – that could be done even given a lack of short-term biomarkers that would predict a clinical response.

So, now we're facing scientific and legal hurdles that may be unprecedented in the Alzheimer's space. And this challenge will presume a higher level of collaboration and cooperative competition. And the goal in this case with Alzheimer's is to expedite the research and to de-risk drug development.

Many of you in this room have heard me many times cite the aging of the baby boom generation. In 2011 we crossed that bright line going from 6,000 Americans turning age 65 every day – from 6,000 to 10,000 a day – that was the first day that the first baby boomer turned 65. And now at the rate of 10,000 a day they are pressing onto the Medicare roles – and while that does not doom

them to Alzheimer's disease, we know that we've got a population that is now swelling beyond almost imagination; and in the not-distant future we're going to start seeing the clinical impact of that in Alzheimer's disease and in many other diseases that are all associated with – and in fact driven by underlying biological mechanisms that we call 'aging.'

So our job now is to try to define how competitor companies can work together in what is generally called the 'pre-competitive space' to solve problems that will be of benefit to all. And we also need to recognize the need to expand our definition a bit of preclinical space beyond what we've thought of it until now.

And we have a couple of successful examples of this new thinking about pre-competitive collaboration that are specifically relevant to combination therapies that we discussed in our November meeting.

One of the examples that we heard about was in the area of tuberculosis drug development. And we will hear in a bit from Diane Stephenson from the Critical Path Institute describing the critical path to TB drug regimens – or CPTR. And we will also – we also heard in our November meeting about the role that the new National Center for Advancing Translational Sciences – or NCATS – at NIH, and how it is beginning to play a role in this area.

First, in terms of tuberculosis, we now see a growing global burden of drug-resistant strains of tuberculosis, and this prompted the Critical Path to launch their initiative in 2010. This was something that was funded by the Bill and Melinda Gates Foundation. It brings together scientists from industry, academia, regulatory agencies and global organizations to speed the development of new and improved treatments for tuberculosis.

And core to this mission is combination therapy and the application of modeling and simulation throughout all phases of drug development. And when Dian speaks to you in a moment she'll be able to tell you more about it.

As for NCATS – The National Center for Advancing Translational Sciences – that was set up just last year in 2012 to expedite the translation of new scientific discoveries into drugs, devices and diagnostics by breaking down barriers, developing new tools, and collaborating across institutes and regulatory agencies, as well as with academic and industry partners.

If that sounds familiar, that's why it's so relevant to what we're describing today.

And several of the programs that have already been developed by NCATS are relevant to combination therapies. They have developed a drug rescue and repurposing program which works with pharmaceutical companies to make both approved and abandoned compounds – those that are no longer of interest to the companies – available for research in combination.

And recently it was reported that NCATS had now assembled a library of 58 compounds that are contributed by eight companies treating such things as a no-longer commercially useful arthritis drug being used to treat chronic leukemia. So really interesting cross-fertilization here.

Another NCATS program is funded by DARPA – the Defense Advanced Research and Projects Administration – and the NIH – a Microsystems initiative to develop a tissue chip that mimics human physiology for drug development.

So CPTR – the TB initiative – and NCATS have been successful consortia in part because they developed tools that are then available to multiple stakeholders across the research landscape, and by convincing partners to share some of the data from clinical trials.

Moving forward, sharing additional data – including biomarker data – would provide extremely valuable information that could be used to build and simulate novel clinical trial models.

So, back to our November meeting again, many in the room felt that despite the challenges, the time really has come to begin to apply some of these strategies and modalities for combination therapy in Alzheimer's research.

We agreed to convene again for an intensive retreat to settle some open questions and to articulate a coordinated pathway forward to implementation in Alzheimer's.

And among the challenges today are at least two. One, how to assess the synergistic affects of combination therapies in a short timeframe in the early stages of AD; we know that that's where the action is and yet there are some significant hurdles in terms of

measurement because the clinical rate of change is very slow and how do we measure that to the satisfaction of reviewers?

And two, how do we better connect biomarkers with those clinical outcomes in phase three trials?

Now a lot of us were very enthusiastic about this, but I'll be the first to acknowledge that the pursuit of combination therapy – some feel that this is still premature, it's more a matter for the future than it is for today and that monotherapy is really the only viable option in Alzheimer's disease.

Some feel that there's not enough sufficient scientific rationale for understanding the pathophysiology of Alzheimer's disease in order to make the leap to combination therapy development.

Some also believe that the challenges to collaboration among the companies are simply insurmountable and that the best we can hope for is that an individual company will start pursuing combination therapy development within that company rather than exposing what might be viewed as trade secretes to a potential competitor. So what we hope to do now is to de-risk that proposition and see if we can articulate a way forward that addresses those concerns.

Some of these hurdles will seem daunting over the next two-and-a-half days but we also know that in the months leading up to this meeting we've experienced a willingness among many partners, in both the private and the public sector, to offer time and effort to tackle this challenge and the opportunities in a constructive way.

Coming back to us from our November meeting, David Dilts, Don Berry – experts who have seen this happen outside of the Alzheimer's space – and will be bringing their organizational know-how and wisdom to the task.

It will take courage and optimism to try something – anything – for the first time in order to work together to pave the way for what can be a transformational shift in the way Alzheimer's drug development is done.

So we thank all of you for participating. This is not just another meeting that you go to and then you get back on the plane and go to another one. This has at least a significant potential for paving the way forward for something that is truly new. And given all of

our disappointments and discouragement with the failures in phases two and three of many promising therapies, this is – reflects both our optimism, but also our sense of urgency that we have to start trying something truly new.

I want to thank two important organizations that have joined AD in co-hosting the meeting today, tomorrow and a bit of Thursday. The Alzheimer's Association asked to be part of the co-host of this, and The Critical Path Institute that also was there at the beginning back in November.

I'm going to ask Diane Stephenson, executive director of The Coalition Against Major Diseases – which is a function of The Critical Path Institute – to make a few remarks and then I'll make a few more in setting up our first speaker. Dian.

Diane Stephenson: Good morning everyone. Thank you to Dan and especially to Cynthia and Maria for their support of this meeting here today.

I stand before you in just a huge amount of gratitude for taking this big chunk of time to do something that's seen as game-changing. To me, personally, this meeting means so much. You know, I came to Critical Path Institute at a time – after 25 years in drug development – and I'm here with my coworker, Deb Hannah, who also joined me at The Critical Path Institute – also coming from Pfizer – at a time where, despite the exciting advances in being in the largest pharmaceutical company in the world, we have faced daunting challenges.

And every single time we had a drug go to patients that did make it to the market we regrouped internally and tried to get enthusiasm for the next target.

And I'm sure you remember at Pfizer their logo's around not the next target: the best target. And here we are today realizing, after yet another phase three failure just last month with Gammagard – and that was not an Abeta therapeutic; that was a different target.

How many individual targets are we going to face where we find different ways to think about this disease, because we cannot – without all of us who face the devastating impact of this disease on our families and in our lives – realize that we cannot sustain over and over again these failures. It's having a negative impact in the world and in industry and in our confidence for getting targets for these patients that are in need.

So what I want to say is this is why we're here today. We have to figure out different ways of thinking about tackling this disease.

We heard – a lot of things have happened since we met last fall. There have been phenomenal advances in the regulatory science. I stand and commend Rusty Katz, who sits in the back and very humble as he always is, for the transformational work that he's done: it was really his idea to gather, even last fall, and here we are today, at a time when you're going to look back and realize this is very game-changing in terms of your role in advancing or understanding in the regulatory space and in the field.

Since we met last fall there have been two new guidances put – draft guidances – by the FDA: one on the recognition of enrichment of clinical trials – not specifically for AD, but clearly with the recognition that we need to think more about patient stratification and target patient strategies like we do in oncology. And also commend the agency for their work on early AD guidance – Nick Kozauer is here as well – again, showing that regulatory recognition of the sense of urgency and it needs to pave the way thinking through things like accelerated approval. This is exactly the kind of thinking that we need to foster.

In addition to the regulatory advances, we heard one of the most exciting presentations at the ADPD meeting in Florence recently with a presentation by Roche showing that a combination of their amino therapy for Abeta, in addition to their BACE inhibitor, pre-clinically showed additive affects; again, fostering this concept of combination therapy – which here also sitting with us is Reisa Sperling, whose championed the idea of augmenting Abeta reduction for – particularly for prevention.

So all of you have made phenomenal advances in your ideas, and that's why we're calling on you here today.

We also learned at that meeting that there's huge gaps; not everyone was on board with this concept and suggested some of the issues and challenges that are facing this field. We need better animal models, we need better targets, we need to understand the disease better, we need better biomarkers, better outcome measures. Yet, despite all these challenges, we ask all of you to find ways to share what thoughts you have and how we can tackle this problem.

So what are the solutions? How do we think through this?

Well, we have to collaborate. We have to expand the pre-competitive space and look to the success of ADNII to find ways that really enable success through sharing knowledge, learning from the failures and fostering this idea of public/private partnerships.

So, I have the pleasure to lead a large pre-competitive consortium – Coalitions Against Major Diseases – that was founded many years ago with the visionary leadership of Ray Woolsley, Rick Meyers and the agency in how to think through novel, innovative ways to advance through formal regulatory path drug development tools that will accelerate the treatments for both Alzheimer's and Parkinson's disease.

And in this consortium we bring together diverse stakeholders – many of you in this room – industry, government agencies, patient advocacy groups – Cynthia and Maria, who work with me – with several other of the patient stakeholders that are here today – to find ways to convey a sense of urgency and expanding the pre-competitive space for these drug development tools. And on our teams are the experts of the FDA and the EMA who also help shape the way forward to these novel approaches.

I'll just show this slide just briefly because at the time that this concept was raised several years ago, many different stakeholders said to us, "If you think you're going to be able to get all the companies to share data together and make that information publically available, you might as well go home." And even people after the meeting last fall said, "Good luck." But, it's possible.

So today I share with you that we now have a large unified clinical trial database from now 24 clinical trials of over 6,000 patient studies now available for qualified researchers to access, to pose research questions about what we can learn from this disease based on what's been done in the past.

This database was not just put together to have fun and have big data because the people in Tucson are great and a lot of our leaders at C-Path worked at IBM and know how to do this; but it was really to answer a research question. And this database was put together to come up with the first modeling and simulation tool that has been advanced for a formal regulatory decision with FDA and both EMA to enable improved clinical trial designs to simulate how affective one can be in designing trials for the future with

accurate estimates of numbers of patients in duration based on what we know from the past.

So when people come to you and say this isn't possible, what we want to do is glean upon these examples where clearly we were able to find a way. And again, it's through the pre-competitive consortium collaborations that made this possible.

So, CAMD – Coalition Against Major Diseases – is one of seven consortiums at Critical Path Institute. And, as I said, I'm joined here today by my colleague Debra Hannah, who leads our tuberculosis consortium that you're going to learn a lot about at this meeting. Core to their mission – as Dan said – is combination drug development for the purposes of treatment of tuberculosis.

I'm not going to have time right now to tell you more about it but I am grateful to Debra and her support and also the Bill and Melinda Gates Foundation for recognizing the fact that if you really want to do something this transformational it really does take resources and commitment to make this possible.

And by this example we're going to learn about how innovative approaches such as modeling and simulation have enabled that consortium to be successful.

So what are our goals for today? Well, they're diverse and they also ask that all of you put your thinking hats on, think outside the box and find ways to share your ideas of how to make this meeting successful.

The goals are to convene all of you as experts from your own perspectives to find a way to come up with identification of how we can mitigate the challenges and scientific risks.

The regulatory path is key and I want to congratulate and acknowledge our experts from FDA and EMA who kindly, graciously offered to spend their time to help us in this meeting – again, identify the challenges and ways to mitigate that – and think about new, innovative approaches and learn from our other diseases so that we can be successful, think outside the box, have fun and learn from other platforms, and again, expand the pre-competitive space so that we don't reinvent the wheel and we can work together to help advance our understanding of this disease.

So thank you so much and I look forward to today and this meeting.

[Applause]

Dan Perry: Thank you very much Diane. Maria Carrillo, who is the vice president for Medical and Scientific Relations of the Alzheimer's Association will be arriving a little later this morning. And – oh, she's here; very good. Maria, welcome. I didn't – fast plane; I'm glad to have you here.

Maria will be opening tomorrow's session by recapping some of what we're able to accomplish today. I also – in addition to Maria – I'd like to extend our thanks to her colleagues – Heather Snyder and Dean Hartley – who are also here now and will be participating in this retreat over the next two-and-a-half days.

There is also one other big, big thank you – in fact, if there's any one person that probably we owe all of the hard work in identifying the speakers, inviting back old ones from November and adding new ones, designing the program and doing all of the heavy lifting, it's Cynthia Bens, who is the vice president for public policy at The Alliance for Aging Research, and she deserves a big thank you from all of us. Cynthia Bens.

[Applause]

Dan Perry: And before I introduce the first presentation – speaking of a person who is absolutely essential to all of this, and has been to all of the ACT-AD Alzheimer's Allies meetings going back to 2006 – and that's Dr. Katz. And to Rusty Katz who is now preparing for his well-deserved retirement from The Food and Drug Administration after many years of service, that he is giving us this tremendous access to his time and intelligence over the next two-and-a-half days – Rusty, thank you, so very, very much for being here and being part of this.

[Applause]

Dan Perry: And that appreciation extends to all of the FDA reviewers and staff and other officers who are all here.

All of us who work with patients and with their families, all of us who are devoted advocates for breaking through the barriers and the hurdles that face us in our war against this terrible disease; we

appreciate very much the work of you, Dr. Katz, and your colleagues at FDA. Thank you.

I also want to recognize those that are joining us but not visible: Maria Isaac of the European Medicine's Agency and Gabrielle Strobel of the Alzheimer's Research Forum; and they are joining us remotely, take my word for it.

Many of you probably read Gabriel's excellent three-part series that was initiated following our November meeting. I think she did a magnificent job, both for interested lay public and those that are the scientists that are pursuing our goals – did a wonderful job. And that was in AlzForum following that meeting.

In terms of today's format we're going to have a presentation followed by a panel discussion, and at the panel we'll ask all of you to participate actively. Please do not stand on formality. We have a microphone at the room. This is all being recorded so I do ask that any questions go into the microphone, and because all of this will be captured and we will publish the proceedings, please give us your name and your affiliation.

This afternoon we're adding two working groups to allow additional opportunities for you to make your voices heard and to come up with recommendations on the steps that are necessary to achieve combination therapy development.

These sessions will also be recorded, but that's not for publication; it's so that our co-chairs and chairs who are writing the chapters will be able to have access to the richness of the dialogue that takes place in those breakout sessions.

And for these to work, again, you can't stand on ceremony. We really need you to roll up your sleeves, speak candidly, engage on the issues and – both here at the microphone and later at the breakout. These are being audio recorded, as I say, for a summary, so that will be helpful.

Finally, we have a scheduled break at mid-morning and again with lunch at 12:30. But it's a long day so please help yourself to the facilities outside as needed. And there will be refreshments over the course of the retreat in the foyer.

We do have Wi-Fi available in this room. It's now up and running. If you heard earlier that it's down – no long operable – it's

working. And just see the registration table for details on how to log on.

Now, I'd like to introduce our first presentation, but again, a little more context.

Consensus among scientists is that Alzheimer's is indeed – there are many multi-molecular, biochemical and cellular pathways that converge in order to produce the disease. It appears that Alzheimer's is not a single disease, much as cancer and some others, but rather a spectrum of neuro disease processes that manifest as a trajectory across a lifespan and are exacerbated by other conditions associated with aging, such as diabetes and cardiovascular disease.

And while this complexity offers multiple possible therapeutic targets, it also increases the scope of the effort that's required to find the solutions.

So since the rationale for combined therapy in Alzheimer's is to target multiple pathways simultaneously, and since matching treatments with specific targets requires biomarkers and – in order to improve trial efficiency – it will require the development – we need new biomarkers and new target engagement biomarkers as key to identifying the proper dosing for combining therapies.

And when we spoke to our colleagues at The Alzheimer's Association and The Critical Path Institute, who can open up this discussion, give us the appropriate breadth and complexity, but also have a clear vision of how to thread the needle through all of this, the one name that came up again and again is Dr. John Trojanowski.

John is well-known to many of you in this room. He's the co-director of the neurodegenerative disease search unit at the University Of Pennsylvania Medical School; he's the director of the University Of Pennsylvania Institute on Aging; and along with Les Shaw he is a co-director of the Core Center for ADNII, the Alzheimer's Disease Neuro Imaging Initiative.

John Trojanowski and Virginia Lee have been pushing all of us for years to look beyond the status quo. He's also a vocal advocate for patients and their families. I'm proud to say that John is a member of the science advisory board of The Alliance for Aging Research, and a long-time friend to many of us.

Unfortunately John and Virginia could not be here today, but we did manage to catch John between international trips to capture some remarks. So, we'll be kicking off today's discussion – and with that, I hope to be able to pull it up with Michael Maroni's help. There we go.

By the way, this was one more chore of Cynthia's was to go up to Philadelphia and corner John with a handheld camera and get this.

Okay. Houston, we have contact.

John Trojanowski: Well, I thank Dan Perry for giving me this opportunity to speak to the group today. Unfortunately another commitment prevents me from being at the meeting in person. But this is a most important topic – combination therapy – and both Virginia Lee and I have made a number of proposals on how to combine different types of immune therapies for the treatment of Alzheimer's disease. And I use that as an example for how public/private partnerships could form to accelerate the pace of drug discovery.

We all know there is no disease-modifying therapy for Alzheimer's disease. It's the only disease in the top-ten list of most common diseases or killers of people in the United States for which there's absolutely no disease-modifying therapy whatsoever. We have symptomatic therapy, but the goal now is to find disease-modifying therapy.

As many of you know, Virginia Lee and I have long advocated for the pursuit of multiple drug targets to develop disease-modifying therapies for Alzheimer's disease. As all of you know, of course, the Abeta cascade hypothesis has been a dominate hypothesis for many years for a number of good reasons, and it has been the focus of drug discovery, again, because of the availability of model systems, because targets to either clear Abeta plaques or prevent the production of Abeta appeared attractable; and amazing progress has been made in preclinical studies to advance those targets to the point where a number have gone on to human clinical trials.

We're all aware, however, that none of the Abeta targeting therapies has succeeded so far. There's many, many reason for that. The Abeta cascade hypothesis could be flawed on some way of course, but it's also likely that the recent failures of Solanezumab and Bapineuzumab may be attributable to the fact

that the disease has progressed too far in mild to moderate Alzheimer's patients so that clearing plaques may not be effective.

Indeed, the post-hoc analysis of the Solanezumab data did show a modest affect in patients with mild Alzheimer's disease; so this has encourage Eli Lilly to launch another clinical trial in mild Alzheimer patients to determine if indeed there will be a more robust effect in that subset of patients at an earlier stage in the disease.

We're also aware that prevention trials are being planned and that may be the point of the disease where the greatest efficacy will be seen by any drug, including a drug that targets Abeta.

So the landscape of therapies one can pursue for Alzheimer's disease is very broad and diverse. I've just mentioned Abeta Tau; Abeta is the peptide that forms plagues. As we all know there's mutations in the APP gene that encodes Abeta and there are mutations that alter Abeta processing, all of which have created opportunities to understand mechanisms of Alzheimer's disease better, and of course develop model systems and do preclinical testing of disease-modifying therapies that affect the Abeta cascade.

Tau is the protein that forms the other signature lesion in Alzheimer's disease; so Alzheimer's disease, as we all know, is characterized by abundant plaques and tangles, and Tau is the protein that forms the filaments that accumulate in neurofibrillary tangles and neuropil threads.

And we've long advocated that Tau is a target that should be aggressively pursued, and indeed, many others have too – not just Virginia Lee and I – of course, as we know, with the setbacks and/or failures of clinical trials of Abeta therapy, the rationale for Tau-focused drug discovery has increased. And indeed, I think the meeting you are all at today is considering the use of multiple therapies – combination therapy – for the treatment of Alzheimer's disease.

One could conceive of many other targets that are emerging from GWAS studies. ApoE4, of course, has long been a target. The ApoE4 allele, is – as we all know – increases the risk for Alzheimer's disease in a dose-dependent way, so somehow modifying that risk through targeting ApoE is of course another compelling target.

There's neuro inflammation in the brain of Alzheimer's disease patients, which also could be a substraight for disease modification. And I could go on and mention many other potential therapies.

In referring to some of the targets that I've mentioned – and I do want to emphasis that in order to be able to translate information and understanding about disease pathways into therapies we have to have that understanding, and there are many more GWAS hits, for example than there is information or studies about how these hits relate to mechanisms of Alzheimer's disease.

There are obviously neuro-inflammation pathways, therein cholesterol pathways, but we need far more detailed knowledge on the biology – the normal biology – of the hits that have come from these genetic studies as well as their possible roles in disease. And there just is inadequate funding for this kind of basic science, as well as inadequate funding overall for the translational science to take the targets that we know we – are tractable and advance the science to the point where those targets can be attacked in living patients with drugs that will be disease-modifying.

The point is that I think we are at a place in time in thinking about drug discovery for Alzheimer's disease where we need to pull out all the stops. This is an epidemic like no other – Alzheimer's disease – and I consider it the worst natural disaster that we, as human beings, will ever encounter.

I'm not going to review all numbers of patients and the cost to the economy; I think we all know that. But there is no other threat, I think, to our civilization that looks as ominous to me as the epidemic of Alzheimer's disease.

I'm mindful, of course, of wars and famine and so forth, but this is truly a disease that affects people globally and there is no escaping Alzheimer's disease as our population ages. The alternative to not aging, of course, is death; and none of us feel that's a very appealing option. And we also know that longevity continues to increase, so there will be more Alzheimer patients far into the future unless we find a way to stop the disease now.

The disease goes up in prevalence, as we know; it doubles every five years after age 65. And it's a very poignant observation of demographers that babies born in this millennium stand about a 50

percent chance of living to be 100. We know that by age 80 about 50 percent of people who attain that age, or survive beyond it, will develop Alzheimer's disease. We don't know if the prevalence continues to rise after age 80, but it is fairly frightening to contemplate increasing numbers of people living beyond age 60 – even beyond age 80 – and facing a 50 percent chance of developing Alzheimer's disease.

So, the notion of combination therapy is not new of course. It's used in cancer, it's used in AIDS; there's many examples where combination therapy has proven to be successful.

And indeed Rusty Katz of the FDA has recently contemplated the possibility of combination therapy. And I think all of you have probably read the AlzForum summary of the Alliance for Aging conference that was put on by Dan Perry with Rusty Katz and others to discuss this new turn in Alzheimer's disease therapy – that is combination therapy.

I think embodied in this whole discussion is also the need to think about new ways to pursue preclinical drug discovery as well as clinical trials. And what I'm referring to is the type of public/private partnership that I've seen flourish so wonderfully in the Alzheimer's Disease Neuroimaging Initiative, where pharmaceutical companies, foundations, academia, the NIH, have pooled their resources and have parked their egos outside the door, if you will, to enter a pre-competitive space where the most rapid progress in biomarker development could occur.

This program began in 2004, and I think it is the poster child for the success of a public/private partnership that is changing our understanding of Alzheimer's disease and changing how we'll do clinical trials because of the availability of biomarkers.

So we need the exact same approach for drug discovery now, I believe. There just aren't enough resources on the planet for each company – each entity – to work in private and in secret to advance drug discovery for Alzheimer's disease and make the same mistakes multiple times in a way that none of us are aware of those mistakes, aware of the failures as well as the successes.

So if we could come up with a public/private partnership along the lines of ADNI what would it look like? I'm not a lawyer and I'm not from the corporate world; I'm thinking – as I speak to you now – about how best to accomplish our goal. And it takes no

reminding anyone that the goal is cure; the goal is disease-modifying therapy.

So let me use my example of immune therapy. If we were to conceive of immune therapy as the greatest opportunity to shut down the major pathologies of Alzheimer's disease what we would need to do is not just have antibodies to Abeta and to Tau; we would also need antibodies to _____ and the protein called TDP-43. Recall, Alzheimer's disease is heterogeneous; 50 percent of Alzheimer patients also have Lewy bodies; 50 percent of Alzheimer patients also have TDP-43 inclusions. So we could design antibodies – different antibodies, obviously – specific to pathological variants or species of each of these disease proteins and reconstitute them in an infuscate that would then be delivered so that people would receive multiple antibodies to each of these different disease proteins.

This is what IVIG is all about, as you know, except the antibodies there are not designed to be optimal re-agents to block progression or clear the pathologies that I just mentioned.

So if we were to form a partnership we would be begin perhaps with a massive campaign to generate the needed antibodies, learning a lot, of course, from what has already been done with passive immunization with Abeta. We know there are antibodies that work better than others, perhaps due to the confirmation, the pathological species of Abeta they recognize rather than affinity for an epitope, but we don't know all of the factors that figure into making an anti-Abeta antibody the most optimal to clear plaques.

If we shared this information in a public/private consortium we could extend it to the production of antibodies to Tau, to the production of antibodies to synuclein, to TDP-43 – and this could be done in industry and in academia; we could pool our resources, our efforts and our knowledge to generate the world's best panel of potentially therapeutic antibodies to each of these four disease proteins.

We also could reinvent the animal models that we are going to test the antibodies in by taking advantage of the recent, exciting discovery that the disease proteins that I've just mentioned appear to spread from cell to cell; they are transmitted in a prion like manner from one cell to another. Alzheimer's and Parkinson's do not appear to be infectious. I won't go into all of the data on that but Dr. Irwin at postdoc in our laboratory reported earlier this year

in *Archives of Neurology* very compelling evidence such as one can marshal from studies of subjects who were treated with autopsy-derived pituitary extracts for growth hormone that there was no incidence of Alzheimer's disease or Parkinson's in this cohort of subject despite the fact that pathological Tau, Abeta and Alpha-synuclein can be found in the normal as well as the Alzheimer and Parkinson disease of a neuro hypothesis and amyloid hypothesis.

So what I think we could go on to do then is – both in industry and academia – optimize the animal models that we would want to test these new antibodies in. And we have transmitted Tau pathology in a Tau transgenic mouse before it would normally develop Tau pathology due to the trans-gene through the use of preformed Tau fibrils that are sonicated to form little seeds that facilitate their entry into cell and their spread from neuron to neuron in the brain.

We've begun to immunize these animals with some of our own antibodies and are seeing signals of efficacy – I'm not going to go into any details on this – but others have certainly published papers demonstrating that passive immune therapy using Tau antibodies can indeed slow down the progression of a Tauopathy in a mouse model.

Similarly we've done – we've taken the same approach to transmit synuclein pathology, and we can do that both in synuclein transgenic mice as well as wild-type mice: and here too, we've begun to immunize our new model system for synucleinopathies with antibodies that we've produced.

But what we could do very quickly if we collaborated between academia and a pharma is to test out multiple different approaches to optimize these model systems to find the most affective test system, if you will, for evaluating efficacy of single antibodies. And then of course we could take triple-transgenic mice that express – over-express synuclein Tau and mutant APP to see if we could take an infused egg that has antibodies to each of these three disease proteins and if there would be an affect on slowing progression of disease – or blocking progression of the disease or slowing the progression of the disease.

Of course there is no mouse model yet that has a Tau, synuclein, Abeta and TDP-43 pathology, but of course that would be on our to-do list in this public/private partnership.

It's also important to emphasis how critical it is for studies to be replicated. This is increasingly discussed at multiple levels of the NIH, among academicians, and certainly in the pharmaceutical company. We know that if a result only can be obtained in Philadelphia at Penn it's not a good result. It's got to have scalability, it's got to have generalized ability, and again, the only way that this can be done is for multiple people to replicate each other's work, and this should be done in the fastest, most expeditious and well-planned way feasible to get us to the beginning of the next stage in the development of combination therapy, and that would be designing the clinical trial and determining at what stage in the disease we should launch a clinical trial, should it be a prevention trial, should it be in mild Alzheimer's disease?

So this is an example of a drug discovery strategy; one that I think is easy to understand – we've already seen efficacy of passive immunization with Abeta antibodies in clearing plaques – not clinical efficacy – but the ability to do this in animal models, to clear plaques in animal models and in people; and where we need to get to now is to demonstrate clinical efficacy and hopefully that will come from the clinical trials that I mentioned that are prevention trials and the new Solanezumab trial in mild Alzheimer disease. But we've got to get on as quickly as possible to also add the other antibodies that I've mentioned.

And, again, this is just one example of a combination therapy program that we could launch today. We could launch it today if the people in this room all looked around the room at each other and said, "Yes, we want to do it. We can do it. And we will do it. Because this is what our patients need, this is what our country needs. This is really a global problem that the people of the world need."

So let me just close by again thanking Dan Perry for the opportunity to be present at this meeting through this video. And I applaud all of my colleagues who are there working so hard to find a way forward, to develop combination therapy, and hopefully through the vehicle of a public/private partnership, which I think is the winning solution, the winning way to find disease-modifying therapies for Alzheimer's disease. Thank you again.

[Applause]

Dan Perry: Well, you can see that we were not led astray; that John was the perfect person to lay out the entire menu, to point out some very recently-published research, some research that's still underway, give us some examples of private/public partnerships: so John's done a wonderful job with that.

At this point we're going to have a brief break – about 15 minutes – and when we come back our first speaker is going to be engaged with our first panel discussion. And please come back on time and we'll get underway.

Again, thanks to all of you for being part of what we hope will be an historic meeting. Thank you.

[Part 2]

Dan Perry: One minute warning. Please move to your chairs. I'm going to ask our panel to get ready to take their seats. Thank you all very much. It gives me great pleasure to introduce our first panel that will be chaired by Dr. Reisa Sperling of Brigham and Women's, and it will include Dr. Katz, Steven Potkin of UC-Irvine and Don Berry of Berry Consultants. Take it away Reisa.

Dr. Sperling: Great. Thanks very much and it's really exciting, actually, to come back after last year because when we started to talk about combination therapy I got really excited. So we've actually – our group was given a very somewhat generic title to talk about, but we got together and decided we would really focus on giving the expertise here on clinical design. So Cynthia asked me to set the stage. I'm going to start with just a couple of slides really quickly.

So I think John Trojannowski already went through this issue of the rationale for combination therapy, but I do want to point out one issue when we talk about the challenges, which is if we really are still convinced that at least for some mechanisms of therapy we have to go early in Alzheimer's disease, some of these issues of challenging trial designs are gonna get even tougher if we're talking about earlier stages of Alzheimer's disease clinically.

Again I ultimately agree we absolutely need a beta and tau and neuro protection, but I think while we're waiting for some of these drugs to come along we may start with rational combinations that we may already have in hand, including even within the A-beta space. And we can talk a little bit about that in our panel. So I just want to say every time I'm on a panel or I hear Don Berry talk I

get all excited and I go home and I start dreaming about how we could build an ISPY 2 for Alzheimer's disease. Last November in particular, I went home – or even before that – and started getting excited and came up with the acronym, which is the most important thing in building a trial, which is COMBAT: Combination Alzheimer Therapy.

But then I went back and started to talk to my colleagues, Paul Aisen and others, who were a bit of a naysayer of some of the challenges and how we would build an I Spy-like design. So I hope our panel is really gonna tackle those today. So though there's a lot of parallels with cancer in Alzheimer's disease and being a long disease that has a presymptomatic phase, there are some challenges in using adaptive designs in the same way that is done in ISPY 2 in Alzheimer's disease. And in particular, there are three I'm going to highlight which are what we'll talk about today in our panel.

One is how do we assess signals of efficacy in a short timeframe in Alzheimer's disease, particularly when we move into earlier stages of AD. And then some, which have already been discussed a bit, how do we send companies to work together in a very highly-competitive space, because I think when we're in clinical trial design we're no longer just talking about pre-competitive, we're talking about competitive collaboration, and especially how we're going to resource a large-scale effort in the current fiscal environment.

So I'm a very practical person. I love coming to these retreats, but I have to admit I'm getting a little retreat and summit fatigue because I feel like we keep coming up with great ideas and we haven't been able yet to really translate them into action and to operationalizing these ideas. So I'm gonna be very specific. So I think the first challenge in terms of finding signals of efficacy, again we need a read out in a very short timeframe if we're gonna take full advantage of Don Berry's kind of adaptive designs and I think there are some challenges here, particularly biomarkers.

It would be fabulous if we had a biomarker that could tell us in three weeks, three months or even six months that was predictive of a clinical outcome, that would be great. But we've done a lot of our biomarker development separate from trails and I think we need to embed the biomarker development into these trials so we can ultimately predict longer-term response. Similarly we need better clinical measures, particularly going earlier in the disease

process when there's a very slow rate of decline. We need dynamic cognitive markers.

I don't know whether computerized tests can help us do this as something we're working on, but other ideas of how can we see a short-term change that will predict long-term clinical disease modification. So the second challenge, again, is this incentivizing cooperation. I've learned sadly that companies don't just want to work together because it's the right thing to do, and so I think we have to build something that they all want and so that they'll be banging down our door to come and be involved in these combination therapies.

So one is to build multiple animal model access. This is something all companies need. We want to test drugs in multiple models simultaneously and offer this if companies are willing to give us their best therapy. And then I think we need to build a cohort of well-characterized subjects in whom the biomarker status and genetic status is already known so that they're ready to enroll very rapidly because the bottleneck and expense for companies is starting up each of these trials on their own. So if we could build this and get it ready to go I think that would incent companies.

We'd also provide access to cutting-edge tools for assessments and biomarker cognitive and statistical expertise that companies often have to outsource to get additional help with. And importantly – and this goes to Rusty – that we hope that we could offer open communication with regulatory authorities. That this would be a way, in a consortium, that there would be a very good cross talk and this would be an incentive for companies.

And then finally, this challenge of resourcing. It's very tough right now, as I'm sure you all know. Some companies pulling out of the central nervous system all together, and the NIH with a budget sequester. But we've also seen some positive movements with public and private partnerships, not only ADNI, but now in clinical trials with A4, DIAN and API. And the sense of some shared risk with multiple companies contributing may actually offset this concern that CNS and Alzheimer's disease in particular is too much of a risk to go into.

Philanthropic. My colleagues in philanthropy very much like to see us working together, so I think if we can have evidence of cooperation this will help philanthropy contribute. And finally I'm just going to end with this before we open up to the panel that I

think we have to think big – even bigger than we're thinking now. I think building a COMBAT cohort of 10,000 individuals is not too big to be thinking about ready to go. Alzheimer's disease is a big problem. And finally I was just on the Hill last week and so I have this down as my mantra, but it's really amazing to me.

Federally, in terms of all federal resources, I understand we spend less than one percent every year on research of the annual cost of dementia. So we could fund a COMBAT cohort with one percent of the annual cost of AD research, which is estimated at 200 billion. So we have to think big, but it's not that big. All right, so here are some questions that we talked about for you guys to think about. I don't know if you want to each go in a row or whether we should just have a more open discussion.

So the first is how can we actually develop an ISPY 2, so phase two trial designs for AD combination therapies that will tell us which of the combinations to take forward into phase three? And if it's not possible, because we've had previous ACT-AD meetings about how difficult phase two is in Alzheimer's disease, could we develop seamless phase two/three designs using adaptive features early, but then transition to a registration trial design. This is a question especially for our regulators.

And again I think there are other avenues on this, but I think at the end we need to figure out in these trial designs how do we make them attractive to get companies started working together very early for safety data phase one, even into phase two. So I'm going to stop there and who wants to start? Don, why is it we can't build ISPY 2 or COMBAT today for Alzheimer's disease, or can we?

Dr. Berry: I think you can.

Dr. Sperling: How?

Dr. Berry: Should I say a little bit about what ISPY 2 is? ISPY 2 is a trial that's funded by the Foundation for the NIH. Now is moving into a nonprofit sponsorship with Quantum Leap. It's a platform trial. It's a trial where drugs come and go and it's a screening process in phase two to evaluate the effectiveness of individual agents with the standard therapy – this is at _____ breast cancer – and combinations. And as opposed to – there is a neurology, this notion – at least I've heard it from neurologists – of cancer ending as though things are done wonderfully in cancer. I have news for you, they're not.

I mean if you look back in the 1970's, we did combination therapy, but we would do things like comparing CMFVP – five drugs against four different drugs, VATH, in breast cancer – and conclude that VATH was better but we had no idea why. This is to try to understand why and to build a drug development and combination development program where different companies are contributing their drugs. And they're contributing really good drugs. We have eight regimens – experimental regimens now – with five companies contributing drugs.

These are experimental drugs. Merck is one, AbbVie – formerly Abbott – is another, Merck, Amgen and Genentech, and there is a single control which is, you know, before you do anything clever, just having a process that has high quality data, you understand what the patients are and you're comparing against a single control. There's an economy in that process and companies are playing together. It's not like there's a whole new world out there, but there is a different attitude. And if I might say, the impetus in breast cancer, although different in Alzheimer's, is still a – to use Reisa's word – incentivation or to incentivize.

They're incentivized because in breast cancer we've had so many successes that the events are very long in coming, so we are now running, in adjuvant breast cancer, 10,000 patient trials. This is not sustainable. Companies are not doing it. The number of adjuvant breast cancer trials that are ongoing is – you can count them on one hand. In Alzheimer's, the other incentivation, the reason to get religion, is the failure in phase three, which is well documented that the last 20 phase three trials failed. This is the worst place to fail because it it's so expensive.

So ISPY 2 is working. Companies are interested. There was a good bit of hype associated with the trial early on which got people to – this has to be the way to go. So I think there is an aspect of doing it right and in Alzheimer's, the big deal – the big difference, although not insurmountable – is the early end points. And biomarkers, just a word about that. We talked about surrogate biomarkers. We talk about validating biomarkers. It's probably the enemy of research. We can incorporate biomarkers that we hope are correlated with the longer-term end points, and in the trial itself see whether or not they are predictive.

If they are, we get to use them and if they're not then we're back to the same situation that we were if we weren't considering the

biomarkers. So let's have a panel of biomarkers that we're entertaining and we're doing some confirmation throughout. In the combination realm we're doing factorial designs within the context of an ISPY 2-like program where we do adaptive randomization. If it turns out that the early indications are that the individual agent is not doing as well as the combination, you start to focus on – and indeed could drop the single agents and focus on the therapies that are doing better – the advantage of doing an adaptive design.

So it's completely possible and we need somebody like the people who are sponsoring this to take the initiative to get funding. CRO's are very interested in this and indeed I'm working with two major CRO's in other diseases that are subsidizing the process because they see it as the way to go. They see it as the pharmaceutical industry model is not working. We're going down the tubes and taking the economy of the country with it and something has to be done.

So I think ISPY 2 is not the final answer, but it is a step in the direction. You've got to experiment with experimenting. You can't do the old-fashioned thing and keep failing. Let's try other things. The ISPY 2 concept is one of them.

Dr. Sperling: May I just ask how long that readout is in ISPY 2? So not just the biomarker, but what's the length for decision making time in phase two in breast cancer?

Dr. Berry: So in adjuvant breast cancer the problem is that we take the tumor out and we don't have a reading for whether or not there is a tumor issue until it comes back, which is long in coming. Neoadjuvant reverses the process of delivering therapy in surgery so that you leave the tumor in and you pummel it with various therapies and the endpoint is pathologic complete response at surgery, which is six months later approximately after you randomize. So there's pretty early information.

A neat thing, since we started ISPY 2, the FDA has a guidance on using pathologic and clear response at surgery as a part of a registration pathway, so you can get accelerated approval on the basis of it. So it's pretty early. Interestingly however, it's not early enough for me and so what we do in ISPY 2 is we model the tumor size by MRI and we do predictions within the individual patient. MRI itself is not a surrogate biomarker, but it's helpful. It's predictive, recognizing the uncertainty in the prediction, and it's like MRI in other things in Alzheimer's disease that could be

modeled as to their predictive ability within the individual patient as well as predicting where the study itself is going.

Dr. Katz: Yeah, a couple of things. The idea that you can model, or that within the trial itself you can "valid" or see whether or not the effect of the biomarker has predicted the clinical, it might be trickier here – particularly as everybody moves to earlier and earlier patients, so trying to correlate the outcome or predict the outcome from the basis of effect on the biomarker – may be – and we have to think about that – but it might be problematic.

On the other hand, if we're talking about six months and we have very sensitive cognitive measures, for example, which would certainly be plenty good for this purpose to see whether or not the biomarkers are useful, it's also, I guess, possible that in sort of an early phase two I Spy kind of a design or adaptive design, it may not even be necessary. I mean if we think we have an understanding of what the mechanism of action is and if – if, if – we have a biomarker that we can see and move in on in some reasonable period of time, it may not be that critical to know or to learn within that study whether or not it predicts the clinical outcome.

Again if we had that data it would be great, but even if we didn't, it might still be a very useful way to identify compounds or combinations of compounds to take forward. From the point of view of – just sort of generically from the point of view of adaptive designs, and certainly in sort of phase two, whatever that is, we're wide open to that. We don't see them very often. We're starting to see some sort of rudimentary types, but we haven't seen anything I don't think that really is novel, at least in our field, certainly from trying to figure out which drugs to take forward.

We're wide open to that once we start getting into seamless sorts of things, we think long and hard about those. There are some where we're perfectly fine with those, but that's where we get a little skittish, it's been my experience. But certainly for trying to identify combinations – dosing combinations of particular drugs – I think that's – we are wide open to looking at that.

One other point I want to make – a number of points – but just briefly I have heard in previous conversations about developing combination treatments, and I've heard this from pharmaceutical company representatives, and of course I have no idea how that works. But what I hear is that there's a view that one of the

combinations has to be developed up to some certain point where people are confident in that sort of thing and then we can move the second one along. These are comments typically from within one company.

So I think we ought to be thinking about developing a combination from day one. That includes the animal studies. The animal models, that's complicated, but on the other hand I'm not even sure – well, from a regulatory point of view – the animal models' effectiveness are not particularly critical. But it would be great to have an animal model that was a perfect reflection of the human disease. Of course we don't have that, but if you had independent animal models where you had a model of inflammation or a model of degeneration or a model of ____ or a model of synaptic function, even in the panel you had independent drugs that worked in those independent models, I don't know how critical it would be to have a model that incorporates all of those changes.

So I think that's something we should be thinking about much, much, much earlier in the development. Again that could be a naïve point of view, and I don't know how it works inside companies. I had one question for Don. When you said in ISPY 2 that companies are playing well together, what exactly does that mean? *[Laughter]* No, so we have ADNI. The companies are playing well together but they're not sharing any data. They're sharing placebo data, but they're not sharing information, I don't think, about the drug – about the –

Dr. Katz: Right ___drug. But my question is are they sharing data about drugs – I mean data that typically companies wouldn't share? Because my vision is you identify a compound and as I say, you develop it in combination on day one but it would be a lot easier to do that, I suppose, if as they say Macy's talked to Gimbel's. I'm wondering what are they sharing? What does that mean?

Dr. Berry: They're sharing data. The way ISPY 2 works is that we control the data. The ISPY 2 team controls the data up until the time the drug graduates. The drug graduates means it has a high predictive probability of being successful in phase three and we, at that time, because patients are still being treated, we don't announce to the world but we do tell the company who is the sponsor of the experimental arm what the predictions are.

Six months later they get the data and there's a six months lag. Six months after that, the data becomes publicly available. So it's not only the control arm it's the actual arms. So if you have a PARP inhibitor, you don't have two PARP inhibitors. We have one PARP inhibitor. The other – but some companies who have PARP inhibitors have actually contributed funding to the trial. So they're going to get the answer to the question, but access to the data.

I don't mean we're going to put it on the web for everybody in the world, but it is on the web and you can get permission to go in through the ISPY 2 team. So it is really sharing data in an important way.

Dr. Katz: At the individual level?

Dr. Berry: At the individual level.

Dr. Katz: Yeah, that's great. My vision would be Company A identifies a compound that acts on a particular pathway that's known to be effective in Alzheimer's disease. Company B has a compound which acts someplace else. From day one, they say look I have this, you have that, let's work together. Maybe that's incredibly naïve, I don't know. But to me it has to start there.

Dr. Sperling: I don't think that's naïve. I'm going to be very specific now, partly because there are, at least in the A-beta world – so pairing a beta secretase inhibitor with an antibody, maybe one that's going after aggregated, that seems – most people think that would be a powerful one-two punch for a beta. That's not everything, but it would be one. And there are some companies who obviously had this within, however for an academic kind of consortium, we want the best beta secretase inhibitor and the best antibody and they may not be from the same company.

But why can't we start that now? Especially again, the question is at least get some animal safety data going and – why is that naïve?

Dr. Potkin: It seems like the ISPY program, in fact there's different compounds that are being tested against a placebo group, thus not exposing people unnecessarily to compounds' faster turnaround time. But there's no combinations. There are combinations? Okay, great. It's that different because, in fact, it's a more homogenous diagnosis. What we're talking about is, in fact, how do you deal with heterogeneity. The reason I'm raising this is because the mean - as a statistician I'm really in trouble by even

mentioning this – the mean tends to obscure as much as it reveals. There's lots of variability. There's people who respond one way and another way. How do you deal with that?

Dr. Berry: I heard Dan Perry talk about cancer as a single disease. I know he didn't mean that, but in breast cancer – pick up an article about breast cancer and the first line is, 'Cancer is a heterogeneous disease.' It's so heterogeneous that we are moving to the point where every cancer patient is going to have an orphan disease. The ISPY 2 recognizes that, and actually most of the hype is associated with the heterogeneity, and the ability to achieve a path CR is incredibly different in an ER-positive/____-negative patient than it is on a ____-positive/ER-negative patient ranging from 60 percent to 10 percent.

So it's hugely heterogeneous and we actually – you can graduate. When you graduate, you graduate with a grade in each of 10 different biomarker signatures. And you can be, through the adaptive design, if it's turning out that it has, by the way, that the drug is not effective or a therapy is not effective within a particular subset, the probability of being assigned to that drug drops and eventually goes to zero so you're focusing on where – it's like enrichment. We're focusing on where the drug is or _____.

Dr. Potkin So you're embracing the heterogeneity.

Dr. Berry: Absolutely.

Dr. Potkin: So that would apply then, I would think, to Alzheimer's disease, which is perhaps the leading heterogeneous or equivalently heterogeneous –

Dr. Berry: Yeah. And so the ISPY 2 is being adopted in a number of areas. In acute heart failure, for example, where the heterogeneity is associated with phenotype. In sorry and acute respiratory infection, which is incredibly heterogeneous in the world, including the availability of different therapies in different geographic regions. So again, it's phenotypic as opposed to genotypic.

Dr. Potkin: I'd like to pursue this a little bit more because – so what – if we were to apply this now to Alzheimer's disease where we don't have a tissue diagnosis for most patients and we're relying upon biomarkers that are differentially reflective at different stages of the illness, how would you – and the fact that you embrace

heterogeneity – would you just want to confine this to one stage of illness, early Alzheimer's prodromal, or would you like a wide swath of a variety of stages of illness and genetic risk factors?

Dr. Berry: So – anything. *[Laughs]* If it's the entire set of disease it's possible there may be biomarkers that differ depending on the circumstances of the disease or chorus on the treatment. So we could both. I suspect that we're moving toward the early side, but I would help you design a trial in the whole set of disease. Just a point about what Rusty said about tricky and biomarkers. If I can interpret that as being possibly less informative, think of a statistical model where what you do is you have this sub-panoply of biomarkers and you build a statistical model that allows for predicting depending on, and including longitudinally.

If it turns out that the sum set of these parameters are predictive, then you learn that. And if it turns out that it's tricky and you're not – you know that. With apologies to Donald Rumsfeld, we know what we don't know and if it turns out that it's not really predictive then the statistical model is saying you're dealing with something that's not predicted.

Dr. Potkin: Just to continue this for a moment, in ADNI there's 800 subjects or depending on what you want to talk about, maybe 1,200 depending on which groups. When you're talking about this heterogeneity, what are the kinds of ends that we're talking about that one would need by groups taking – I know we don't know exactly but we have a lot of information from ADNI. So what are we talking about?

Dr. Berry: We designed a trial and adaptive trial. We put a maximum on it. I thought that might be a problem with pharmaceutical companies that the budget is variable. Maybe it's gonna cost this much and maybe it's gonna cost less. It turns out not to be a problem. What we like to do is have that maximum be as big as possible and we determine how big the sample size should be depending on the results in the trial. As it goes on, we're completely, constantly reestimating. How much are we gonna need in this subset and that subset? So it could be big and it could be in the 800's.

Dr. Potkin: So what's the number?

Dr. Berry: So a number. A thousand patients. I mean something – it depends on the budget. It depends on who's paying. We model – the way we did it in ISPY 2 is we modeled the various possibilities, again

assuming there's a therapy that's effective and this subset, how big is it going to be to get some reasonable power that we've identified the signature? Power is now much more complicated because you could get the biomarker signature. If there's a true biomarker signature you can identify it, but maybe you identify something that's bigger. Well that's good because you've got the signature, but it's bad because you're treating patients that are not benefitting.

And by the way in cancer at least, most patients that get treatment are not benefitting. If we can decrease that proportion, that would be a very positive thing.

Dr. Sperling: I actually really like the idea of adapting on stage of disease. I hadn't thought about that before. So one idea, since I'm actually afraid we're more Rumsfeld than I'd really like to be – that we don't know everything we don't know. And one of the big questions is are all therapeutic mechanisms going to be helpful at the same stage of disease? I think this is a big thing we don't know and I don't know that we know when we'll know.

Dr. Berry: So the more you don't know the more you should be adaptive.

Dr. Sperling: Right. So I really – I actually really like that idea and I hadn't thought about that. I've thought about kind of E-4 and non-E-4 kind of things. High amyloid, low – low – but that would be something else we could do is start out with pre-clinical prodromal in AD dementia, have some readout that helps tell us early on whether a combination is gonna be used across the spectrum of disease or only at one stage. But then I'm back to what is the readout because certainly some readouts are gonna be much easier to see in later stages of disease because they're changing more rapidly. But that might not be the best stage for intervention because it's too late.

So I don't know. Do others have a thought about how we could – I like the three stages or multiple stages, but how do we have variable readouts across the stage to tell us whether it's successful at stage of disease?

Dr. Katz: Just to follow up on that, I think, a related question. You say you model the predictive nature of these things, but I think it's fair to say in Alzheimer's disease, we don't have the other part of the equation. We have no empirical data that says if you change the biomarker in this way you'll change – we know the clinical will

change. Yeah, you have the natural history data, but you don't have any on-treatment data. So how do you model that?

Dr. Berry: I'm okay with that. You model that and you get the end points. Some may come after the trial, but during the trial you're gonna get some information and it would be updating on the basis of what you're seeing. And to this point –

Dr. Katz: I'm sorry. I guess what – in very early disease there may be an expectation that there will be no clinical outcomes to measure. So the question is how do you update when you don't have that?

Dr. Berry: So if you don't have any information that's gonna tell you anything about how the patient is doing during the time in which patients are being accrued to the trial, you can't be adaptive. You can't learn because there's nothing to learn from. And to this point, it may be that you want to build a process that doesn't accrue as fast as in the old days. In ISPY 2, of course, we do accrue reasonably fast relative to getting the drugs back to the companies. Maybe in Alzheimer's you can't do it that fast because you want to – and the fact that you've got a single process here and you're accruing through a number of drugs and a number of treatment regimens, you're getting more information en toto but less information about an individual drug and an individual biomarker subset.

Dr. Katz: Could you model – can you base your predictions on how the biomarker is moving? In other words, some drugs may be less effective at moving a particular biomarker. You wouldn't really know anything about whether it predicts, but you might learn something about which is a better drug.

Dr. Berry: Yes. So I report to the Data Safety Monitoring Board for ISPY 2 and they ask – every month, actually – and they ask me many times, 'Okay, so Don tell me again about MRI. How is it involved in this process?' What we do is we model – tumor size is sometimes predictive and sometimes not. There are famous examples in cancer where it affects the tumor but it doesn't affect survival. And so modeling that process individually may be borrowing across treatment regimens to some extent, but allowing for the possibility that if the therapy is decreasing the tumor it's not affecting _____ rate. Here, if the biomarker is being affected, it might be for one drug predictive of a benefit and another drug not.

Dr. Sperling: So if we – I think the slow accrual is a possibility but it also may be that we're just gonna have to run our first set of adaptive designs for a very long time. Not just accrual, but just realize that we're gonna need three or even five-year outcomes. And we can embed earlier biomarkers, but we're not gonna get an answer as to which of these biomarkers are gonna be useful until we see some clinical movement. I think that's where we're stuck in early disease, although I like the idea of simultaneously starting later disease because maybe we'll get an answer there in six or 12 months and can move forward. Steve?

Dr. Potkin: I just wonder. I'm intrigued by what you say, as everybody else is here. That's why I keep getting invited back. So the question is how do we apply this? What I'm wondering about is could you take the ADNI data, which is stage related and is longitudinal, and use that as a model for what happens and then take any of the trails that failed and see how good your prediction is? This would give us a great deal of confidence in how to shrink the universe to be more manageable. There's too many biomarkers. There's too many stages. There's too many ways. I mean there can be an infinite budget. So how can we constrain this in a way and use what data we already have that's been collected but not analyzed in this way. Is that something you think could be informative?

Dr. Berry: I think it could be very informative. What we do is we build trials in silico and we simulate all kinds of possibilities. So we tell people that in cancer, at least, the first patient we kill we want it to be a virtual patient, so we do lots of simulations. But if we can simulate, maybe in deed in the ADNI data and in other circumstances, there may be some aspect of simulation Reisampling. Using actual patient data to see how well would it work if we had this panoply of biomarkers and we're using it to predict and we've got this model, absolutely.

Dr. Sperling: I think it's a great idea, though I would encourage us not to just use ADNI data, because I think ADNI would have said use hipocampal volume or ventricular volume. That's what the ADNI data might say and that's not what turned out to be particularly useful in trials so far. But this is a chance to take trial data from phase two and phase three programs across multiple immunotherapy programs and look at them. And I also think that there's some kind of a new sage ADNI challenge coming up to actually use ADNI and other data to model, and maybe this would be a useful way if you could go across ADNI and these data sets from phase two and three from immunotherapy together.

I have one other very specific and then maybe we can get off just the ISPY 2 because there are certainly other combination designs we should consider, but one is the issue of in this shared placebo group, about different routes of administration and frequency of administration, how you deal with that. Again being very practical thinking about a beta secretase and an antibody that's either infusion or sub-Q, how do you deal with that in the double blinding and in the single placebo group, or do you not deal with that?

Dr. Berry: We don't deal with that because we're not double-blinded. The information across the centers – we have 20 centers. The information across the centers is not shared during the treatment phase. It can be dealt with and we work in other areas where we want to be double-blinded and it can be complicated in terms of the placebo, but not impossible.

Dr. Sperling: This is for Rusty and other regulators. To avoid this very complicated double blinding where everybody gets oral and everybody gets multiple types of infusions or injections, what about the idea of having one placebo group get oral and one placebo group get this, and then if they are similar after six months or 12 months combining them. Is that something you guys would consider?

Dr. Katz: Yeah, I think we have considered that. It's not like everybody gets everything. You sort of tailor the treatment of what the placebo people get by what the individual treatments are. We've seen that, and of course it's not perfectly quadruple dummy design if you look at it closely, but yeah. And again, of course, the more objective the outcome and this kind of thing, which isn't always the case. But the biomarkers, I think, we certainly think that is the case. I don't think that's a major hurdle that's going to get in the way.

I just want to throw out some other random thoughts. Again, I want to sort of get back – I don't want to harp on this day one collaboration. Maybe there are other panels that will talk about that or in workgroups we'll talk about that. For example, we talked – Dan talked about the guidance that's come out about combination drugs and it talks about non-clinical studies. I'm talking about toxicity studies, not models of the disease.

There's a lot of room, I think, for negotiation of what those studies are going to look like, but certainly we're gonna want combination toxicity studies at some point, and maybe only combination possibly. So that's a place, I think, where people are gonna have to collaborate on day one. People are going to have to figure out how to do that because the animals are gonna get the combination. And if one company has one drug and the other company has another drug, in order for those studies to get done, that has to be shared data, I think, or somehow they have to get done somehow.

So I think there needs to be discussion about how that could happen, because again if we're gonna do this as early as possible in terms of the lives of the drugs, we're gonna have to solve these problems. The other thing I want to say is I think we should be thinking – and this is easier said than done – but we should be thinking about really moving beyond combinations that attack a particular pathway. We should be talking about combinations that attack multiple pathways.

This disease screams out for that. It's not – even if A-beta causes the disease, you've got as much amyloid in your head when you have early MCI as you do when you have advanced dementia. So something else is happening, even if amyloid is starting the cascade, there's many other things that are happening. So I think we should be thinking about looking at all these or many of these other pathways. The Alzheimer's Association Research Roundtable had one of their research roundtables a couple – however long ago it was – which looked at non-amyloid targets. Obviously there's many, many and people should be thinking in those terms.

Dr. Sperling: How do we incent – so I agree with you. We have to go beyond amyloid and let's say we want to incent a company who's got a tau drug or a neuro-protective or something to combine with an anti-beta as a first combination. So again I feel like we have to put something on the table that will incent these companies to work together because they're in the, 'Oh, I've got the wonder drug. I've got to get this drug to market' even if, again, it might be much more efficacious if it were combined with something.

So one thing that occurs to me, the NIH has this tox that you guys will do a tox for new compounds. I wonder if there's a way to kind of have a specific initiative around what that service you offer that would bring companies together so they could nominate a couple of compounds and kind of get this paid for. That might be

one piece, or again we could build a new consortium that would have this combined animal – make it cheap and quick because all companies are struggling with animal toxicity, definitely they are even within one compound.

How do you do it? How do you deal with these small things that show up? Is there a way to build something that would be value-added to bring companies together and say is this worth their while to bring their best two drugs?

Dr. Potkin: An odd idea would be – that's why I'm on the panel, for odd ideas – kind of a combinatorial approach. I wonder if it was possible that companies would submit drugs to this consortium and there would be a series of animal models, not an infinite number, and that different combinations would be tried out by the consortium. And if you got a good efficacy signal that is not just additive but synergism – which is what you'd look for, not just the two things worked additively together but they actually seemed to potentiate each other, then you have to deal with toxicity and everything else.

But the incentive for the companies would be great because you now have not just a small signal, but you have an enhanced signal which would suggest that if you have an alliance with these two companies together that you have a much greater chance of winning, toxicity aside.

Dr. Katz: Just to reiterate something that Bob Temple said at the last meeting about combinations, synergism is great. It's hard to come by and there's no requirement for it. If you had a meaningful but relatively meager effect with a single drug and you had the equivalent independent meager effects with two or three other drugs working on different pathways, when you put them all together it's better than one alone. And from a regulatory point of view, that's all that's necessary. It would be great to have some sort of synergistic effect, but it's just not –

Dr. Potkin: It's not required, but that would be – we're talking about an incentive. So what would be of value.

Dr. Katz: I know, but that's – it's hard to incentivize a company based on the effects of their drug after the fact. I think if industry is aware that it doesn't have to be synergistic, but just an additive affect is acceptable from a regulatory point of view, maybe that makes it more attractive. I don't know.

Dr. Berry: It definitely makes it more attractive because you can run a smaller study to prove it.

Dr. Sperling: Right. I do think, just again getting back to the practicalities in animal models, this already gets tough because what is the synergistic affect of what? So I absolutely agree. We've got to go beyond A-beta, but we don't have good models where nerve degeneration of an animal model where A-betas were anywhere in the process. And if you went – so again, is animal behavior what the readout would be? That's scary. I think it's a great idea, but what will the readout be for additive effects in the current animal models? I don't know.

Dr. Katz: That's what I was saying before, and again somebody would have to decide whether this was worth anybody's while. But if you have an independent model of nerve degeneration, you have an independent model of inflammation. You have an independent model of whatever else is wrong and you have individual drugs that work in those models, the fact that you don't have a model that combines everything – of course it could be misleading, but it would be at least – I think it would be at least rational to say okay I have the anti-inflammatory drug. I have a drug that works on neuro-degeneration. I have an amyloid drug. It's not crazy to think if you put them together all those things occur in the Alzheimer's brain.

Of course they may have different pathophysiologies when they're put together, but it's worth thinking about. It's worth thinking about.

Dr. Potkin: If you have, as you say, each of these promising drugs in each of these domains or each of these targets, but you don't have an animal model where you can test the combinations, so in other words it doesn't do you any good necessarily to test an anti-inflammatory drug in a model where there isn't inflammation, for example.

Dr. Katz: Absolutely. That's why I say maybe the best thing you have are independent models and you have to work in those independent models. We know those pathways are all involved in the Alzheimer's brain. I think it's irrational, whether it's irrational enough to get people to investigate, I don't know.

Dr. Sperling: So practically if you had these three different models where you're coming at these different targets, then is one way to get started just

to try the combinations for safety reasons in each of these three models knowing that you're probably not going to be able to see additive or synergistic affects if they're not complete models of the disease, but just to get started and at least to make sure there's not negative synergy – that one compound is not harming the effect in your primary model of inflammation when you add an A-beta. Is that a way to get started?

Dr. Katz: Well again, from a regulatory point of view models of the disease – effectiveness models in animals, they really don't carry – no, obviously people need to do them and decisions have to be made about what drugs to take forward. But from a regulatory point of view, it's not a big deal.

Dr. Sperling: Maybe just to make this a big more interactive, are there questions from the audience – and again, thinking more broadly than just the adaptive design.

Chas Bountra: I don't think animal efficacy or animal toxicity is going to incentivize a company to donate their compound. I think the situation we're in at the moment is that many companies have many assets that have been into the clinic, they've been into patients and they haven't seen a signal. They are only going to invest in this area if somehow they're convinced that they're going to get some sort of return on investment. I think what maybe we should consider is – I mean I suspect with 20 companies out there, there's probably about 30 or 40 assets that are probably sitting on the shelves and the companies are not doing anything with them.

Now I think if we were to ask them are they willing to donate those assets to this consortium, and then we would design some ISPY-like combination studies – we would maybe pick three or four combinations that we are interested in doing, there's a good scientific rationale, etc. Then I think the public funders are probably gonna have to fund that phase two study. They fund the toxicity in animals – the combination toxicity – and the phase two study. Then if that works, then the companies should fund the phase three and the launch. I think that's a model we should consider.

Dr. Sperling: So kind of – because the NCATS models are already happening, so maybe these things that are sitting on the shelf that have been repurposed, that's already been funded, maybe that's a way to start asking about combinations of repurposes drugs to get those started. I guess I'm not fully willing to just settle for that because I want

the best drugs, not the ones they put on the shelf. And I agree with you, animal models aren't going to incent them, but I hope over these next two days we figure out what will incent them to put these together for eventual clinical trials and what we can do to say that this is worth their while for a return on investment, because maybe their drug they can't get to a high enough dose and a combination would be better. Or it's going to take them 15 years to develop this on their own and if they work with a consortium that's a high throughput, speedy consortium, we can halve the time of their drug development.

Chas Bountra: The condition would be, let's say those 30 assets that all these companies donated potentially, we would have to see all of the data that went with them. So we would decide out of those 30 which molecules we thought really were going to test the hypothesis. We would design which combinations we're interested in and it may be ones targeting tau and other ones amyloid and another one's inflammation, etc.

We'll probably whittle that 30 down to half a dozen assets or something like this. And maybe even if we could pull out one or two studies, I think that would be a step forward. I think with the NCATS stuff, all those assets are for any indication. Here we're specifically talking about –

John Allam: John Allam, of Sanofi. So Dr. Katz, when you were speaking I was reminded of two things. When you were talking about going much earlier and thinking in terms of different mechanisms, one of them is actually antibiotic guidance, which has been out there for awhile, where if you know that individual agents by themselves are not effective, but in the combination based on preclinical data are effective, you have the option of developing as a fixed combination from the get-go. If you have no intention of ever separating the two, toxicology onwards, you can just develop and in the end what counts is efficacy.

The other example, I think, is in the oncology space where a lot of these combinations were developed based on pre-clinical rationale, etc., and they were – and the dosage ratios, etc., based on pre-clinical synergy, etc., and then it was meant to be, again, similarly a fixed combination only evaluated only in that combination and never otherwise. Is that something that FDA would be open to in this context? For example, if you knew that an anti-amyloid antibody or a base inhibitor, if you took animals with existing

plaque load, individually they would not be affected, but in the combination you could actually remove plaque, which you couldn't do otherwise.

Could you develop that from the get-go as a combination regardless of whether it's across companies or not?

Dr. Katz: Yeah, the short answer is absolutely. The guidance even talks about in any given case it might be completely appropriate to, for example, have all the non-clinical requirements, Don, with the combination without the individual drugs first. And it does talk about the studies with individual drugs. But if the intention is always to provide that combination either as a fixed combination or always together, the non-clinical data can only generate it with the combination and the clinical data, we have a rule that says each component has to make a contribution.

But that contribution, the evidence for that particular contribution can be obtained not necessarily through the standard factorial design which everybody talks about which is typically used in most cases. But if there's good reason to believe that one component attacks X and another component attacks Y, it isn't a law that a factorial design has to be done. That drug could be developed as a combination with the evidence for the contribution of each component coming from other types of data. So again it's going to be a case-by-case basis.

You can't say all combinations will always be developed this way, but absolutely it can be developed non-clinically and clinically as a combination from day one. That is a possibility.

Conrad Wong: If you did have an anti-inflammatory, one attacked neuro-inflammation and a completely different mechanism for neuro-degeneration and you wanted to develop them completely together, when is the time to talk to them? Do you then go in in a pre-IND setting and saying that here's our plan, here's the biological rationale that we have and then does this mean that we can just go straight through – all the way through as a combination?

Dr. Katz: Yeah. I think more than the typical case, these sorts of development programs, with which we have essentially no experience, at least again in the neurology world, there has to be frequent interaction with the agency. So there's absolutely – you're talking about a pre-IND meeting. More and more in recent years the topics of discussion of pre-IND meetings tend to be the

entire development of the drug and we sort of engage companies at that level. But it's so premature at that point to be thinking about exactly what development's gonna look like.

So there are many notable points during drug development where we meet with sponsors, we look at what's been generated so far, we see what makes sense to do next. But just sort of a general outline can be discussed early on, but there has to be – the slide we saw about open and frequent communication, I think in these cases, more than in the standard case, that has to be true. But definitely pre-IND meeting, it seems to me, and then take it from there.

Steve Salloway: Steve Salloway from Brown University. I have a few questions about the ISPY structure, just to understand it a little bit better. So what's the – and let me just – I'll state all the questions and you can respond. What type of minimum safety data do you require for the combinations before they're introduced into people, and what level of blinding is involved with the ISPY structure?

Dr. Berry: What level of what?

Steve Salloway: Blinding. And how much contact is there between the companies. Say there are two different compounds from different companies. How much contact do the two companies have in working on that arm of the trial? The last one is a very simple one, but are there more than two in any arm? Do you have arms that have three different compounds or approaches that are being tested?

Dr. Berry: The minimum safety data, everybody worries about that in the context of so-called primary breast cancer. This is primary breast cancer. It's non-metastatic. And historically in cancer, the development has been through phase one trials where you take metastatic patients and give them therapies in whatever combinations. That is done and we actually have a paper where we publish what is the minimum, and it can be as few as 15 patients in the metastatic setting and the combination.

The safety data, because this is a so-called curable population – high risk primary – the safety data are meticulously followed and reported to the Data Safety Monitoring Board that meets monthly, as I indicated. And so there's a high level of attention to the safety issue. Level of blinding – there is no blinding. The blinding is only in terms of the surgeons, the assessors of pathologic complete response are blinded, so the technicians and those who read the

films, for example, are blinded. But at the treatment level there is no blinding.

Oncology is different from other fields in this regard where we even have phase three trials that are not blinded, so not to excuse that, but just to point out a cultural difference. Contact among companies – so we meet annually at ASCO, coming up actually Friday evening, with all of the companies. So there are meetings. In terms of the companies that are involved in the combination therapy, so far the only combination therapies – the individual therapies are different companies. The only combination therapies that we have is Genentech with its two drugs – the pertuzumab and TDM-1.

The more than two – I should be clear that the background here, and any kind of placebo that you would use if there were a placebo, was on top of standard therapy. So you can't, in this disease, not give standard therapy. The standard neo-adjuvent therapy is Taxol followed by Adriamycin and cyclophosphamide as a background. The experimental arm is then put on – if it's a combination it's an additional combination on top of the Taxol part of it. So there's 12 weeks of Taxol and then you get whatever the experimental regiment is on top of that.

So we don't have more than two experimental drugs together, but those two would, in a sense, amount to five because we've got the three that are background.

Dr. Sperling: I have just one follow up question. I also have seen when you presented that one of the things you do adaptively is you figure out the dose. You might have three or four doses that you're trying of one of these and then you narrow them down. How do you do that in combination? Do you narrow first within drug or do you try multiple doses in combination? That's something. We don't know the optimal doses in some of these newer mechanisms at all.

Dr. Berry: So far in ISPY 2 we don't have – we've talked about having a dosing question. We don't have a dosing question. You may have heard me talking about, for example, the phase two/three where a recent example, Eli Lily highly publicized in diabetes, we designed a dose finding part. You could imagine that this would be a combination finding part in the phase two and the end points were somewhat shorter in coming. The end points were – the main end point was HBA-1C at one year. But again, we model the

relationship and there, getting early HBA-1C values turned out to be pretty highly predictive.

And the choice – first of all there was adaptive randomization to the various seven doses in phase two, so that if something wasn't working very well or wasn't in the informative part of dose response it didn't get many patients assigned. The program was to switch to phase three before any patients got to one year. So there, the longitudinal model was really important and had been so-called validated in advance. There were many – it was four different end points, HBA-1C, weight loss, heart rate and blood pressure. When we chose the dose, when the algorithm chose the dose, it then triggered four additional phase three trials. This would be, then, continued as a phase three trial and four additional phase three trials after the two doses were selected were then generated. And all were successful, by the way.

Zaven Khachaturian: The idea of combination therapy has been part of the Alzheimer's therapy development predating the idea of using two compounds. It used to go under the name of polypharmacy. The major barriers early on to development of this idea was the regulatory hurdle because the requirement was to be able to show efficacy for each compound independently. Now that's encouraging to know that FDA has agreed to consider this and I think it's a major achievement of this group.

My concern, listening to the discussion, is that the way we're proceeding about it is like putting together which a witches' brew. Company A has this compound, Company B has this compound, can we throw it together and see what comes out? I think that we should – we're at a critical point. We should be proceeding in this effort trying to develop combination therapy a bit more based on rational selection of whether the targets we select – how do we select those targets?

We have, fortunately, multiple ideas in the field. For example, there is relationship between glucose metabolism and _____. There's a relationship between neuro-____ like estrogen and nerve growth factor. So there are these various ideas there that can be cultivated further for therapy development. What I would like to see is another mechanism to exploit the things we have learned from ADNI, from ADCS. For example, why couldn't we expand ADCS' capability where we bring various companies and these ideas and use ADCS as phase one, phase two testing or proof of

concept ideas where companies are not taking the scientific or the financial risk and that's being taken together.

Then once you share that combination, the idea has some efficacy and Company A or B could take it and develop it in the phase three. So the idea would be for this group to work out the logistics, the organization structure, the financial structure. Your questions, how do we get companies to start working together? Well you have to work out the financial relationships and work out the regulatory issues, work out the antitrust kind of issues. There are a lot of those issues. This group perhaps could struggle with those.

But my main concern is to use this group to use more of a rational basis of what we know about the mechanism of the disease rather than just turning things around.

Dr. Berry: Can I comment? First of all, the number of possible components could be greater. It doesn't have to be just two. You could have three, four or more – and try to decide where is the sweet spot. There has to be a committee, maybe the steering committee. We have a separate committee, the agent selection committee or regimen selection committee that would put together the rationale, would hear the rationale and would come to a conclusion as to what is the appropriate thing to do.

It might be we don't really know whether these translate into the clinical arena and so let's have a number of possible combinations and we'll learn, to some extent at least – not that it's highly powered to learn about the individual things – but to some extent we'll learn as to which is better. But the important thing would be, in fact, the science and to incorporate that through something like a regimen selection committee.

Dr. Sperling: I absolutely agree and I'm so glad Zaven brought up the ADCS. Of course I'm biased. I'm working on a trial with them now. But I actually do think that starting with an academic NIH-funded backbone and expanding it to the degree that we have resources to do that I think is ideal. Companies don't always trust each other, but there's been growing efforts to give data to the ADCS from several companies and again, the ADCS is an ADNI. They are, in some ways, one in terms of the clinical backbone of this.

Paul is not a big adaptive design fan, but we're working on him. I think also there's this mechanism for deciding about which drugs you might want to take. It's a very democratic organization where

they fight for days and days on end to make decisions, but I think it really would be an option and it exists. We just need to expand its horizons and move it even further into the 21st century.

Dr. Berry: Can I just add that to make clear, the agents or regimens coming in don't have to be there from the get-go. They can be accrued over time. We started with one experimental arm and added and added and others have graduated. So it doesn't have to be – you could start with individual agents and as you get safety data for the combination you'll include it.

Dr. Sperling: And also I want to mention DIAN, the Dominantly Inherited Alzheimer Network, I think has also done a good job of this, of starting with an academic organization and bringing it forward. I think we need to create cohorts like that outside of familial AD, again in pre-clinical prodromal and AD dementia that are like that and when it's there we can build it and test the best drugs as quickly as we can.

Gary Romano: Gary Romano from Jannsen. So we've heard today several times and elsewhere that biomarkers are not terribly predictable for clinical efficacy. We don't understand them. But when we've been able to measure biomarker – drug affects on biomarkers, they've been very small, so whether it's on _____ or _____ or MRI. So might another use of combination therapies or adaptive design be to see if combining drugs we might see able to see more robust affects on these biomarkers and see if those more robust changes translate into better clinical benefit. That could be either by looking at – targeting a single target like two amyloid – Reisa mentioned the clear amyloid base inhibitor, for example, and just looking at amyloid biomarkers. Or by looking at more biomarkers that are more reflective of synaptic health or synaptic integrity, like a structural or functional MRI, and looking at various mechanisms in the combination.

Dr. Potkin: I just want to comment on – actually it shouldn't be a biomarker, it should be what's the right combination of biomarkers? They may reflect the same pathway or not, and in fact we really need to understand what that set of biomarkers, now they move. I think that's the goal. And then some of those will be very predictive and some won't. They may be differentially predictive at different stages of illness.

Dr. Sperling: That's a really good point. I think whatever we build we should build this with – not assume we know which biomarkers are gonna

work, especially in combinations – and put them all in as much as possible.

Conrad Wong: My name is Conrad Wong from Eli Lily. There's some question as to whether there could be learnings gained from the development of new antidepressants, for example SNRI's. Initially we started off with an antidepressant that hit on one target and then over time and development we now have an antidepressant that hit in multiple targets. I'm unaware that in that development we had to show the independent contribution of each of those different targets for its overall efficacy. So I guess I would ask the agency if a sponsor wanted, from the very get-go, to develop an intervention that operated on two different targets, the rationale behind having to understand the contribution of each of those targets.

Dr. Katz: Like I said before, it is possible that combinations could be developed from day one and the only thing that would have to actually ever be studied is the combination, whether it's an animal tox or whether it's in clinical trials. There is a rule that says each component has to make a contribution and in each case – and traditionally that's, at least clinically, that's been documented most often with the factorial design.

But as I say, depending upon what we believe we know about the mechanism of action and other considerations, it may not be necessary to do a factorial design. It may be enough to say we understand the mechanism of action of this component well enough to know that it acts on X, it doesn't do anything on Y and the other one that works on Y doesn't do anything on X or perhaps anything else and so for various reasons there's no requirement to look at a full factorial design.

So the evidence of the component's contribution can come from other sources than a factorial design. The factorial design is sort of the gold standard, but it doesn't have to be employed in every case. In particular, if we're talking about multi-component combinations beyond two components – three, four, five components, which you could imagine – what a true factorial design would look like – you can't – I'm sure there's some –

Dr. Berry: It would have to be a partial factorial.

Dr. Katz: Right. Exactly. I'm sure there are some with an exclamation point at the end. *[Laughter]* But the point is you couldn't do that study. You could do a partial, but even if you did the correct partial factor

of the design it would be huge and incredibly complicated and you can't even imagine that would be done. So especially as you get into multicomponent combinations, you have to be thinking about where the contributions – how are you going to document the contribution of each component. It has to be done, but again it can be done from other sources.

I will also reiterate something that Bob Temple said at the last meeting, which I hesitate to say out loud what he said out loud *[Laughter]*. Which is that not withstanding the rule that says each component has to make a contribution, if you had a multicomponent combination and you had a big affect on Alzheimer's disease, we're not gonna not approve that because we don't know where the affect is coming from. There's a lot of room for flexibility, but again each case is separate and has to be discussed with the agency but these things are all possible.

Dr. Berry: Can I just – by the way, Rusty, the end with the exclamation mark is called a factorial.

Dr. Katz: I know. I was a math major, but that was a lot of years ago. *[Laughter]*

Dr. Berry: So the – you said huge for the, let's say, five components, but if you had five components and you did, let's say, three different levels of each component for doses – zero, low and high or something – that would take – so the number of possibilities are three to the fifth power, which is a big number; 729 or something like that. But the advantage of the factorial design is – two advantages. One is if the components are additive, then in that circumstance you have a third of the patients assigned to each of the components of each of the drugs.

And so if they're additive, you get to do the independent assessment within that drug. It's five times over, so you get five trials for the price of one. That's if they're additive. If they're not additive, it's the only way to find out that they're not additive, is to get some information. So if you had in that example 729 patients assigned one per but did this process, you would have some information. Technically in the statistical sense, you can't look at fifth order interactions because there's no power to do that, but you can look at, let's say, first order interactions.

Dr. Sperling: Just one last thing on that. Do you ever in ISPY 2, or could be – so let's say we start with a two-by-two factorial and we build it big

enough so when the next drug comes along we could add that and then expand one arm and add it. So you start with two-by-two factorial, but let's say the combination's looking good or one of those arms are now gonna add the third drug. How do you deal with that? Do you start again or do you continue and expand one arm to add a third or fourth drug?

Dr. Berry: We've not come to that, but how would we, we would work with the regulators who would pull some of their hair out because you're not – you're comparing at different times potentially and the current, if you look just at concurrent randomized patients, there may not be much information there because most of the data on the smaller factorial was earlier on.

So it's possible to do and in the phase two setting I think I hear Rusty say and I've heard regulators say that it's to decide where you go in phase three and you're building a thing and they're okay with lots of things. So it is possible to do. If it gets very complicated then the credibility of the company, even if you go back to the company and say this is the data we have, you maybe have a hard selling job. So we try not to make it too complicated.

Dr. Potkin: Some questions and a couple of comments. So Dr. Berry, I think if I understand it correctly – and correct me if this is an incorrect assumption – kind of when you're using the word combo therapy, it's actually very different than, I think, what we're really trying to address here. You're really talking about adjunctive therapy here, right? Is the ISPY ever designed up front that two companies can put two investigational agents together?

Dr. Berry: Yes, but these are on top of the standard therapy.

Dr. Potkin: So in that design where you put two of the investigational on top of the adjunctive part, so you've got two investigational and an adjunctive, what is the mechanism for that moving forward or how is that designed to move forward for, say, the animal combined tox? That has to be done first, I assume?

Dr. Berry: That's done first. Safety has to be done first. That's correct. The mechanism for moving forward, we actually don't – the mechanism for moving forward is by regimen. So if the regimen of the combination shows that in a phase three trial there is a biomarker subset where it is very likely 85 percent, highly likely to be successful, then it graduates at the end of that trial. We continue to follow the patients until they get surgery or whatever,

but then we go back to the company with a full scorecard of the various signatures.

But the decision – and meanwhile, one of the experimental agents is still in the trial potentially, so we do not tackle the question in a factorial setting, if one graduates what would you do with the others? It's still regarded as being an individual assessment – individual regimen and assessment. *[Crosstalk]* It's likely, actually, that the individual agents will drop before the combination graduates. If one worries specifically about the factorial setting or the multiple combination setting, you would want to do a better job than we did as to what will happen when you see that the combination is doing better than the individual agents. So far we've not done that.

Dr. Potkin: I'm curious a little bit more on the logistics aspect, on the very earliest part of this. Not how you make them select the winning, but if Company A and B, in your consortia or whatever, if they have two new drugs not entered into patients yet, they have to go do the combo therapy and then do they enter like combo talks and then they have to do – then they do their phase ones separately? Or do they have to do their phase ones separately and then do they - usually they'll do the combo talks and then they will enter as a unit together, as an adjunctive?

Dr. Berry: So as I said, the only example we have of combinations of experimental agents is a single company, but that has to be done – safety has to be done separately, so we have to do safety in a single agent and you have to do safety on a combination. It is possible that in a new trial that you could address more specifically the combination issue and the factorial issue and what would happen with different companies if they come in with their own agent. It would not be the case, however, that just because you're adding a single agent it automatically becomes a combination with others out there. That would have to be decided on the basis of the regimen selection committee and what the various scientists have proposed.

Dr. Potkin: So I guess my other comment is about biomarker and selectivity. So I think one of the difficulties we have – I keep thinking I'm a vascular neurologist by training, so it's easy for me to think about cardiovascular disease and its analogies of what we're trying to do here. If we were in the 1930's and we were sitting here trying to figure out how to cure heart disease, we would have the atherosclerosis people on this side of the room and we'd have the

thrombosis people on this side of the room arguing as to what the right target is to test. And then we'd have people up in the front of the room saying we'll pick the best biomarker to go off of those things.

We know today now that you get all the Lipitor you want, it doesn't affect the coagulation pathway biomarker at all. You get all the aspirin you want, it doesn't affect the cholesterol pathway at all. We're assuming right now in Alzheimer's that some of these biomarkers are directly linked, but unless you have a final common pathway like in cancer, which is maybe self-proliferation or mitosis, until we have that common pathway, I'm not so sure how – and this is going to be the problem, I think, in front of us – what are we levered there for the outcome unless it's a final common pathway for us right now, which I think is the clinical aspect.

Dr. Berry: There is no common pathway in cancer. I mean we've found again and again, BRAF inhibition for example. It's wonderful. It has a great affect on the disease until it comes back – and it always comes back. There are multiple pathways that you have to hit, so BRAF inhibition is now combined with MEK, combined with AKT, etc. So there are all kinds of combinations that are absolutely essential, even though the individual drug is showing a great anti-tumor effect early on at least. Cancer is amazingly intelligent. If it hadn't been, we'd have cured it a long time ago.

Dr. Katz: I think the contemplation of using combinations, particularly on different pathways, it sort of presupposes that we don't know the final common pathway, or maybe there isn't one. It's just that these things all exist together. Who knows how they end up causing the clinical symptoms, but they're all there. They're all pathological. They presumably contribute somehow to the patient's clinical condition, and –

Dr. Potkin: I think we're all actually saying the same thing. So unless you have a final common pathway, you could use that as the biomarker readout, but if you don't have a final common pathway, you need a clinical readout, whether it's recurrence of cancer or whether it's cognitive decline or something like that. So where it's easy to get the biomarker – so I think what I'm saying is we'll find it will be easier to do the same pathway. So if it's amyloid, use two amyloid targets and then maybe use one of the amyloid readouts, or if it's tau you use tau. But when you put amyloid and tau, then that biomarker – we may not have that, actually, so it's the clinical readout that uses that.

Dr. Berry: Most pathways we've found in cancer after the fact. And this is to relate to Steve's point about having many biomarkers. We find if we do that retrospectively we learn something about the disease and the treatment of fact, depending on the type of disease. In adaptive approach, it's the attempt to try to do that actually online where you're observing the results and trying to do some sort of confirmation for the false positives that are ubiquitous.

Dr. Katz: Even now we know very little about all these things. We've told sponsors, 'Measure all these biomarkers in your studies,' even though actually they're really looking at one mechanism. This one drug maybe has multiple mechanisms, but presumably it doesn't. You know us, we live by the principal of prospectively designating what's your outcome and you have hierarchical testing. But here we've said the sponsors measure all these biomarkers and don't designate one as primary. When the data are done and you did something good, we'll sort of try to figure it out. So we're certainly on board with the concept of looking at multiple biomarkers, and certainly in a case where you think you have multiple drugs that are targeting specific ones of those, looking at all of those only makes sense.

Dr. Sperling: I think we're about ready to wrap up. I'll just summarize a couple of points that I didn't realize before that maybe you've said, especially that we're going to have to think about this from soup to nuts, that we're really gonna have to figure out how we're gonna get companies together at the animal tox in the phase one part, which I hadn't really thought about yet. I was already at phase two and I think we're going to have to make this consortium and this process really be from early drug development all the way through to thinking about how it graduates to phase three. I can't wait until we graduate our first combination.

Dr. Berry: Can I just make one comment? We talked about the need to incentivize. It's amazing to me. What more need do you need? I mean in sports – think of baseball. If a batter comes up and he strikes out 20 times in a row, they do something. In fact they probably would have done something before that. They changed his stance and all kinds of things. They'd probably get rid of the batter. We have to, I think, get rid of the standards that we've used to build clinical trials and develop them in Alzheimer's. The data are telling us and have been telling us for some time, you've got to do something different in my term of experimenting with experiments.

Dr. Sperling: So in the baseball analogy, we need to build all stars, right? So we need to get a good batter, a good pitcher, a good catcher together on the same team.

Dr. Berry: The combination of a left-handed and a right-handed batter simultaneously.

Dr. Potkin: So remember the baseball analogy about the money – what's the name of the?

Dr. Berry: *Moneyball.*

Dr. Potkin: *Moneyball*, yeah. So there's another way to do things, so I vote for the Berry Plan. I actually began research under the Berry Plan, but this is a new Berry Plan. What I like is putting the data together to find out individual trajectories or meaningful subgroups – what the data can tell us. We can't decide. We need the data to help us figure it out. I think we can also apply the Berry approach to the animal data. If we have multiple animals that we like because they seem to reveal some aspect of the pathology, there's no reason that a battery of submitted compounds or chosen compounds can't be tested on those and use the data to figure out what the projections are, what we're gonna be able to do. That will help us figure out what biomarkers we have.

So the same kind of data analytic plan, I think, can apply to the animal data as well as to the human data. And I guess finally, we're all stuck with this. It takes forever to do these trials. Everybody in this room is here because they're impatient. The numbers are incredible. So let's move ahead. The idea of having a large group of people that would enter some sort of an ISPY-like trial because they meet these criteria, no matter what came up they would agree to it, could just jump start this years and years ahead, and I think with no detriment to anybody. Everybody would benefit from this.

Dr. Sperling: I totally agree. One thing I think will incentivize every company starting at the trial losing six or 12 months every time we start this up, that we can shorten. So I'm gonna end by thanking you guys so much. What a great discussion among really smart folks, so thank you.

[Applause]

[Part 3]

Dan Perry: We will hear from the chairs of the two working group sessions now and get a report of the meeting that you weren't in as well as hear how the work of the meeting you were in get summarized. I think we will start in order if – is Diane Stephenson with us? Is Diane here? Val, you're co-chair. Where is she? Well, then in that case let's go and start with the – we'll do it in reverse order with group two. Is Debra Hannah here? All right, great. Diane and Val, do you want to share the honors of summing up what we did on identifying targets?

Diane Stephenson: Okay, so Val Gribkoff and I had the pleasure of moderating a very dynamic discussion in which we covered far more than what our initial topic or theme was, which was what would be viable targets to consider for combination drug development.

So first I'll introduce Val from Elan, and he, like I, come with a background in having survived the industry in the area of stroke, as well as John, sitting here, and Mike Krams, who is not here today, and kind of walked into this with a background of not wanting to have happen in the industry what happened to us in stroke. So I didn't say that yet but that's something that we share in common.

Val Gribkoff: That's right. Where it's about as hard, I don't know, to talk people into taking drugs after stroke as it is to get people on The Hill to talk to each other.

Diane Stephenson: Yeah. So we're very well-versed in challenges. But this forum brought together the diverse perspectives, and we started off the discussion to talk about what would be viable therapeutic targets, and it was discussed around trying to consider –

Val Gribkoff: I think digital would probably be easier.

Diane Stephenson: Yeah, maybe. The target space could be perhaps divided into those that are already existing targets versus novel new targets that would need more exploratory research to understand if those really would be viable targets.

But I think the themes that we heard – before we get into the whole topic of the viable targets – is around independent of what target it is you have to have a way to advance the therapeutic targets in

combination to help enable decision-making at all stages of drug development. And we know in AD that that's a tremendous gap.

But in terms of classes of targets, you know it's clear the Abeta-focused targets are already very advanced and it's not just one mechanism to lower Abeta. We've already seen some successes, at least in the preclinical arena, in taking at least two targets that modulate Abeta from a perspective of a BACE inhibitor plus an immunotherapy – and there was strong support for utilizing this as the platform in the short term that has the most chance of success, because, as the field knows, that we want to modulate and reduce Abeta as much as we can and in the right patient population to be able to help address the key question of how much Abeta lowering is going to be necessary to improve outcome and change the trajectory of biomarker declines.

So we don't know exactly what outcome measure of a biomarker is going to mediate the short-term decision makings, but the path is viable – at least at the company level of one individual company – and hopefully multiple companies – that would come together to advance their best therapeutic targets directed at Abeta to enable a platform in which one could get the most distinct reductions of Abeta that would help enable the path for decision-making in the clinical space. And the recommendation was to target those patients as early as possible, perhaps in the preclinical prodromal phase of the disease.

Val Gribkoff: Well, I think in addition that – regardless of which pathway that one went down – whether it was after a single mechanism, which I think was a consensus for the near-term, or multiple mechanisms – that target engagement is critical and that significant target engagement – that not using inferior compounds in combination and expecting a better outcome than we've seen is unlikely.

You know, there are a lot of operational definitions that bring difficulty into that discussion, but I think there was general agreement that the molecule should adequately test a hypothesis in each case about the degree of that particular molecule's mechanism being maximally reduced or maximally reduced within practical limits. And that only robust target engagement is going to lead to success; whether it's through a single mechanism and multiple drug approaches or through multiple mechanism and multiple drugs.

Diane Stephenson: Right. And that concept of target engagement is very key, especially when one thinks about other classes of targets. So I'll at least share with you the other categories in the classes that we discussed as a team; although I would say at this juncture the teams did not really achieve consensus that there was a viable short-term path to advance other classes of drugs in combination at the present time, and we can talk through that in a minute.

But the classes of targets that really belong to categories in which there is relatively compelling scientific rationale – and our understanding of AD fall under the known categories of Abeta and Tau, but other targets around lipid metabolisms – specifically ApoE4 – risk, the targets that we heard about from John, TDP-43, Alpha-synuclein, and then agents that would modulate inflammation – although we really need to understand more from the science and which direction we would want to modulate inflammation and whether there are existing targets in the area of neuro-inflammation that could be viable to bring forward, particularly in a combination strategy.

We also talked about another category of targets that would be viable targets from the perspective of there are perhaps already chemical agents – or class of targets or molecules that could be relatively ready in a relative short period of time that we didn't spend a lot of time on because these weren't the focus of the discussion, but these fell under the category of things like Alpha-7 or nicotinic receptor, modulators, growth factors such as NGF, insulin, mitochondrial agents, calcium channel modulators and neuro-protective agents.

These are target space that many of us have worked on for many years, and again, taking a single approach of one drug going forward to these patients, but in light of the fact that we're now into this space of what would be viable targets for combination development that these belong in this kind of class.

But I want to go back to what I think we heard in this forum is the challenge with the thinking about advancing other categories of therapies that are at these other classes or kind of a way to pave for the future. And there was a recommendation that we would get together – convene a group that would help really decipher through more carefully what specific targets belong to these classes with perhaps even a list that we could come up with that would include activities from even startup companies on drugs like TDP-43 and what stages they are in drug development, so that even if they're

not ready for phase two now that we'll have some kind of idea of a map – at what point those drugs would be available for human trials, and then perhaps even foster ways to think about how such agents could be tested in more innovative non-clinical models – cellular and animal models – to help find ways that advancing those drugs through combinations early on might be a path forward.

Val Gribkoff: And I will say that startup companies have advanced things a lot farther than people who are outside of the licensing end may know about. So there are a lot more things out there than I think meets the immediate eye, and a lot farther along. So I think it's worthwhile convening something and getting together and talking about future targets.

Diane Stephenson: And then the other category that we agreed perhaps would be useful for further discussion is around what kind of targets exist in the area of the NCATS repurposed drugs, what viable targets around AD might be present, and what data exists in terms of target engagement on those particular compounds that might make them viable candidates for combination therapy.

I think we all heard some themes that I'm sure have come across in the other session and will come across in future sessions is it's critical to convene and create a platform of what would be the roadmap. Is it through ADCS that we could share data where there's clearly an alignment with government-sponsored organizations that already have a track record? Is it a neutral third party? Through other consortia's, such as C. Path, that make sense? Is it viable to suggest how we can get the companies to start talking and working together already? Because, as Reisa said, is we don't want to just take any agent; we want to take the best agents forward because what is the hurdle here is that there is going to be high expectations for success and we want the seminal accomplishments of this team to be a success story that we can share to foster further investments in this idea going forward.

We also heard that there's a key need to think about safety – particularly as we go in earlier and earlier patients, because these trials are going to be long duration to look at outcomes.

And then obviously we're going to have this critical need to look and define early signals of efficacy as biomarkers or readouts that would help for short-term decision-making on any combination that's brought forward.

Val Gribkoff: And it was also discussed at some length on how you define sufficiency with respect to biomarkers. I mean you don't want to make decisions on biomarkers that turn out not to be correlated with the disease later on, so it's not a straightforward process at this point in time how you would validate the absence of efficacy data.

And the other thing that I think was an ongoing theme is that – at least from the company perspective – that I think we're all interested in sharing risk; I think that was brought up a number of times. And so any kind of novel ideas about how that could be accomplished are going to be at least entertained, if not welcomed, but that IP issues and ultimately remembering that the pharmaceutical industry is a business – how money can be still made – are important drivers in terms of the interest.

Diane Stephenson: Thanks Val. So for those of you who are present are there any gaps or things that you think we didn't cover that you'd like to have highlighted from this discussion?

Great. It was a great discussion. Thank you. Yes; Gail.

Gail Hunt: I would like to just reiterate that the issue of expectations _____ and _____ are very high and the idea of baby steps is not something that they are _____. There's a desperation where they are now and _____ occasional _____ or I take baby steps.

Diane Stephenson: Thank you Gail. There's a huge communication portion of this that we have to manage expectations even internally of what's viable and what's going to be a very important path forwards, so thank you for pointing that out. Great. Any other comments? Okay, thank you. Thanks Val.

Dan Perry: Thank you very much Diane. Debra.

Debra Hannah: Yep. I'm ready.

Dan Perry: There you go.

Debra Hannah: So I'll start by just saying thank you to all of you who had participated in the modeling and simulation breakout, and to each of you for hanging in there. It's been a long but a productive day.

So modeling and simulation can be a tough topic, especially for a group of folks that really don't come from a modeling or mathematics background. So I really want to thank Yaning and others in the room who have some experience in this space. And what we're going to do is provide a general summary for you. We talked about modeling and simulation for AD from a couple of directions, so first what opportunities are there working from what we say from the top down? So from the clinical trial data space down to a deeper understanding of what's happening from a biomarker endpoint perspective, but also where can we do more to leverage what is happening in the early target space, which I think is why we're glad you were able to share your information first – more in a systems/pharmacology perspective, understanding that there's going to be a big gap in the middle, but how do we work from both ends to be – help you to be successful in this field.

So we tried to approach this really big topic by highlighting a couple of key areas. So first talking through the gaps and challenges with modeling and simulation for AD, talking a little bit about opportunities – so where we think there are data and some tools that could be developed in this area – and then ending on some specific actions that we think we can take forward from the discussions that happen today; and we have a couple of those, so I think that's progress.

Again, tough, tough field but I think we did make some progress. And I'm going to let Yaning prepare this summary, but ask others that participated in the discussion – if we forget items, please do chime in.

Yaning Wang: Okay. We actually started with the review of other therapeutic areas where modeling and simulation has been successfully used to help drug development, such as infectious disease, HIV, including the TB work recently done, and also transplantation where combination regimens were guided with modeling and simulation type of work.

Then we realized, by comparing AD versus the other areas, we realized the so-called gaps or challenges, and the one obvious, I guess knowledge gap, is in those areas like infectious disease the pathophysiology is very well understood; you know, how the bug enters the cell, duplicate, eventually affect more cells; that's why you have clear targets with clear outcome.

But in AD that knowledge piece is missing; in other words we probably still don't understand which – I mean actually that's close-linked to the targets. You know, which target you should use a drug to lower what protein and which eventually will affect the clinical outcome.

We felt that's probably the missing piece in AD area, and that's why we consider that as gaps or challenges, and we also acknowledge – we already collected a lot of data in the bottom-up field – or the system biology field – by quantifying different drugs at different exposure leading to different levels – for example, amyloid reduction – and we also spent some time analyzing the clinical data – mainly in the mild to moderate population – on the ADAS-Cog score longitudinal profile, even drop-out in the clinical trial.

So we agreed that we analyze the data on both ends – clinical endpoint side and also the fundamental, more _____ side – but the middle piece that links certain biomarker reduction – for example, amyloid reduction – to the final clinic endpoint; that piece is missing.

And I guess the reason large phase three trials that failed sort of made people think maybe we're studying the wrong patient population are still believing that amyloid reduction may be relevant for improving clinical endpoints; therefore, overall, we are moving to the MCI population, which actually may serve as an opportunity hoping that the current drugs – or at least the belief is correct – but at the same time it created a new challenge, that is we have less clinical data in the MCI population and maybe not even clear on what clinic endpoint will be relevant to prove a drug is working in the MCI population.

So that actually served as an opportunity because, you know, in honor to address this question we were trying to come up with some actionable items, and one proposal was – for example, we already have a lot of data – clinical data – in the mild to moderate, and we can look at those subgroups that have relative to mild symptoms closer to the MCI population, and also including the ADNI data that already includes MCI patients, together with some more recent trials that are specifically targeting MCI population, and see whether we can identify some more sensitive clinical endpoints even within ADAS-Cog subcomponents or whatever other clinic endpoints that are considered clinical meaningful.

And by analyzing those data and hopefully we can come up with some more sensible kind of endpoints, or even including identifying more sensitive subgroup, you know, by saying, "If I can identify a certain subgroup that is showing a faster disease progression on a certain clinically meaningful endpoint, can we focus on those subgroups or endpoints?" And ultimately, again, the middle piece is still missing; that is linking this new endpoint – clinic endpoint – back to all the whatever biomarkers we're studying, and see what magnitude of biomarker – or what type of biomarkers we need to modify in order to, for example, improve the MCI population clinic endpoints.

And the last I guess actionable item is to facilitate this kind of data mining or analysis – a data standardization will be a very important piece; so that's different sponsors or different organizations – they at least collect data in a same or consistent manner that will eventually be combined to facilitate this kind of either _____ analysis or linking back to certain biomarkers to ultimately, you know, put the initial mechanistic model – the middle translational piece that's linked in the biomarker to the final clinic endpoint – and finally the clinical longitudinal endpoint into one big model that can be utilized to not only probably identify relevant targets for multiple drugs, but also _____ those and trial design during the drug developments.

Yeah, I think that's the nutshell of what we came up with. Others can – if you have questions or others can add.

Don Berry: Yaning and Debra, I'm sorry I couldn't be at your session. Simulation – so you touched on this just a bit – I thought that one of the things that you would do is talk about simulating clinical trials – so phase three trials. And, you know, the last 20 phase three trials that have failed – it's clear from that – if you don't even believe otherwise – that the power calculations that we do have nothing to do with the success of a trial.

It's critical to simulate the trial. It's critical to use the information from the – previous from the phase two data – however horrible it is – from other classes, and incorporate that into a formal analysis of 'What is the probability of success of this phase three trial?' And I've done some of them, and I tell you it's abysmal and the results are no surprise.

If we can carry forward the baseball analogy – if somebody is batting 800 – you know, these are powered at 80 percent or 90

percent – if somebody is batting 800 doesn't strike out 20 times in a row; there's something wrong with that picture. And that picture could be elucidated substantially by simulating – and I don't mean that these are complicated trials – I mean whatever – you know, the vanilla trial – just use all of the information to address the question 'Is it going to be a success?' And if it's not then maybe you out to look at another design of the trial. Like, for example, being adaptive.

Yaning Wang: Yeah, I think the fact that people are moving to MCI is already showing that – after all it is fair – people are already started at least doubting this hypothesis, or believe maybe the MCI is a right population.

And I'm not sure the – let's see – the power calculation – whether they did it, again, with the belief that lowering amyloids to a certain level should improve the ADAS-Cog score or the disease progression to a certain magnitude. That piece, again, is based on certain assumption which was not proven to be true, I guess, scheme and sample size, including all the phase three trials.

But I guess given enough failed trials people may realize that it may not be a power issue, it may be a wrong hypothesis in the wrong population; therefore, as a result they're moving to the MCI – again, with this hypothesis which I don't know whether we will – again, we allowed the link between any biomarker change and the clinic endpoint; without that piece you can do a good power calculation or even any trial design because you just don't know moving any biomarker is clinical meaning for you in the end.

I think that's probably the most challenging part.

Don Berry: No, I think the challenge is to quantify the uncertainty. So a power calculation is based on a particular assumption. You say, "I'm looking for a 25 percent improvement," or "I'm looking for two points in the ADAS Cog," or something. And it is that assumption that we know to be wrong – we make it just to power the study – incorporate a sensitivity analysis or incorporate a probability distribution on that, recognize the possibility that your assumption is wrong, and you get incredibly different power calculations even if your point estimate is the same.

And so what I think you should be doing is actually recommending or somehow getting into the Alzheimer's world this notion of quantifying the uncertainty, incorporating that into a simulation

process which can include the non-clinical aspects, it can include other stages of disease, it can include everything that you know and that you don't know, and put probability distributions on them, and simulate based on that uncertainty, and that's what gives you incredibly different but much more accurate assessment of the success.
But – and I don't know if you can do it – but somehow you should incorporate into the fiber of the people that are running these trials – these failed trials – that they should be simulating and that they'll learn a lot with the simulations.

Yaning Wang: Yeah, I totally agree. Actually we highly encourage the sponsors to simulate phase three trials for any therapeutic area, not only for AD. In fact I can briefly talk about the recent drug development tool submitted by the CMD from C. Path and reviewed by FDA. That was mainly focusing on the mid to moderate AD population which was originally designed to help design phase three trial – you know, delay the start design or parallel design – to help develop those disease-modifying drugs.

But the tool is exactly designed for the simulation purpose. Before you do any phase three trial use this tool to, again, assess the probability of success of your phase three trial, compare different designs – I mean including some adaptive designs – to improve the efficiency and reduce the feeder rates, and I think that should be done for any therapeutic _____.

Dan Perry: Okay. Thank you very much. So I want to begin by thanking the co-chairs of both of these sessions for summing up and for – since we – the physics of this – we can't be in both sessions at the same time – we get a good sense of what was discussed and there is some overlap.

I think, just to characterize the day, we've been talking a lot about the science, we've been talking about the recent failures and how to move beyond that by beginning to look at combination therapies. We've looked at it in a practical sense of how to do it, but by and large we've talked about prioritizing the science and how to identify the targets that we would go after.

Tomorrow is going to be devoted much more to the practical business of how do you get competing entities – and also government and private sector and patient groups – into some kind of a structure that can move forward, can attract funding, and can

bring a certain moral clarity along with the scientific urgency of this disease.

So we will begin with a recap tomorrow, following a continental breakfast again, in the hallway at 8:30. We'll begin at 9:00. Maria Carrillo of the Alzheimer's Association will recap some of the lessons learned from today. Then Debra Hannah, who you just heard, will draw upon the experience with the Critical Path to TB progress and will give us a sense of how to structure a partnership for combination development using TB as a model.

And then David Dilts – and you don't want to miss that – will chair a session on effective partnerships that do foster collaboration. And then we will move onto to concurrent sessions tomorrow that will be looking at how to build a consortium: who gets involved, how to get started, where does the funding come from, and how do we share data in an effective way across all those entities?

So, again, I am very grateful to all of you. We're especially grateful to Dr. Katz and his colleagues for lending their time, and to all of you for struggling through what is a very challenging area where it's difficult not to go off into tangents and to keep focused on what is possible in this area. Because if we find ourselves saying, "There's too many different conflicting issues; we just have to keep plowing along the same way," we will have missed a great opportunity and we'll shoulder a burden for not having made the changes that need to be done.

So thank all of you, have a good evening. We'll see you here tomorrow morning at 8:30 and 9:00. Thank you.

[Part 4]

Dan Perry: Good morning everyone. Hi, how is everyone? I trust you had a restful evening and had a chance to continue some of the dialogue over dinner last night, wherever you might have gone, with some of your colleagues.

So here we are, beginning of day two or act two, if you see this as a drama, as indeed it might be. I want to just start this morning again by welcoming you back on behalf of the ACT-AD Coalition and our co-host, the Critical Path Institute and the Alzheimer's Association.

And to start off today we're going to ask Maria Carrillo of the Alzheimer's Association – she is their vice president for medical and scientific relations. She was here all day yesterday and an active participant, and I'd like to ask Maria to come forward and give us a bit of a recap of yesterday.

And then we're going to launch into a panel chaired by David Dilts and that's going to be very interesting as will be the rest of day. This afternoon is really devoted to this idea of what might come out of common purpose that is generated by this meeting in terms of something – or at least the germ of some kind of potential structure or partnership or collaboration among companies, patient groups, government, that might carry forward a plan or thinking about how to pursue interventions against Alzheimer's disease by use of combining different therapies, including those that are still in the early stages of development.

So, for that recap, Maria, I invite you to the podium. Thanks very much.

Maria Carrillo: Thank you very much Dan and good morning to everyone. I'm going to keep this actually very short. I think yesterday was really very eye-opening for me. This is my first meeting and I want to acknowledge Dan and his team, Cynthia Bens and of course Diane Stephenson, my partner in crime, for a lot of these things, for inviting me to participate and brainstorming sessions and the planning of this meeting.

It is my first time and I think it's been very exciting and eye-opening. We've talked esoterically I think at the Association and other meetings about combination therapies. Talked to Reisa about it in a little bit more of a realistic fashion with her ideas, and I think that a lot of these have really great merit.

I think some of the things that I came away with myself from yesterday – and I don't know how much agreement there is among the group about my personal reflection on it – was that certainly on the modeling side we probably need a little bit more work and perhaps a little bit more expertise, right, to come in and share knowledge with us about what the possibilities are.

I think that that is an area that needs exploring, and I in particular was in the target section – the target group – that talked about what the realistic possibilities were.

I think we came out with a lot of caution about how to proceed, a lot of caution about proceeding too large too quickly. And – but that there were definitely possibilities.

I think from my point of view as a representative of a patient advocacy group we have an urgency. We, as families affected by Alzheimer's disease – myself included – feel that urgency and really need to scientific community at large to be bold. We really need the scientific community to take brave action, and I think that the – our agency representatives that are here share that need and urgency with us, otherwise they wouldn't be here spending three days of their very precious time to listen to the possibilities and the boldness that was discussed yesterday and will be discussed over the next day-and-a-half.

So from my point of view that is necessary. How it gets accomplished is a different story. I heard about starting a consortia, heard about different possibilities for partnerships. I'd like to say, first of all, The Alzheimer's Association has always – not only is it a patient advocacy group but we also fund science, and I think all of you know that.

We fund science through a peer-review program that's very similar to the National Institute on Aging, and we partner with the National Institute on Aging, who also has representatives here, and we partner with them very well.

We work very collaboratively to ensure that the science is robust enough that it would be funded by the National Institute on Aging or other institutes after it leaves the Alzheimer's Association. But we've also made some significant investments and commitments to global partnerships where we see a need to accelerate science.

Those global partnerships, for example, are like the Cerebral Spinal Fluid Quality Control Program, which is a global program with now over 90 laboratories that are monitoring CSF on an actually quarterly basis.

And the basis of that program is really to try to find a gold-standard method and material for CSF measurements of Abeta in particular. We have not made as much progress as I think we could have, but we are at a point now where we have an international organization actually looking at our program and accepting a program that over the next three years – if we can provide stability and commutability within that three-year

landmark for Abeta – we may actually have a company that makes this gold-standard matrix for the entire globe free-of-charge. So that would be a fantastic step forward for standardization of Abeta. And I'm talking about Abeta 42 only at this point in time; we're starting with kind of the lowest-hanging fruit.

So that's what the effort that we have been able to continue in that sense. And we talked a lot about biomarkers in our group because biomarkers are critical to the advancement of being able to measure effectiveness of any kind of treatment within a shorter amount of time; and that being critical to our mission, as we all understand.

So those types of partnerships we see as a way for The Alzheimer's Association to interact with research, to ensure that global efforts are really carried out so that we're not moving forward in parallel and not without talking to each other; certainly that's the key.

Science is global now, and so that's one of the things we can bring to the table. And I will tell you that when I hear – personally – and I think all of you have said this as well – about a no-consortia being formed, I cringe a little bit and wonder like 'What are we going to do? What is that consortia going to do?'

So the reason I tell you all of this is that, you know, I heard a lot about a consortia being formed to really talk about how to move this forward, and I would suggest – and I think I had some conversations with Chas and others yesterday at dinner – that perhaps we not move forward with that type of grander vision, but talk about what we take from this group; actually select a few key people that can carry out some planning, some planning about combination therapies that we can start and then present it to The Alzheimer's Association, The National Institute on Aging, to others that we have partnered with before – including Fidelity Biosciences, who's also here – we, actually together as funders and as representatives of the patient population, the families affected by this disease, can help you be bold.

But a new consortia formed to do that, I would not suggest. I would suggest a small think tank. And I will tell you that as an organization – The Alzheimer's Association, Fidelity Biosciences – we actually have helped the Collaboration for Alzheimer's Prevention – CAP – meet quarterly so that they can talk about the

three or four prevention trials and plan those trials and actually synergize those trials.

This is something we can do for combination therapies. I don't want to put words in – or make a commitment on Fidelity's behalf or Stacey – but certainly I think I would be willing – and I can't imagine that she wouldn't – to co-host a think tank that would take this forward if we thought that idea was possible. And I see her nodding, so I apologize Stacey, but I think we have done these type of partnerships in the past and that would be a route forward that I can see; if at the end of these three days we feel that this is where we want to be.

So I'm just putting that out there and saying that we certainly would be willing to consider a think tank discussion, but, as Chas mentioned, a project does not get formed by committee. You're not going to decide on a whole scientific program by a committee this large; but we can take the best ideas from this group and actually move them forward in that type of fashion. We've done this before, we can do it again.

And so this community, I would encourage all of you, think boldly, proceed with caution and intelligence. So that's what I would ask of all of you. Thank you very much for the time. Good luck today.

[Applause]

Debra Hanna: So you have a right to be surprised. So I am the non-CNS person in the room, so I appreciate your willingness to have me speak to you today.

So I was asked – I met several of you at the previous meeting – I was asked today to give a little bit of an updated version, really talking to you about the structure and the strategy of what we call 'The Critical Path to TB Drug Regimen Initiative.' This is a large consortium that is lead by the Critical Path Institute with our partners at the Bill and Melinda Gates Foundation as well as the Global TB Alliance, which is a product development partnership focused on moving forward new regimens for the treatment of TB.

I know this seems like a very different disease area but I actually think there are some components behind how we pulled ourselves together and the milestones we've set for ourselves that maybe can

bolster some of the thinking and discussions that have occurred over the past day or so with this group.

And so we thought we would set the stage for the panel in this way and happy to take any questions at the end.

So as Diane mentioned yesterday the Institute is made up of seven or so large consortia. Critical Path to TB Drug Regimens was launched in 2010. There are some commonalities amongst all of these consortia that are led by C-Path. Really we tend to work in high, unmet medical need areas.

And we have some common sort of talents and core competencies that we bring to the table, largely around biomarker development qualification, the development of clinical outcome assessment instruments where that's applicable, we have a strength that we're developing in clinical trial simulation tools – and I'm going to talk in-depth about what we're doing in the TB space in this arena – as well as the development of data standards, which are really necessary when you're trying to aggregate large data sets across multiple clinical trials.

So someone asked yesterday how big does the need to be before you actually take action and try and make impact in some of these high unmet need areas? Well for TB the need got pretty great. I know a lot of folks think this was a disease that we've dealt with many, many decades ago but that's really untrue.

The treatment for TB actually requires a combination therapy, but the current regimen that's used to treat patients today is really over five-decades old. They were never developed to be used together; they were developed independently and just put into a cocktail because it met the needs of patients at the time, but there are lots of drug-drug interactions and toxic side effects that come from prolonged treatment with this regimen.
It's a really prolonged treatment and you have to take it for six to nine months if you're lucky enough to have drug-sensitive disease. If you have multi-drug or XDR TB it's an entirely different story.

There are lots of issues with concomitant medications in this space, so a lot of TB patients also have to take a large drug cocktail to treat HIV, and so that just compounds the issue.

And so we've known for decades that we needed to develop a new drug regimen. The problem is most companies weren't investing

in this area. If they were doing any antibiotic R&D they certainly weren't going to do it in the TB space because this is really viewed as a disease of poor people, there was going to be low return on investment and the hurdles are high; it's not easy to develop antibiotics. And so that created a barrier.

So we ended up with a huge unmet global health need where problems were in the scientific, economic and regulatory category.

So no new treatments for over five decades, with the exception of the accelerated approval of bedaquiline a few months ago; so that's an exciting new advancement in this space. So Janssen put forward the first new single agent for TB, but what we're really working towards – as are you – is a combination therapy in this space.

We know that we have to have a multi-targeted approach in TB; we don't want to generate new resistance. But we know that from any complex disease like AD it's likely that you're going to have to intersect that pathway in multiple, multiple ways in order to really have a positive impact on patients.

We struggle with the fact that TB-prevalence is highest in the developing or underdeveloped world and so getting people in the US to fund or care about this is a real struggle.

I'll say that scientific innovations that have happened in the antibiotic development space over the past five decades haven't been applied to TB drug development. So it's like really being behind the eight ball. You may have the tools but if you don't know how to apply it to your specific bug, I think that's given R&D folks a real challenge.

And during the development of new drugs for TB lengthy regulatory approval times for in-country – so we're talking about not just EMA and FDA, we now have to go to in-country and get their approval as well. And clinical trial application really hampers sponsor's ability to complete clinical trials in a timely way.

So there's a need to identify more efficient drug development and regulatory pathways as well as really innovate on the science in the areas of new biomarkers, how to apply modeling and simulation tools to decrease the risk and increase your chance of success for

combination trials, and how to really test entirely novel drugs very early in the drug development paradigm.

So this is what we're really trying to impact. So if we know we need four new drugs for an entirely novel TB drug regimen – if you go through the drug development and regulatory pathways sequentially for each of those – we're talking a multi-decade proposition before that entirely new regimen is available.

And that's just saying if scientifically and clinically you're very successful along the way for all of those four individual agents. So what we're trying to do is develop a new pathway using new tools to help you select those best combination partners very, very early, decrease your risk, and shorten that drug development timeline.

So I'll say this has been a challenge that folks have been trying to tackle for two or three decades now. The problem wasn't getting solved; companies were leaving and exiting antibiotic research, not getting back in. There was a flurry of a few novel TB compounds that were being pulled off the shelf within different drug companies. And our partners at the Bill and Melinda Gates Foundation felt the time was right to start talking about an initiative like this.

And so what they came up with – what we came up with – was a structure that would tackle all those major categories of problems using a consortia model; that's the path they chose to go.

So we, at the Critical Path Institute, lead the regulatory science consortium. This is really focusing on those novels, tools and biomarkers with a gear towards regulatory qualification or approval that would enable that early combination testing.

We have a research resources group which dealing with very specifically clinical trial infrastructure and policy issues in the developing world. And then the Global TB Alliance which is a product development partnership that actually can do a combination drug development in the TB space, and so I think that's a unique fixture of this specific consortium compared to the others within the C-Path umbrella.

So we are a public/private partnership that brings together drug developers, clinical trialists, academic scientists, global regulatory authorities, nonprofit organizations, civil society organizations to focus on one single mission, and that's to accelerate the

development of new, safe and highly-effective regimens for TB by specifically enabling early testing of drug combinations.

So I will tell you that this group was launched in 2010, but the year-and-a-half preceding its launch we heard every reason why it's not doable, why a consortium isn't the right approach, why ten other groups are already doing this and they're going to do it better. We heard all the issues of bringing together industry partners under legal frameworks – you know, there's a lot of stakeholder management that was involved in this process.

And it may not be the right fit or the right model specifically for AD, but I just want to share with that this wasn't smooth sailing. This was a very hard sell – especially in a community where people said, "Well, the old drugs we have are good enough." And companies say, "Why should we be part of a consortium for developing drugs where we're not going to make a ton of money?"

And in the end of the day this was the reason for them to join because we've helped them move things forward in a way that they are not bearing the entire cost of the effort.

So the types of partners we have – they'll seem very familiar with you – so in terms of our industry members we have members from many companies. Those that are specifically held under the competitive legal framework are those who have compounds actually in drug development for TB. There are several companies that have compounds in the early pre-clinical space; they're part of the regulatory science consortium but they don't participate in conversations where there are competitive data that are being shared or discussed.

As, I mentioned, we work very closely with folks at NIH, NIAD, CDC, FDA, EMA, et cetera, as well as our patient advocacy group, which is the Treatment Action Group – or TAG – as well as the Foundation folks and Stop TB Partnership.
So really, the folks who are members of our consortia – it's by strategic design, right; they're people that understand and have a stake in that overall mission that I shared with you.

I just wanted to quickly share with – I mean this is what we struggle with – there are very few drugs that are actually in the development stage for TB. Most of these are compounds that were discovered many decades ago that were brought back in for evaluation against TB. Bedaquiline has been very successful; it

received accelerated approval. But our goal is really not one drug at a time; it's early combinations.

And so what we're going to focus on are now these early compounds that are moving into early development, how can we develop a better paradigm for them to be tested as thoughtful, rational combinations?

So how are we going to do this? So I'll focus most on the regulatory science consortium, again, and not get into a lot of detail of the science of TB; but I think there are some common themes here about goals and areas of focus that you may wish to consider.

So at the time that we started this work there wasn't a data standard developed for TB. And if the ultimate goal is to take the limited data sets that were out there in the space of TB we needed to be able to evaluate them next to one another, and we couldn't do that unless we could aggregate those data, and so we had to develop a data standard; so that was one of our first goals.

Biomarkers and clinical endpoints. Yes, we measure bug, what's the effect of drug on bug – whether you're measuring that drug in blood or in sputum – but there were really old methods being employed in terms of just basic colony counts and plates. That can be very confounding in this field because you get lots of variability in how those plates were incubated, at what time points were they read?

There have been advancements in the reading of that bacterial biomarker using other technology – midget technology, liquid culture – which is what was employed in the bedaquiline studies. We're now working with the FDA to move this forward, either through qualification or to imbed it as part of draft guidance; so that really is a more efficient measure of clinical outcomes.

So although it's still bug being measured, it's not entirely novel; it's an advancement for the field to standardize across that way.

There are newer technologies coming along with things like – for example; PET scan imaging of lungs in patients rather than relying on them to cough up sputum. You know, we're years away from that being something that can be implemented readily across clinical trial sites, but what we're trying to do is help those teams design those studies so that we can actually rigorously evaluate

how the biomarker that's currently used would translate to those scanned images. And so this has allowed us some prospective thinking on how we might advance the field in the future.

From a preclinical/clinical sciences perspective we are focused very much on the preclinical tools, whether they're in vitro or in vivo that help us make rational decisions about selecting early and combination partners. So this is requiring some optimization of what we call 'gold-standard in vivo models,' which are not perfect – believe it or not – for TB either, and advance in vitro tools actually that allow us to simulate human pharmacokinetics and dynamics of potential drug regimens and in moving those through potential regulatory pathway as needed.

Translational pharmacology is a fancy term for modeling and simulation. We have a hugely embedded approach that we've just kicked off in the last six months within CPTR.

I'll sort of end on that theme. And what I want to share is at the time that we kicked off this consortium, we weren't ready to commit resources and lots of investment into modeling and simulation because we weren't sure what data were out there. We weren't sure what models had been developed.

And so we spent a year-and-a-half scoping out an inventory of what had been done and where are the gaps in terms of really being able to implement modeling and simulation tools in the field of combination therapy for TB. We've got a really good sense of that. We've brought all the right experts on board and I'll show you approach that we're going to take.

So I will simply say that we consider the regulatory science phase a pre-competitive data sharing arena; so we have a legal agreement that covers the data that are being shared currently on biomarkers from clinical trials for programs such as bedaquiline within that arm of CPTR.

We do have a separate legal framework that covers competitive data sharing under the Global TB Alliance Drug Development Coalition, so I'm not going to spend a lot of time on that. We can ask questions while I'm on the panel if you have them. I just wanted to share that it is possible to develop such a legal framework; whether or not companies decide to make use of it is another story.

So our role in accelerating the process I mentioned; identifying tools and methods that accelerate early combination regimen development. Really trying to bring along scientific consensus by sharing expertise information and data, data, data; we don't get anywhere if we don't share data. And so that's core to the principle of CPTR.

And then we're proceeding with regulatory qualification or evaluation of those tools where it's appropriate.

I'll just quickly mention – I know Bob Temple spoke to this – there is a guidance that talks about drug combination that FDA has put forward. This is specifically intended to assist sponsors in developing two or more novel drugs to be used and treat disease; I think this has provided us a lot of important value within CPTR.

Where we're really focusing now is on how do you select those partners and what are the tools and the biomarkers and decisions you're making to make that rational, early decision on combination partners.

And we also closely follow the guidance that's provided around the development of new drug development tools, as I've mentioned.

So this is how we've designed ourselves. So we have a focus on biomarker clinical endpoints, TB data standard and integration, preclinical/clinical sciences – which spans a lot of things, including preclinical and vivo and in vitro models – and then modeling and simulation.

And the reason that I share this slide is that all along the way we have regulatory expertise from our industry partners and we have our partners at FDA and EMA that participate on many of these working teams to help guide our thinking so that we're not just getting focused on the exciting, nice science; but that we're clearly always thinking about the mission to accelerate drug development. I'm not going to spend a lot of time on data standards, but I know the interest really has been around modeling and simulation, so maybe I'll end on just a couple slides in this space.

So I mentioned to you that we did a huge assessment of what has been done in the published space around developing models that help either describe the disease of TB, but also really what tools are being implemented currently with our industry partners in

terms of combination drug development. And we decided there were lots of gaps or there are ways to improve on the models that currently existed.

And so we are working now on a number of programs, included are the development of a physiologically-based PK model – or a PBK model – an actual TB disease progression model; so even though this disease has been around forever, nobody's really described this disease progresses in a mathematical way. We are going to end up with a clinical trial simulation tool if it kills us.

We're also focusing on a systems biology model because there is a lot known in the target space that – the mechanism of resistance space, et cetera, and it's time that we describe that in a way that helps us, again, choose combination partners to address those multitudes of mechanisms as well as a population PK model.

And so this is how those pieces fit together. For any individual drug you want to make sure that you're hitting the pathway of interest; wonderful to get to know what target you're actually acting on.

Then you need to really be focused on are you choosing the right molecule – and in this case right molecules. Then it gets complicated. You need to know how to dose that molecule or molecules – if you're talking about a combination therapy – and then you also need to have the right patients in your trial and you need to understand how this drug is going to impact those patients.

And so we are looking at applying these novel models that will help us have a rational and informed approach all along the way.

So the _____-fiber model – I won't go into detail – but this is an in vitro tool that we are using to simulate human pharmacokinetics of novel TB agents as well as regimens to help us select those right molecules using those data in that early-systems pharmacology and PBBK approach, and then using the more advanced models as you moved around the drug development paradigm.

And there are many of you who this is entirely gibberish to you, and then there are those in the room who think this is a very high-level summary of what modeling and simulation is. So I've tried to at least show you where it fits in the pathway.

This is the more complicated schematic, right? But what I like about this slide is it helps me to articulate the types of questions you're asking by using these models. So for quasar modeling in the very early stages, the decision you're trying to make, 'Is the drug acting on the relevant target?' For our PBBK model, 'Is the drug exposure adequate to achieve the affect that we desire?' From a clinical trial simulation standpoint, 'What is the most efficient trial design to demonstrate the affect?' And I know there was some conversation about that yesterday.

And then the therapeutic decision support through modeling is really, 'Is the benefit risk associated with the use of this combination optimal? And can you, through multiple simulations, help assess the risk of either the design or the use of this combination that you would be proposing?'

And so what I will say is that this is not something that, as a consortia – there are five of us sitting around developing these models, right? We're a mixture of a lot of different kinds of expertise. So in this particular space we've brought in a core of subject matter experts who are known in the field for every type of model, and we are working with CRO's, academic institutes and industry partners to develop those models.

So it's not something – I know it came up in the breakout session – that we sort of had a diffused group yesterday. If this is something that you really wish to pursue, you do absolutely bring in the right subject matter experts that will always start with doing inventory of what's known or done in the modeling space currently for AD.

Even if it's minimal, there's some work that's being done; and so that's always the best inflection point.

So I want to just spend the last two slides talking about opportunities and challenges and try – and comparing and contrasting the TB space to AD.

So we know that multi-target approaches offered by combination therapies – it's not just critical for us; it's a must-have. TB has to be treated with multiple drugs. And a lot of the drugs now that are being used are failing because of resistance.

So the challenges that we face are similar to the challenges you face. Selecting the best combinations _____; how do you do that, especially when you don't have lots and lots of target

information? How are you going to choose the dose for those agents and combination, right? How are you going to share data so that you can build these models or work through a consortium and share learnings amongst the different targets? What's the appropriate clinical trial design and infrastructure going to look like, right? The current design probably isn't working: we've seen lots of failed trials.

We have the additional burden of dealing with global regulatory issues outside of the US and Europe, so what I would share in terms of the successes that we've had: we have funding.

So when we decided that we were going to take on this enabling early-combination mission we knew it wasn't going to be given to us and it wasn't going to work for free. We do have lots of in-kind contribution from experts and industry partners, but the work is actually funded; which helps encourage sharing of data and the uptake of new advances that we generate through CPTR with our industry partner. The implementation of the data standard and new and ongoing trials is an example of a success for us.

And then I would just share sort of comparing and contrasting this space: TB and AD. The advantage that you have is you have high amounts of clinical data. We are very, very limited in the TB space because there was absolutely no drug development in the space, essentially, ongoing for four decades.

You have a limited understanding of pathophysiology and so you're going to have to look very closely to the early basic science in the space to help inform early systems biology models.

We have a more extensive understanding of pathophysiology, but I will say that it's still not easy; it's a complicated disease, TB, and there are lots of issues with _____ infections, lots of inflammation, granulomas, all of that stuff. So it's not a simple disease.

Translatability of animal models isn't great in your space. We have better translation but I'm here to tell you they're not perfect either. A mouse-modeled TB infection is not, by far, a real model of human disease. And so we've learned to deal with those issues as well.

You're dealing with a chronic nature of disease; we're dealing with a more acute state, but both are going to require quite possibly combination therapies.

I think both are advantaged by the fact that there are therapeutic area standards and so you can make use of the data that are there, I think, in a very informed way.

And so with that I'll just thank my partners and then maybe ask my fellow panelists to come up and I'm happy to take questions as part of this panel session. Thank you.

[Applause]

David Dilts: Good morning. It's like teaching freshmen. Good morning. People in the back are still not paying attention. Good morning. There we go. Okay, thank you.

This is the first panel of the day and what you're going to see is three very different ideas as to looking at consortiums, how different people have approached this. Our next speaker is going to be Chas, whose going to talk about having put some of these together.

I'm going to talk about in the non-biology space of consortium; dealing with things like USB ports and things like that. So Chas, I'm going to let you go next.

Chas Bountra: Well, thank you very much David. Thank you ladies and gentlemen, good morning.

What I'll try and do in the next few minutes is just share with you this question: Can we create a cross-pharma collaboration for combination development in Alzheimer's disease?

And what I'll do in the next 10, 15 minutes is just share with you what we've been doing and what we're planning on doing, and then we can sort of maybe come back to this question.

So two experiences. So I head up a group called 'The SGC,' The Structural Genomics Consortium. It was started in 2004, and the remit of the group was to generate structures of novel human proteins – so this is a 3D x-ray structure – the shape of the protein; generate those structures and make them freely available to the whole world immediately.

Don't worry about publishing; put them into the PDB and share them with the world. Then in 2009 I started this program. I wanted to use the structures that we had to design novel, small-molecule inhibitors, and I decided to focus on a class of proteins called 'epigenetic proteins.'

I don't have time to go into why but I think epigenetic proteins, I believe, are going to be great drug targets for multiple therapeutic areas.

So this is what we are. We're a public/private partnership. We're about 200 scientists based in Toronto and Oxford. We receive a lot of public funding. So in the UK the Welkin Trust have given the Oxford group 50 million pounds in the past ten years.

We currently are working very closely with eight large pharmaceutical companies and they're listed here: GSK, Pfizer, Novartis, Lilly, Takeda, formerly Abbot, now AbbVie, Janssen and Boehringer Ingelheim. And we've got a queue of other companies frankly waiting to join and we'll be announcing another two in the next couple of months.

Each of these companies is contributing $8 million. So we have $64 million of private funding in addition to our public funds.

So what do we do? What's our output and what's the way we work? What we do is we generate novel re-agents to enable new biology and to enable new target discovery.

So we only work on novel human proteins. We establish new assays. We work out the shapes of those proteins. We design small molecule inhibitors, and we generate antibodies.

These are starting points for drug discovery. And everything we make freely available. We give it away to academics, to biotechs to pharma because I believe that's the best thing I can do to facilitate science and therefore facilitate drug discovery.

And all of our data we publish immediately. So what's been the impact? I'm just going to give you one example.

Four years ago when I started this project on epigenetics people thought I was mad, the protein families we're working are impossible, nobody's ever generated a molecule.

One of these families is called bromodomains, and altogether in humans there are 61 members of bromodomains. Any way, we generated a molecule and it actually is an anathema – it exists as an anathema; on is active and the other is inactive.

This is the compound. This is the active; it's nanomolar potent. And this is the inactive anathema; it's inactive.

We showed that this compound reduces tumors in a xenograft model of a very rare cancer called 'the NUT midline carcinoma.' So this is a plot of volume. This is – in the presence of vehicle – you can see the tumor getting bigger; in the presence of this compound here completely wipes it out.

When we generated this molecule with a colleague, Jay Bradnir at Harvard, Jay wanted to take this molecule into patients because he knew that his patients within three to six months are dead. There is no treatment for NUT midline carcinoma.

Let me just share with you what this one molecule the impact has been. We published that molecule in *Nature* in December 2010 – so two-and-a-half years ago. That paper has been cited more than 200 times. Because of that one paper there has been 172 papers published in very eminent journals, peer review journals, in two-and-a-half years.

This has been the impact of one freely available probe on science. We've given that molecule out to more than 300 labs all over the world. And these labs are profiling that molecule in other types of cancer, inflammation, infection, et cetera, et cetera.

Now you can imagine the breadth of biology and the depth of biology that is being generated by this academic network. There is no way that GSK or Pfizer could afford to do that themselves.

Many of our pharma partners have started proprietary efforts on that target. And our colleague Jay BrADNIr in Harvard secured $15 million of VC funding to set up a new biotech on that target. This has been the impact of one freely available probe on science and drug discovery.

So this is what I think are the benefits of public/private partnerships. They allow pooling of resources, leveraging of funds, sharing risk. They allow us to reduce duplication and

wastage. And currently in biomedicine and drug discovery there is massive duplication in science.

And it allows us to freely access global academia. My group in Oxford are currently collaborating with more than 250 academic groups all over the world, and I pay nothing for those collaborations.

Now let's think about the clinical situation and what we're now setting up. This is my view of the situation in drug discovery. Many groups, many companies, many academic groups work on the same few targets in competition.

The tragedy is that most of them fail when we take them into patients for the first time. The failure rate is 90 percent plus and that's why we're in such a crisis.

Frankly we are wasting resources and we're wasting people's careers.

Importantly, the way we're doing drug discovery today we are exposing patients to molecules that other groups already know are destined for failure. Ethically, morally wrong.

The costs of this failure are becoming unsustainable. The public funders, the patient groups and the regulators are desperate to help. We desperately need more what I call 'pioneer medicines'; so completely novel targets for treating patients.

I absolutely believe that target validation takes place in patients; it doesn't take place in animal models, and it doesn't take place in cellular assays.

So what I want to do is I want to take new targets into patients as quickly as I can. So we urgently need more clinically-validated pioneer targets. I'm not interested in targets validated in rats because I can generate hundreds of those and I can generate hundreds of papers.

So the question, can we create a public/private partnership to more efficiently generate clinically validated pioneer targets?

So this is what we're going to do. We're going to treat this as a knowledge creation endeavor. The reason drug discovery is such a

lottery at the moment is because we don't understand human disease.

In the target section yesterday, Zaven was talking about all these different pathways that contribute to Alzheimer's. We can't prioritize those pathways. We could list hundreds of targets and hundreds of mechanisms that contribute to Alzheimer's. Can we prioritize those? I don't think so.

We need to increase the knowledge base if we're going to reduce this failure rate in the clinic. What we will do is we will share all of our re-agents freely just like that inhibitor we're giving out to 300 labs. We're going to publish everything we do immediately to reduce duplication and wastage.

The targets we work on will be selected by our partners and certain academics. Patient groups and regulators have said that they want to be active participants in this knowledge creation endeavor.

And industry will lend – once we have a clinically validated target – they will create proprietary assays.

It's good for industry, it's good for patients. I would also argue that it's good for public funders because we're not wasting money on failed targets.

So this is what we intend to do. Take completely new targets all the way through this process to what we call 'proof of clinical mechanism in patients.' Some experimental medicines, some phase IIa, possibly phase IIb studies.

In the process we will generate these re-agents in blue, and we will use these re-agents in blue to generate these publications in red. These re-agents and these publications, they will facilitate more collaboration, they'll allow us to leverage more funds, and they'll allow us to do more proof of clinical mechanism studies.

I may decide to work on one of these bromodomains proteins and, working with John Allam, I might decide to do a clinical study in schizophrenia. But if Dan said to me, "I think that molecule is going to work in Alzheimer's," or something like this, we'll say, "Look Dan, here's the molecule; you get the funds and you do the study in Alzheimer's."

This is crowd sourcing clinical studies. That's what we need. We need to crowd source clinical studies, not crowd source animal studies.

Who will do what? The target selection will be done by our industrial partners in some academics. The lead identification could be done by various screening infrastructures, possibly by us or CRO's. Lead optimization actually coming up with the clinical candidate. And the pre-clinical activities we will do virtually by CRO's. And then the phase 1 and the 2-A study will be done by key academics.

Using probably a completely new way of stratifying patients or a completely new biomarker. This is going to be very much innovation focused, and of course innovation focus means greater risk.

Where have we got to? We've already started this hair-brain idea in cancer. We've got the world's biggest cancer charity – Cancer Research UK – we've picked a target – it's a demethylase – it's an epigenetic enzyme – we're going to generate an inhibitor, we're going to take it into patients and we're going to do the clinical study and we're going to share all the re-agents and all the data as we go along.

Now the Canadian Institute for Health Research have taken a phenomenal step. They have put $30 million on the table to initiate this project in neuropsychiatry. They're holding a meeting in a few weeks' time in _____ on July the 8th, and at that meeting we now have eight pharma R&D heads – or neuroscience heads – attending that meeting. And together we will decide what disease we're going to do, what targets we're going to do, et cetera, et cetera.

I'm often asked about 'What's in it for pharma?' Let me just put up some simple figures. Let's assume that within pharma, to take a novel target and do some sort of proof of clinical mechanism study it costs $30 million. I've done many of these programs; I can tell you usually it costs a lot more.

We estimate that within this public/private partnership – because we're going to work with academics and I'm not going to pay them anything, and smart clinicians, and with patient groups, et cetera – we believe we can do it for on average about $15 million.

The public funders have already put $30 million on the table; I'm absolutely confident I can get money in the UK, Europe and hopefully also in the US.

Now, we've got eight pharmas coming to this meeting. If six pharmas each put in $5 million we'll have $30 million. And this is over five years, so it's only a million dollars a year. And I think this is eminently doable when you bear in mind what money the SGC is getting to generate pre-competitive probes.

If we have $60 million we could do potentially four of these studies: four clinical experiments. And we're going to share all that data, all that knowledge, all the re-agents with the whole biomedical community in the world.

The cost to each pharma for this experiment is $5 million. This is pretty good leverage of funds.

Summary. To rapidly generate more pioneer medicines; we have to. This isn't just Alzheimer's; this is schizophrenia, this depression, this is chronic pain, this is all the chronic diseases we need treatments for.

We have to pool resources, we have to pool expertise. We need to make full and rapid use of public infrastructures and global academia. We need to harness the resources and the expertise of patient groups and the regulators. They are desperately keen to help.

I believe this is all doable if we delay IP and competition.

What's the point of taking out IP on novel targets when nine times out of ten, five, six years later they are going to fail?

So now, the question. Can we apply this sort of model or some variant of it to develop combinations for Alzheimer's disease?

I can tell you that part of the discussion in Ottawa, some of our pharma colleagues are saying we should consider this model in Alzheimer's.
They have already said – many of the pharma companies – that they are willing to donate existing assets to this endeavor.

My concern, based on a meeting that Neil and Susana organized a few weeks ago, I think in Alzheimer's at least, doing a proof of

clinical mechanism study for such a small amount is going to be a challenge. But working with Reisa I'm sure anything's possible.

Personally, I believe the answer is yes to this question. Frankly we have to do it because I honestly don't see another alternative.

Ladies and gentlemen, thank you very much.

[Applause]

David Dilts: Thank you Chas. Thank you. I'm David Dilts. I didn't understand most of what anybody was talking about yesterday. My latest thing I had in biology was a sophomore class on biology I took over the summer because there was a cute girl in the class.

So one of the things talking about is – you heard this morning – is do we want to build yet another consortium or do we not? If we don't build another consortium how are we going to advance the progress of Alzheimer's disease research?

We've heard two excellent presentations on different ways of looking at advancing research in Alzheimer's: I'm going to talk to you about a completely different look at consortiums coming primarily from the manufacturing side, and so I'm going to have a very different perspective.

But, by the way, I want to know if any of you noticed that you're now in rock science. This was yesterday's *Wall Street Journal*. There's been a study of rocks in Alzheimer's patients where it was actually published and they found that patients who took a blend of whatever _____ is in vitamins experienced fewer disease symptoms on a 12-point rating scale. This is what was published about Alzheimer's research in yesterday's *Wall Street Journal.*

If you want to have something else that's really condemning to me: today's front page *USA Today* is all about problems of baby boomers, and it doesn't mention Alzheimer's. That's a problem, right? It's an awareness issue.

Okay, one of the things that I've studied in my career is lots and lots of different industries. I've studied – a friend of mine says 'from roses to rockets' – I used to work for FTD – then I used to do stuff on missiles, and then I did a lot of work with the automotive industry, and now I'm dealing with cancer; so I've learned a lot by studying industries. And most of the stuff that I do

is what I try to do is figure out how to put things together. I don't look at the uniqueness's of things; I look at the commonalities.

I absolutely guarantee you there is total uniqueness with Alzheimer's disease compared to tuberculosis, compared to cancer, compared to any other disease. Promise you. I look for all the 80 percent. You're all doing clinical trials. You all have to go to the FDA. You've all got to get paid for by somebody. Those are the things I look at.

And I look at how can we learn from the mistakes that they made? And one of the things you find out by looking at lots and lots of different industries is lots of people have made some phenomenal mistakes that you can learn from.

But one of the things that every time I give a talk to any organization – and it's always true – is this: everybody is special where the normal rules don't apply, right? Nobody knows the trouble that Alzheimer's researchers have because we're totally different than TB. And we're totally different than cancer and there's – I mean it's just amazing how many differences there are.

I look at again, how are people common? How are people when they share things? So I'm going to address a bunch of different things about consortiums.

Number one is 'What's the scale of the problem you're looking at, and are you focusing on the right problem? What's the overall goal?' And I thought we had two excellent ideas of what's the overall goal we're shooting for as opposed to lots of what I call 'proximal goals.'

What direction are you going – I used to do a lot of work in heavy industry called 'road mapping': what is the state of the world and what do we want the state of the world to look like in ten years?

If you want to know why computers are so bloody fast today, it's because a guy by the name of Gordon Moore, about 30 years ago, came up with what he calls 'Moore's Law.' And he said computers will double in speed every 18 to 24 months. Now, when he said that every single company said, "In order to succeed, I need to double my performance." Which means he set what's called the 'clock-speed of the industry' that has to be fast and nobody wanted to be left behind; so they all pushed that, and guess what? It became a self-fulfilling prophecy.

What's the road map for research in Alzheimer's? What are the critical gaps – not necessarily in research – what are the critical gaps in technology? What are the critical gaps in infrastructure that need to be filled before you get to the next step?

That's what you do in road mapping. Who should be part of it? Who are the key members, and how do you make decisions?

So this is the largest scientific instrument ever built. It's the Hadron Collider in Switzerland; it discovered the 'God particle.' Millions and millions and millions and millions of dollars. Okay?

Key thing about this; it's a very focused, multinational effort by literally thousands of worldwide scientists on one problem. In other words it's a very focused issue.

And a colleague of mine who was at Oregon Health and Science University used to say this, "You don't get a working cyclotron by funding a thousand RO1's." Are you funding a thousand RO1's on Alzheimer's and you're getting a thousand point solutions hoping like crazy some of them will come together.

You need a more formal mechanism of putting it together.

By the way, there are some joys with not collaborating. This little toy here made a fortune.

Now here I want to talk about an absolutely brilliant person. Imagine creating a product you're going to sell for a premium price when your competitors are giving away two for the price of one. That's what Steven Jobs did.

He basically said, "I'm not going to collaborate with anybody. I don't care. I'm smarter than the average bear and this is what I'm going to do."

Key question. How did he get there? Well, he got there by building a collaboration of record companies. He said, "If we all get the record companies to collaborate together and share under a standard model, I can make a fortune." This is the genesis of being unique with a collaboration. Okay?

So one of the things I look at is I look at are we focusing on the right problem. This is how I got into cancer. I got into cancer and

I talked to a clinical researcher because he asked me to and I said, "I have no idea what this stuff is. Tell me what it looks like."

And from right here – which is when you have a good idea – until right here when you close down the study; I just said, "Let me map out the process."

Well, come to find out, this is what happens. That's where you open a clinical trial, that's when everybody studies clinical trial steps and nobody looked at how long it took to get ready to work.

I spent all my time on efficiencies and how to get ready to work: how long does it take you to get a trial ready to go, not just 'run it'? It is astounding how much time it takes.

By the way, is it a big percentage of the effort? This isn't cancer. Half the time in cancer, at a phase 2 or phase 3 – any of you have teenagers or remember being a teenager? Remember how long it took you to get ready to work? Right? It takes you just as long to get ready to work to do work.

That's part of the problem with doing clinical research. How long does it take to get ready to work, because every single clinical trial is absolutely unique; we've never seen one before. Like, "Really?" You've seen hundreds of these things.

And you listened to Don Berry talk about a beautiful design for clinical research, but you know what? Once you know how to do it; do it again and again and again and again.

How did Steven Jobs make an absolute incredible fortunate to this? He changed colors. Seriously?

Why do you act like a new clinical trial is absolutely unique; you've never, ever seen it before? Are you focusing on the right problem?

If you ever want to look like cancer: don't. The time it takes to open a cooperative group for The National Cancer Institute – a clinical trial is 920 days. Right? Two-and-a-half years. That, ladies and gentlemen, is not the problem.

The problem is it takes a little over a year or a little under seven years to open a trial. Note: Open a trial. Not getting anybody to show up, not answering – just getting started. Okay?

By the way, it takes an enormous number of steps and processes but I want to show you this one. Thirty-six separate people have to approve a clinical trial before it can go forward.

Chas, you can't run an experiment unless 36 people approve it. It's not right. It's insane how long it is.

By the way, the big condemnation; they didn't know it. It took somebody like me to say, "Have you ever added it up?" Right? That's a problem.

Here's a major issue I find in all research – and this is just clinical trial, okay? The blue is how long – each one of these is an individual clinical trial that's going out for approval. The blue line is how long it took to do basically scientific revenue; the red line is how long the investigator sat on it for God knows what reason; they're going to conferences in Washington, they sit in some basement. "Don't worry, if a missile attack happens we're safe."

And the green line is how long it took for IRB approval. These are real, honest to goodness data from an organization.

Now, what does every investigator think? This. "Those IRB pigs; look what they've done." And what does everybody of NCRB say? "Look, the stupid investigator sat on it forever." Right?

What I find amazing is nobody says, "How much of a percentage or review –" nobody ever complains about that. Right? As a management scientist, looking at this whole area of consortiums and everything else, is variance. How much does it vary?

High variance equals high uncertainty, equals high dissatisfaction. If I don't know it drives me crazy. So when looking at the whole issue of consortiums and developing stuff, how long does it take and can I plan for it because if I can't it's just crazy.

This was last week. 'Prominent lawyer calls for improvement in the 510K program citing intolerable processes.' I have no idea what this is other than just to get the FDA regulatory approval process. The major problem is excessive unpredictability. It's not that it's long; it's that I can't plan for it.

One of the things about getting a group together is saying, "Can we plan better for this? Can we actually structure what we're trying to do?" Okay?

By the way, does time make any difference to get stuff started? This shocked everybody. If you don't open a clinical trial in cancer within two years you might as well just not open it. No patients are going to show up for it. You might as well stop it.

By the way, you want to hear the other scathing condemnation of cancer that's on those slides? You've done all this work. You've done molecules, mouse, you've done all this brilliant stuff and you put it out in a clinical trial. In the six of the top-ten cancer institutes in America what percent of clinical trials do they open that grew zero patients? Nobody shows up. What size number do you think that is? Twenty-nine percent. One-third of all this wonderful effort; nobody shows up for.

Another third enroll less than five patients. Two-thirds of cancer research is useless. Not because it's bad science, but because no patients show up for it. Okay?

By the way, these are the premier cancer centers in America. Imagine what it's like in a typical center. Okay?

You need to focus on the right overall goal. In the 1960's – this is what I'm talking about – in the 1960's we had two goals: number one was, put a man on the moon. Consent itself to achieving the goal before this decade is over, landing a man on the moon and returning him safely to Earth. Very specific, very pragmatic. Did you do it or not, yes or no? Yes.

The goal in Vietnam – this is a quote from Lyndon Johnson 1965. The primary goal is we intend to commit to Communists that we cannot be defeated by force of arms or by superior power. And guess what? We achieved that goal; they beat us by something else. Okay?

In this particular war – take a hill, let it go, take a hill, let it go – people are going, "What the heck? I'm not going to play anymore." Right?

And this – you went to dinner and you can – and everybody knows about it. And by the way, the other wonderful thing about dealing with rockets; when they don't work it's really scary.

Okay. This is the latest consortium on information technology. All the computer folks are getting together because memory's getting bizarre. In the IT field everything you work with today, probably two-thirds of it was built by a consortium.

The USB's – you know, those little thumb drives that everybody loved, including myself: that's a consortium. They all got together and said – in 1995 – "This is a mistake because everybody's going to do custom interface. Make it so it's plug-and-play."

I heard yesterday about lots and lots of different – I'm going to say molecules because I don't know any better. Those should just be plug-and-play. Plug them into your clinical trial: unplug them. That's what I Spy Two was all about. If you've got a drug for that; plug it in and let it go.

By the way, I should let you know – in interest of full disclosure – I'm on the board of directors of Quantum Leap, which is now running I Spy Two. Okay? But I'm coming at it as an efficiency problem, not a scientific problem. Okay?

Proximal goals should be clear, concise and measurable. They should be stretched – they could be stretched or rated through a continuous improvement. Do a big thing or do you want to do small things? Okay?

How are you going to get there? That's called road mapping. I used to do a lot of this work. What are the critical activities to get you to where you want to be? Number one's where do you want to be in ten years? We want to have simultaneous drug development. We want to have new molecules in the market. Exactly what is it going to take? What are all the steps and who has to play?

And – which is really fun – what's not being funded? What's not part of this entire process? Funding basic science is fun. Who funds good laboratory practices? Who funds good manufacturing practices? Who funds all that other middle stuff that people really don't care about because it's not really thrilling. But you know what? It's absolutely important if you're going to do it.

This is from Bob Gavin who started it. 'A road map is an extended look at the future of a chosen field of inquiry composed from the collected knowledge and imagination of the brightest drivers of

change in that field,' and that's you. How are you going to get there? What's the things you're going to go for?

There's lots and lots of different parts to the road map – I'm going to skip that – but remember, there's two sides to the problem; you have to figure what's going in – which is all the standards and data and things like that – and what's going out – which is the endpoints – and who should be involved?

I'll tell you one thing that really surprised me about this meeting; that the people who are actually going to pay for what you develop aren't here. And you know what? If the FDA approves the drug; CMS doesn't have to pay for it. If you want a lousy financial model, "Hey, it's in the market: you can't get it paid for." Whoops.

I dealt with one company that neglected that and spent an entire year with no cash flow trying to get CMS to pay for it. Right? So who are the people that are asking you to pay for it – and then I always like starting small with a focus – we talked about a small core group, that this is really what we're going to go do; people who have sufficient clout to day, "This is important, let's go do it."

And then I use – and I'm sure you both have used – it's called 'the bandwagon effect.' I want to be part of a party that everybody's part of, okay? I have the coolest phone on the planet and all my friends want to have a cool phone. That's a bandwagon effect. By the way; businesses use it enormously.

Now, decision making. One of the things about consortiums is to say 'This is not what we are.' What do we not do? Okay? Again, one of the things about missiles – I used to deal with these a lot – you had what's called a 'shared destiny model.' Shared destiny model says if the missile didn't work, we screwed up.

It's not the guidance system screwed up, it's not the – well, we, as a collective, did not succeed. That's why you need a nice, simple, straightforward goal – as Debra talked about – it's very straightforward. Did we achieve it or didn't we? There it is. And we're all in it together.

The problem is you have to say no even to good ideas. There's not enough resources to fund everything, so you've got to say no to good ideas. And the best person who said no, believe it or not, is Mahatma Gandhi. A no uttered from deepest conviction is better

and greater than a yes merely uttered to please or what is worse to avoid trouble. Just say, "That's not part of the research we're doing." Okay? That is a major issue.

I heard yesterday – as people noticed, I was the guy sitting in the back trying to figure out what you people were talking about – you are brilliant folks. You have hundreds of ideas. You can't pursue all of them. It would be great if we could but we can't. A, there's not enough money, and B, there's not enough people.

So which ones are not going to go forward and why, and how are you going to focus to get it deliverable? Whether you have a consortium or road map; you have to say, "This is why we exist and this is what we are doing." Okay?

Then you need to manage toward it. Scientists – God love them – love you Chas – typically don't do project management because they get distracted.

Have you ever seen the movie "Up" where the dog's going, "Squirrel, that squirrel." Right? Scientists go, "Molecule. Oh, Pathway, molecule, pathway," right? And just all over the place.

I'm like, "Did you get what you said you were going to do?" You need somebody who's formally trained in it and that's called 'project management.' What's the deliverables you have to achieve by when? And if you don't do that you're a failure.

Note: deliverable means we ran all the experiments and we found an answer. It doesn't mean the answer was yes. It means we ran the experiments. Okay? We didn't get distracted.

The key is what's productivity at a particular point in time? When do you want to be where? What are you trying to do? Okay? So should you create a consortium? That's an open question and that's why we have a panel. And so those are the kind of questions that we want you to ask us and we'll talk about as a collective, okay?
Thank you.

[Applause]

Dan Perry: Questions? We didn't have a chance to ask Debra any individually or any of the other panelists; so this is your opportunity to pursue some of these wonderful ideas that we've heard hear today.

Male 1: In the spirit of the talk we heard I would like to know to what extent the problem with Alzheimer's disease – the fact that we do not have any affective therapies – is due to the barriers posed by regulatory hurdles, in contrast to the fact that we do not have any viable molecules that work. Where should we put our emphasis? Can anyone tell me that there was a viable molecule for Alzheimer's that was delayed from marketing because of regulatory barriers? So that's one question.

The other question is even if we cut the time for regulatory hurdles to half or zero, what do we have at the end? Do we have any molecules that could be used for therapy development?

I think that the real question for us is what are the barriers of what goes into the pipeline and how can we extend that? How can we reduce the risk – scientific risk, financial risk – of what goes into the pipeline, rather than worrying about the process – the regulatory process? I think that's where the challenge is, and that's what we need to be focusing on.

Chas: So my own sense is of – and I think those are two important questions. I don't think the challenge is regulatory. I think either we've not picked the right target or we've not had the right molecule or we've not had the right biomarker, or we went into the wrong patient group.

Male 1: Or we have the wrong ideas about the disease. I think that's fundamentally is the difficult problem.

Chas: Well, that's where the wrong target comes in. I agree. And that's why I said I think it's – we just don't understand the disease. And that's why drug discovery is a lottery.

Personally I wouldn't invest my own money in this. Seriously. I mean, you know would you invest your money in an endeavor, which has got a 90 percent failure rate, and you find out at six years later and there's 20 other people doing exactly the same experiment. I think the issue is organization.

Male 2: I think this is a great discussion. I was wondering, in terms of a road map for success – kind of framing it within the question of a consortium – if you were able to demonstrate success, maybe the answer ends up being yes and you end up solving all your research

questions – should the consortium have lifespan where it's now answered the question and now kind of dissolves back because it's actually solved an unmet need? Or do you think – kind of what are your perspectives on kind of continuing – because, you know, if you look at the Sematech model, you know, it's still kind of being pushed on but it maybe has reached its purpose.

David Dilts: Sematech is pretty much dead. Yeah. You get – how many of you remember the March of Dimes? Okay? And where are they today? Yeah, so what happens is, from an organizational perspective, organizations are loath to die. And so they recreate themselves with a different mission.

And let's just say in a number of cases they shouldn't have. They should have just said, "Declare success and go on." But it's the – for example, I think you've got a sufficiently difficult problem that I don't think worrying about having it solved in the next ten years is really going to be a big issue for you.

But I think that one of the things – again, from outside the industry – and it's outside all drug development – it absolutely amazes me the number of almost pure duplication of effort that are going to be failures that everybody knows is going to be a failure. And everybody – again, it's the bad part of the bandwagon affect. 'If they're looking at a COX-2 inhibitor, I've got to look at a COX-2 inhibitor, and let's all play with COX-2 inhibitors.'

And then they all start failing. And then the next thing comes up and the next and it's like – everybody's kind of like – let me phrase it this way: have you ever watched five-year-olds play soccer? Right? If you ever watch five-year-olds they all run towards the ball – and I call it 'pack soccer' because it's like this big crowd that all runs around the ball, other than the goalies who are in the goalpost picking daisies.

That's kind of how you do drug development. It's like everybody's kind of – as opposed to – think of a pro soccer team. If you think of a pro soccer team; there's not a lot of running, but boy, there's lots of placemen and lots of structure and lots of who's doing what where, and it's a very different model.

In the computer field they've learned how to play pro soccer because they've had to; otherwise they'd be out of business. So it's a different industry structure.

Chas Bountra: Just to follow on from that, a colleague of mine in Oxford has been working on kinases – and so you're all aware that in humans there are 518 kinases. Now as a biomedical community we have been working on kinases for nearly three decades, but if you look at the tens of thousands of publications on kinases 90 percent of the publications are on 50 kinases.

There are 300 kinases that nobody's even touched. And if you look at the patents 95 percent of the patents are on 30 of the kinases, because industry looks at those publications, they work on those targets, et cetera.

So I think even in academia we tend to work under the lamppost. And there are some even funding issues here because as an academic if I apply to the Welkin Trust in the UK 'I want to work on kinase number 400.' I can't create a story on that. And so I end up working on the 50 kinases that everybody else has worked on.

So there's some major – we have to push out into this new space; that's where the new drugs are going to come.

Male 2: I guess kind of what I was discussing is if you were to start a consortium should it come with a limited kind of lifetime where at least the ambition kind of – the level of ambition kind of matches something that you could accomplish within ten years. Or should you just not have that end put? Kind of just in your opinion though; I'm not trying to be leading at all, I'm just curious.

Debra Hanna: So the approach that we took. So certainly we have an ambitious goal, but that goal is very clear. And so we made sure that we developed the proximal goals that were needed to prove that we had the right teams, that we had the right project support, that we had the right focus in order to deliver. And we check milestones every year. We reassess funding every year. And we have actually expanded the work that we've done and the funding that we've received as we've learned, as the science has advanced, and as we have demonstrated progress.

And so you have to be careful. You don't want to set a goal so far out that everything feels diffuse and you can't show progress. But you don't want to set your highest level goal to be so proximal that really you're not addressing what the field needs you to address, which is how do you move forward on a path of early combination drug development for Alzheimer's?

Chas Bountra: I think Debra's point about metrics is incredibly important. So, again, from personal experience within the SGC, you know, my group in Oxford has to do – this is what we've agreed with our funders – we will do five structures a month. Now there are many academic groups in Oxford that do one structure every two or three years and we do five a month. That's the throughput we've got.

In terms of the clinical program, you know, the metric were setting ourselves – if I get $60 million I'm going to do four clinical experiments. I'm going to take four novel targets all the way into the clinic. If I get $75 million I'll do five, et cetera. So metrics are key.

Male 2: And so going to TB, again – and more broadly actually, antibiotics – where – I believe this is still true today unless that, as a whole, there are very few examples of target-based _____ antibiotic drug discovery successes. And I think it's one of the fundamental issues in the TB field of getting to new therapies that is an advance of everything that you talked about.

And so my question is – it's a combination of I think which is the fundamental issue in AD, before we can even start getting to the combination, is how do we solve the drug discovery problems? And my question is is that being solved and what is the role that the consortium is playing in feeding back data and understanding to actually try to solve the drug discovery problem?

Debra Hanna: So I won't say that we've solved it. I'll say that we are certainly trying to address it. So we have this gentle balance of trying to help our partners move forward the compounds they currently have in development. But again we know those were never designed and chosen to be part of a rational combination therapy. And we know some of those things in development will fail.

So we do have a focus on how do we help our R&D partners in the pre-clinical space make decisions about compounds? There are some animal models that are sort of good enough, but we know that there are gaps there. And so we are working to build a road map or a critical path to the early combination from pre-clinical to early clinical R&D space.

And so we have – our industry partners are involved in that, we have the NIAID in that, we have academicians who are either optimizing models or are pioneering new frontiers in that model space. And what we're trying to do to bring in the regulatory loop

is say, "Look, the mouse and the counting of bugs on a plate have been the gold standard for however many decades from an R&D perspective. That's not just going to disappear unless we build the evidence that these newer tools and technologies give you better – equivalent or better information."

And so what we're trying to do is bring together all of those partners to do that right comparison, to help build a prospective plan of validating and analyzing those new tools so that you can make smart decisions about where those tools can be implemented in the early R&D drug discovery and development process. Does that make sense?

And there are certainly other consortia, so the foundation funds an entirely different program called 'The Accelerator Program' where they're working with screening of massive libraries of industry – compound libraries to find new molecules to fund the early pipeline. But again, this comes back to – our mission is very focused on enabling early combination drug therapies. So everything we take on – whether it sits in the early R&D space or actually in the drug development clinical trial space – has to be aimed at that mission.

Our mission isn't to go find ten new molecules for TB. Our mission is to help advise on how to build the right combination for TB. So that's for someone else to take on.

Chas Bountra: Well, I think it is an important point. And you know for me, this consortium isn't just about accessing funds from lots of private organizations; it is about accessing their expertise. Because I absolutely believe the industry is brilliant at certain things, and I believe academia is brilliant at different things; and we're trying to pull together the best of both.

Let me just give you an example, again, in the structural area. You know, generating structures of human membrane proteins is almost impossible. I mean people are getting Nobel Prizes for these.

Until two years ago in Oxford nobody had ever done a human membrane protein structure. Now what we did was we got all of our pharma colleagues together – the bench scientists – and we set up a six-weekly meeting where together we designed what experiments we would do in the next six weeks and we would share the data of the previous six weeks.

In the past two years we've generated two membrane protein structures, we've got another two coming out this year – and let me just also share with you that one of the structures we generated a year-and-a-half ago we published it in *Science* about a month ago.

Eighteen months after generating that structure we published, but we released that structure 18 months ago. We told the whole world we've solved this structure, this is how we did it, because we wanted to reduce duplication. But we still got it published in *Science* 18 months later.

We've just got to completely destroy this current model. You know, everybody's obsessed about their publications, and the fact is we are wasting money.

Debra Hanna: So I'll say part of our mandate is that any of the work that's generated within our consortium is made public; so that's part of the mandate. But I will tell you we have a harder time getting our academicians to share data than we do our industry partners. And there's a reason for that.

Male 2: So a somewhat related question because it comes to the old question of target specificity, et cetera. In the '80's space – and actually kinase is our good example – the active kinase drugs as a whole, there are very few that are really as selective as we think; it's the spectrum of activities that lead to the clinical activity.

In AD if you actually got to a proof of mechanism result with a molecule in the clinic – that you were able to take into the clinic – would you really go back and try to de-convolute the target versus just going forward? And how do you, in the consortium, then decide who takes that molecule forward?

Chas Bountra: It's a great question and I did have a slide and I didn't go through it in the interest of time, so let's just walk through this. So let's say we do ten of those clinical experiments. Nine times out of ten they're going to fail. So what we will do is we'll publish everything. This is the structure of the molecule, this is how we selected the patient, this is the biomarker we used, these are the plasma exposures; it's absolutely everything.

We will also publish this molecule – this is everything we know about its potency and selectivity. Now what that will do is it will reduce – it will not stop – but it will reduce other academics, other biotechs, other pharmas, doing exactly the same failed experiment.

Now one time out of ten it will work. Now of course you and I know many times the first molecule we take into patients rarely becomes a final drug because there's something wrong with it, the PK isn't right, the bio-availability isn't right or whatever.

So then our pharma partners have an opportunity, now they have a clinically-validated de-risk target; they can go and do what they're good at. High throughput screen, lead optimization, come out with a proprietary molecule, take it into the big clinical studies and launch it. That company benefits and patients benefit and society benefits.

Now your question is in that very, very, very rare circumstance that molecule has worked and the molecule has got the legs to go all the way – because this molecule we're going to have has no IP on it. And it's an important question.

So we've agreed to do – this is following many conversations with lawyers and regulators and industry, et cetera, et cetera; this is what we've agreed to do.

We will auction the IND for that molecule to our partners. If Sanofi buys our IND – and it's important to bear in mind the IND contains data that would not be in a normal academic publication; like 'How did you scale up the molecule? What are the impurities?' And you need that IND to do the subsequent 2-B, 3 studies, et cetera.

If Sanofi buys that then they take it all the way to the market, then based on today's laws – this is not a change in law – based on today's laws they would have five years of exclusivity in the US, six years of exclusivity in Japan and eight years of exclusivity in Europe; five, six and eight is not bad.

And then of course everybody else you can take out patents on combinations, et cetera, et cetera.

Dan Perry: Debra, I want to start by apologizing again for getting ahead of myself and not teeing you up for your individual talk. I thought it was marvelous and I was captivated by the parallelism of what Critical Path has done in the TB space and potentially carrying that over, and the differences as well.

One of the circles at the bottom was the TB Alliance, which you said is the development arm and extremely important. Can you tell us a bit more about how that's structured? Is there a steering committee to it? How large is it? Exactly what's that role?

Debra Hanna: So the Global TB Alliance is an independent nonprofit product development partnership that was set up by the Bill and Melinda Gates Foundation, and they may have some additional funding sources at this point.

So they are an option for companies to work with them to develop combination regimens in typically the drug-sensitive TB disease space. So they're a separate nonprofit PDP that were brought in as one of the three major partners for CPTR because of their depth of experience and TB drug development specifically – combination drug development for TB.

Having said that, our industry partners can continue to work and develop their compounds on their own. Some of them are choosing possibly to partner up amongst each other and not work with the Global TB Alliance, with the goal that they'll make some return on investment in their development.

So the PDP offers us a breadth of experience in the drug development space. It won't surprise you if I say that there are some differences in thinking, even in how they approach a clinical development plan as compared to what maybe some of our industry partners would do. But at least bringing everybody together furthers that dialogue about the pros and cons of various approaches for combination drug development in the TB space.

But they are a separate PDP entity, they have a board of directors, they have budgets, they work under, they have contracts with companies – so either compounds that have been donated to them, perhaps compounds that they've purchased for a small fee to move forward on their own in combination regimens – if that answers your question.

Dan: Yeah, it does. Thank you.

Female 1: So again, just to get back to practical and how we do this in Alzheimer's disease, because I – you said a lot of things that really resonated and I'll just tell you the few as a clinical researcher, that – so one, Chas, I absolutely agree that we have to figure out a way to validate our targets in humans because, especially as we move to

non-Abeta targets and a broader thing that may involve synoptic and network integrity; some of this I think we're going to have to do in humans rapidly.

The other thing very much is how much inefficiency there is in setting up each clinical trial as we do it. Because actually I was going to guess a higher number for cancer, because we've looked at this just in our own space in Alzheimer's disease and it's about 35 percent enroll; less than either zero or one or two subjects because it takes so long.

I don't actually think it's the regulators and I don't think it's the IRB; I think it's the coordination in reinventing the wheel each time, every time we do it.

So I guess the question is, again, I very much heard Maria about not wanting to reinvent the wheel for consortium, and I think there's some – she's correct about this. But how do we actually move forward in setting up this rapid clinical trial, kind of an I Spy Two, where we could require people who already have phase one data with each of their molecules, but really facilitate the combination in humans for the first time with good biomarkers and other things to really tell us we're moving in the right direction and maybe take them into phase 2-B to see whether we've got any clinical signal or not.

So I guess the real question maybe is to Debra; how did you get to the point then of bringing the people to the table to set up the clinical trial piece of it? And where do we go from here? Maybe we're going to talk about that stuff this afternoon, but – or tomorrow morning – but I'm anxious to move.

Chas Bountra: You should move to Oxford. I should clarify. It's not that I said I wouldn't invest my money in AD research; what I'm trying to say is the process is so risky. Yeah.

Debra Hanna: So I'll try to answer this question as concisely as I can. So, from a clinical trial network perspective there were some important things that were going on about the time that we launched the consortia.

So the HIV/AIDS clinical trial network within NIAID was being repurposed to be a TB infrastructure. And so that was incredibly helpful. There are certainly clinical trial sites that have been used and identified by our industry partners.

So one of the things that came together is we pulled those different clinical trial networks under one of our bubbles, right – one of our umbrellas – so at least those groups were talking to one another. And as our industry partners were considering where to set up trials there was an inventory, there was a point of contact, there was a way for them to communicate about where were the best possible sights for them to run their trials? And so that is under the larger umbrella of one of the hubs.

I think the infrastructure that was also set up by our PDP partner at the Global TB Alliance has been very helpful and maybe available, right, to our industry partners as well. I don't know if that answers or if you have…

Reisa Sperling: The good news is that I think in AD we do have some networks set up and the ADCS is a great example – DIAN– and we've already had some discussions here about how do we pull in some of the other networks that exist, like NAC, the ADRC's and all of – so we have a lot of really good networks set up, but we don't all coordinate for the common purpose of this combination therapy.

Debra Hanna: And we certainly didn't either. Yeah, so it's a misnomer if people think, "Wow, it's a global health field. We all love each other, we all talk all the time." That was not the case. I mean it surprises people. It was not the case.

And so part of the function of the consortia – for better or worse – is to organize, to communicate, to point people in the right direction. It doesn't mean you all have to agree, but there shouldn't be these silos. Whether you're talking about targets people are working on, whether it's clinical trial sites or networks, whether it's, "Gosh, we just don't have a solid inventory of the models that are being developed and implemented in trial design right now." It's coordinating that knowledge in a way that everybody can tap into and just gain some efficiency.

David Dilts: We actually did some work on clinicaltrials.gov on cancer trials and depending upon the disease site there are radically different network structures. And the thing that surprised us the most is you just look at who's playing together in different sets. In colorectal cancer there are two massive networks that basically don't cooperate at all.

And I'm not talking to the folks who are just – yeah, it's like who's actually running the trials? There are very different networks who have very, very different approaches.

And so when look at efficiencies is – you don't necessarily want one big massive network, but you want very effective _____ and very effective partners. And I'm doing some work with The National Cancer Institute at looking at a very different idea of what a key opinion leader is. A key opinion leader to me is a center that can open a study quickly and accrue; which is very different than a scientific key opinion leader.

So who are the ones that basically all the other clinics want to follow if they open the study and then things are going to accrue quickly.

Chas Bountra: And I think there's a cultural component to this research. I mean I think there are some people, like yourself, who appreciate that you can do certain things. But if we want to do some of these big things then we're going to have to work with other people. That requires, frankly, a little bit of humility, and maybe, let me just say, some of my colleagues don't have that humility.

Zaven Khachaturian: Okay, I will follow David's admonition and say that our problem is different than others.

David: I know you're special, thank you very much.

Zaven Khachaturian: I'm very much an advocate for consortia and collaborative work and I've worked on creating such consortia – and we're lucky that we have several: we have the ADCS, we have _____ and the ones you mentioned, Debra – there's quite a bit we can learn from, including the consortia that cancer and other diseases have done.

Our problem is different in a sense that we are in a situation where we need to consider how we can structure – if we're going to structure consortia to be different and more effective, and avoid some problems that the field has had.

One of the big problems we have in our field is that there is something called 'scientific orthodoxy': an idea about the therapeutic targets– which sort of narrows the options. And we have put blinders in accepting these orthodoxies, and there has been a momentum created where academia and industry, they go back and forth and they feed each other's idea.

So the problem is that those – that that effort has failed to produce any affective treatments. So what we need to do is broaden our vision and open up options. So my concern is that if you create a consortia you're going to try to again create a situation where we're going to try to look for consensus: regression towards the mean.

I don't think a committee has ever discovered anything – novel idea. You don't get a committee to think out of the box. So we need to find a way in which we open up the field for new ideas, new ways of conceptualizing the disease, identifying new targets. How can we do that and at the same time create the benefits or the efficiencies a consortia can provide us in terms of reducing the cost, absorbing some of the risk that industry's avoiding, by finding a way in which you partner with government.

So we need to be very careful in how we go about doing it and not do it so dramatically just because cancer did it or just because of that. In that sense our problems are different; we need to find ways in which we could address our unique problems and solve those.

Debra Hanna: So what I will do is push back just a little bit. So I don't think from the science perspective we seek – we go out of the gate seeking consensus. We have some very polarized groups as well in the TB space; largely around the best models, right? And what we've said is, "Prove it." Right? Prove through validation, you know, your hypothesis and your concept of why that model is more predictive, why it's going to help us gain efficiency.

And so that's the challenge you put to the scientific contributors. And I think you'll find people will be excited about sharing different approaches, different ideas. You're not driving to get everybody in the first month to decide on one target and put all your resources in that space. But I do think you need to send the message and come collectively to some idea about what the proof of concept is going to need to be in this particular field.

I think there are ways to tackle the non-target related issues through some of the consortia, like approaches that I've described. You know, we're dealing with global regulatory challenges; you're not going to have that but you may want to address the clinical trial infrastructure network, information sharing, that kind of thing.

But that comes back to what is your one high-level, long-term goal for whatever collective effort you decide to take forward – whether

it's consortia or not – and work backwards on what's going to be the scientific component you're first going to try and tackle. Maybe there isn't a regulatory component but maybe it is more about clinical trial design, et cetera, and then set those highest-level goals. And bring in people who are going to be willing to challenge on another not just build consensus.

David Dilts: So consensus is not really what you're after because consensus is what you already know. And you saw how successful you've been so far. I hate to tell you this – I'm not in this field – but boy, I mean – again, I'm going to pick on cancer – we've been at war with cancer for 40 years. Yeah, okay.

There's a couple of things to think about. Number one – I'm going to give you two business terms – fast frugal failures. Quick, fast, find out if it works or not; if it doesn't work, stop. Make it quick, make it easy, make a low entry point and go.

The other thing to think about – and this is an interesting business strategy – it's called 'Blue Ocean Strategy.' A red ocean strategy is where everybody's competing and it's red because it's full of blood. A blue ocean strategy says, "Play where nobody else plays."

Classic case. I'm going to start a circus, which means I have to have animal acts and three rings and et cetera, et cetera. Except that guy that created Cirque du Soleil said, "That ain't what I'm going to do." And he created a brand new form of entertainment that never existed before, by saying, "What's truly driving the need?" And he completely re-envisioned what the field was like.

Steven Jobs did not get successful by doing what everybody else did. He was really successful in figuring out what customers would buy no matter how much it cost. Okay? That's why he's brilliant.

And so those are the kind of things that I think you need to think about. And completely agree; getting consensus is not necessarily the best way to do things.

Male 3: I'd like to just share some impressions as a clinical researcher and as an advocate on behalf of my patients. It seems – I think we all would agree we have an urgent need in treating Alzheimer's better. We have a lot of resources and talent in this room and in the

Alzheimer's field and related fields and I think we've heard some inspiring models of how we might collaborate and also innovate.

And I'm agreeing in general with what Maria said this morning, and what some of you have said on the panel, in that we just need to open up the field to bring the talent together to meet the urgent problem. Sort of like the Manhattan Project in you bring the most talented people together to solve a really serious problem in a short period of time.

Our problem is more ongoing than just creating a bomb, but it's creating that type of success and innovation. I think ADNI has provided real inspiration for how we can create a public partnership – a public/private partnership that really works, where the information goes online almost immediately where researchers around the world can use the information – sort of somewhat of what you've been talking about – and we need to do this in the therapeutic area.

And that means breaking down the walls where people – as people have already said – working silos, where we'll really bring the best ideas together in the most innovative way and get the information out there so we don't recreate the same mistakes, and we create innovation, not just consensus.

So – but I'm not clear yet how – I mean start with what we can do, because I envision over time that we will treat Alzheimer's disease with combination treatment focused on multiple targets, and I think it's going to be more than two treatments. Like in TB, it's going to be more than two treatments. That's going to be the wave of the future. I'm not quite clear yet how we get there working through all of the different challenges.

I'm not – I'm very optimistic; I see it happening. I can envision it in my mind down the road, but now we are right here on the ground – ground zero, so to speak – and thinking of how we're going to get there. I know we will get there.

And I think obviously we'll start with the treatments that are already available that make sense, that would be safe to combine, and we'll do it in a deliberate and careful way, that we'll have treatments we can envision very soon coming online once they're a little further along. And then we have treatments we don't even know yet, will be part of that whole eventual treatment regimen.

So I don't really have a specific question or a suggestion other than like in ADNI – the reason ADNI was successful, there was no – it was pre-competitive: how to open up the therapeutic area so that we really can foster innovation.

Chas Bountra: Well, I think you've almost laid out the road map. I mean just starting with what we can do today, what assets are available, let's see what combinations make sense, and let's just start doing one of those experiments and then other things will follow.

I can tell you in our clinical project, as we talked to our pharma friends, there are some people who have said, "We've got all these assets that are sitting on the shelf and you can have those and you can get into the clinic tomorrow," et cetera.

There are other people who have said, "Oh, we want to do completely novel stuff." Patrick Valence, head of R&D in PSK, "Chas, I'm interested in completely novel stuff. Stuff that's early, maybe there's some genetics, it's incredibly high-risk. We don't even have any re-agents." But of course it makes sense – whenever anything is high-risk, it makes sense that we pool our resources, pool our expertise and share that risk, and do that experiment once and not 20 times in parallel.

So I'm supportive of doing both. But I think you almost laid out the roadmap.

Debra Hanna: And that's exactly where we were in 2007, 2008. Saying, "I can see it in my mind. We know we absolutely need a new four-drug cocktail. We have a few things trickling through development, we're not sure if they're going to make it. There is some early screening going on with new chemical matter we can't currently envision. We've got some models that kind of work; I can kind of see it. Maybe we'll do a little here or do a little here." And by organizing around that kind of sort of came the growth and the vision. It's very similar.

David Dilts: The Manhattan Project was actually successful because of two folks. Most folks know about Oppenheimer who is a physicist, but the guy that really made it work was General Grove. General Grove is the guy that built the Pentagon in under a year – which can you imagine a Federal project in under a year building a building that big?

Grove was the guy that said, "Physics is all well and good, but you will have a bomb that can be put on an airplane as soon as possible." And he's also the guy that said, "Here is the project plan. Here's the stuff we don't know but somebody's got to figure out. Are we going to use uranium or plutonium? You physicists figure it out. But you know what? We're going to have one of them." And he's the guy that made sure it achieved its project objective.

So I guess you need to have the scientific community saying, "This is really good science, this is really what we want to do." But you also need to have the project plan or road map that says, "We're going to build a system that learns as we go along because we don't know, but we've got to get started now and we've got to have deliverables in the future in order to achieve it." Okay?

So it's not like we have to know everything, but you have to build a system that learns so that you learn so that you don't keep doing the same mistakes.

Diane Stephenson: So, just to follow on those themes, I just want to emphasis that the catalyst for this meeting really came from last fall. And we have many of you that were there that are here today, but we have a lot of other people here that think outside the box, and some also think that this is tough. We knew this going into this. We knew last fall, we've known today; this is not easy.

And even by having three days we're not going to figure it out. But what I want to say is – on behalf of both Debra and I – is we want to manage expectations and figure out what is the low-hanging fruit for – no matter what combinations we take forward – to Abeta molecules and Abeta and _____ – what is going to enable that to happen independent of what drugs we decide or what targets we decide.

So what didn't come out yet in this discussion is for us at C. Path and _____ one of the biggest hurdles is getting agreement to share the data from what has been done in the past. And we have ADNI as flagship public/private partnership in which sharing of data was key to make that successful, but when it really comes down to it, to get all the data to be shared openly from legacy trials – that includes biomarker data, active treatment arms – we're still not there.

One biggest challenge for that is the informed consent for the clinical trials. And here we have Pete Schneider – who's not here today – who's already initiated a phenomenal idea to have a universal informed consent for patients with neurodegenerative diseases.

This is something that's a no-brainer that's going to enable anyone designing trials for combinations that want to learn from existing trials with single agents and how that could help you inform how to combine those drugs.

And to me – you know, that is one example – the other example is – that Debra and I didn't get a chance to talk about – is what we do at C. Path – and thanks from our funding from FDA – to help develop data standards for specific diseases.

There's not any allocated funding for that because it's hard, it's not innovative or cool or sexy to get an NIH grant to do data standards. But it's another reason why ADNI was successful, because they agreed upon data standards.

So what I ask everyone today is let's hard in the breakout sessions of what are the low-hanging fruits that could come of – maybe not even would require yet another consortia – but how could existing infrastructure and funding be put in place for enabling those low-hanging fruits to help us pave the way for any combinations that we bring forward.

So just food for thought.

David Dilts: The people that know how to share data the best, believe it or not, are the physicists and astronomers; because before they do anything they've got to agree that everybody's going to share the data, because it's – I mean their tech toys are so phenomenally expensive everything is shared and everything is free.

With respect to the IRB forum let me give you a caution that happened in cancer. In cancer they set up a centralized institutional review board that anything that went through a cooperative group got approved by the CIRB – Centralized IRB – and it was a phenomenal failure.

Because what happened is that centralized IRB would not be the IRB of record in case anything went wrong, so every local institution said, "Oh, we're going to be responsible? We all have

to review it." So when they put in the central IRB it became an additional step rather than a benefit.

They've since – and I don't know whether they've announced it or not – but they're right in the middle of saying, "We're looking at a change in the common rule and we will be the IRB of record," which then achieves their intended purpose.

So there's funny things like that that happen and it's right now being fixed in cancer.

Chas Bountra: My own sense, Dian, is that we need to sort out the plan – what are we going to do – and we need to sort out the three or four people who are going to put their neck on the line. Because – and then I think money will flow. I think we'll get the funding.

You know, whenever I've made big funding decisions it's always based on those two things. In fact it's usually based on the team standing in front of me. So we get the people and we get the plan; we'll get the funding.

Rachel Schindler: There's so many elements to this it's hard, but probably helpful to try to isolate – I mean the three of you have – and some of the comments that have come up – you have each talked about a number of the critical elements, and it might be helpful to identify those and then prioritize those.

I'm actually less concerned about the logistics of this happening. I think that can happen. People say companies don't want to share. I don't – and maybe I'm wrong, but I think that the major companies are sharing their data. But there has to be – as with all the stumbling blocks that have been mentioned earlier about – I think you mentioned that – for example – industry shares information more than academics. What's that about? Well, because academic livelihoods depend on intellectual property and publication. And if they share that information they lose their one currency on which their livelihoods most depend; so there would have to be, for example, something there.

In industry I can tell you – at least I can speak from one company perspective – we're very willing to share data. But when it comes to something that – we are for-profit. And in fact, if you look at the speed at which certain discoveries have been made there's always some – there's usually some price – it may not be monetary – behind innovation. There has to be something, whether the

currency is publication, or whether the currency is cash, and you have to remember that.

So, for example, right now companies are sharing placebo data because it doesn't cost them anything. Industry, in some ways, is more rapid and _____ because industry is for-profit. And so there has to be – I mean most companies – almost every company – major company that I know – does a tremendous amount of work as good citizens or it's philanthropic or all of the – but in the end there's still a shareholder to answer to.

Ara who is right behind me – Ara and I had an interesting discussion yesterday about the informed consent and he said he came to realize some of the issues, including who's going to pay – people are willing to do it but the question is who's going to pay?

So I think incentive is a key thing that was mentioned and has to be addressed for each of the critical stakeholders.

Another thing I think is real critical is innovation. And maybe it's not innovative drugs, for example, as in TB – some of the combinations and whatnot – but there has to be some innovation. And one of the things that somebody had mentioned earlier – and particularly in this field – is everybody tends to listen to the same two or three or four people and it's like when that person speaks it's like the oracle spoke and that person could say something a little – either not so new or a little really kind of wrong, and everybody runs to that.

And I think to some extent we need some new blood, some new voices; as in any endeavor everybody wants to be the lead, everybody wants the credit, everybody wants to be in charge. And I think, particularly in this field, we have to find a way to kind of get around that, because I think we're a little bit – I mean everybody gets that – but I think we, as a field, are a little bit stuck on that right now.

I do think the concept – lastly – I do believe in a consortium, I do believe in the combination therapy – I too can see it – but the last point – and I don't want to reiterate because half the group heard me say this yesterday in our breakout – but I have great concern also in this field about the huge history of failures behind us and I think were largely due to us jumping into something for the sake of doing something.

And I think that – for example – a lot of the compounds that are maybe available, so to speak, may not quite be ready. And I think we have to be very careful: everybody's really quick to take a drug and put it into a population.

And I think – this is something that I've learned particularly in my – sort of the latter half of my career – the first half of my career was in academics, the second half of my career has been in industry – and I've learned that more in the second half. For this to be successful and not to fail, we have to be really careful about what we use and not just rush into something again.

Chas Bountra: Can I just make a comment, Rachel, on the incentive comment. And sort of – and you're absolutely right, I mean I've noticed this working in the SGC, there are many academics who want to take out IP and do their own thing, et cetera. We don't collaborate with them.

I gave a talk at an NIH/FDA meeting last October, which was on pain – pain research – so it was called 'AAACTION' – A-A-A-C-T-I-O-N – so basically the premise was we pumped all this money into addiction, analgesia and abuse: where are the drugs?

And so they had all the great and the good all over the world at this meeting, and Allan Basbaum was one of them at UCSF, Clifford Wolf at Harvard – Allan got up and said, "Chas, I won't be able to do this at UCSF." So I said, "Okay, in that case we won't collaborate Allan." It's that simple.

I think there are enough academics out there who are willing to relinquish some of this and do something that's probably more important, and we will collaborate with those other people. So I don't worry about the incentive stuff.

But one thing I do worry about is that increasingly I see universities pushing academics to take out IP. And I think that is destroying us.

Rachel Schindler: Well, it's incentives not just for academics, but it's also incentives for commercial companies and whatnot. There has to be – for it to work, there has to be something in it for everybody.

Chas Bountra: Yeah, absolutely. Yeah.

David Dilts: Let me get – two different ways to what you said. Again, I'm going to pick on the physicists. The physicists who built CERN figured out they couldn't build it without this massive cooperative.

Well, when you go for a tenure promotion at a university, as you well know, you've got to show you're distinct, unique contribution, which means you're first author on a paper. Well, better than half the people would never be first author on any paper because they were doing fundamental issues, but part of a big team.

They, as a collective, said, "We – the Nobel laureates – we'll write letters of support for their tenure promotion as a key member 'of the team.'" And so those people are now starting to change how tenure promotions are looked at.

With regard to industry – and like Chas, I used to run basically a consortium – and what I used to sell them is exactly what he sold them on, which is a multiplier affect: 'You give me $5 million, I'll give you $50 million worth of research.'

Now, I had one little trick that's different than yours – 'And I'll give you year's head start.' We will keep this information closed within our consortium for a year and then after that it's public domain, anybody can do it.

And companies were more than willing to get a ten-fold return on investment and a year's head start over anybody else. That was an easy incentive for them.

And – one last thing – everything we tried was a failure. Everything we tried was a failure. None of it worked. And I finally went up to one of my funders and I said, "You're an incredibly smart person Debra. Why in the world do you keep giving me money, because none of it works." And he said, "You don't understand. I gave you $5 million because I was going to build a $2 billion plant based upon that principle, and you just proved it wouldn't work. You saved me $2 billion."

And so it's not necessarily the money they get in; it's all the money you're saving that they don't have to go spend.

Rachel Schindler: Well, that's – all of the things that have to be done along the way, all the rocks that – how do I say – that need to be turned over as part of the process. I don't mean to overstate the incentive for

industry and there needs to be a profit, because there doesn't. I mean I can tell you dozens of things that we do that – for which there's no profit; so that's not really exactly what I mean. I think some of it is intangible, as you're discussing – as you mentioned.

I just think we just need to do a little bit more – we just need to get together in some small groups and think a little bit about those sorts of alternatives.

Ara Khachaturian: Hi, I'm Ara Khachaturian. I'm executive editor of *Alzheimer's and Dementia* and I'm also leading the effort to put together a national IRB for neurodegenerative diseases, and I just wanted to at least slightly set the record a little bit straight to say that I don't think that the Cancer Institute's Central IRB has been a complete failure.

David Dilts: Not a complete failure, but it certainly didn't achieve it's massive success it was hoping for.

Ara Khachaturian: Well, in any case I think it actually went through a lot of iterations, and I think that the road that cancer actually sort of blazed in terms of trying to centralize the IRB approach is something that's worth noting. And for our part the effort to develop such a neurodegenerative disease IRB actually started back in 2008 with the Leon Thall symposium.

Paul Aisen an attendee at that meeting and I distinctly remember him sort of slamming his hands on the table at the end of a session very much like this in frustration, saying, "You know what would really help therapy development is a centralized IRB."

And so that basically sort of started off a long process to actually get this thing launched. We've talked to NCI, we've talked to other groups and they've all been very supportive. Jackie Goldberg, who is the head of that project, actually explained the very long process of trying to get universities and other groups to sort of really embrace a brand new idea.

And I think now with their third contractor they've been actually quite successful in doing that. I think they have a very good record of achievement and something that's worth replicating for not just Alzheimer's, but more broadly speaking, all neurodegenerative diseases; and that's where our effort is focused.

In terms of actually starting consortia-type efforts, these things are really difficult. We have a lot of good will, we have a lot of support for our own idea, but really trying to operationalize that to get startup financing, getting down into the weed and into the tactics; that is really where the work is.

And I think that any consortia project really should have – I think as you mentioned in your presentation – very well-defined deliverables, timelines, and actually really understanding who all the stakeholders are, and have a very broad recognition of what it's going to take to get success, and then also to recognize where the failures might be in the future. Thank you.

David Dilts: Yes, I painted them fairly negatively, but they've done lots of really good things more recently. But they – the intention was, you know, they would replace – and they didn't – but they're now doing much better on that, so I will say that.

The second thing – and I will also caution you with this, because I'm a process researcher; I look for bottlenecks – the bottleneck in cancer research is not the IRB. The bottleneck in cancer researcher is getting it through contracts and grants. It's getting all the money flows and all the IP's and all the – all that kind of stuff takes an incredible amount of time.

And I've studied over a dozen cancer centers and everybody – all the researchers complain about the IRB, but when you really look at the process it's all upon how do you get the contracts and grants through? So it's a different problem.

Debra Hanna: And I just want to touch on a point that you made because it's one we often forget about, but I think it's hugely important, and that's running the operations of a consortia-like effort. That is a huge component to why TB chair works as well as it does is that we have program management, support for absolutely everything that we do. We have project plans for every project we undertake. We have points of accountability for all of the work. We check regularly on milestones.

I mean it's not just something where you write a work scope, you say, 'Everybody go; we'll check-in in a year.' It takes a lot.

And so from a funding component I would just say you want to also be able to run the operation so that you manage it with the

vision of achieving milestones. So thank you for reminding me to say that.

Ara Khachaturian: Thank you.

Cynthia Bens: So a lot of you know me in the room, I tend to be the organizer of these things but I don't get up a lot and say a whole lot at the meetings. But I think it was really – my interesting observation is that everybody's talking today about forming a new consortium and the implication is that we need to form a new consortium. And if you actually look at the title for today it's 'Identifying the Partnerships.' It's not actually talking about forming a new consortium.

And Maria did a great job of highlighting everybody who's in the room, who really plays a role in currently funding and structuring a lot of what we're doing.

And I caught a little bit of flack when we were planning this meeting and heard a lot of questions about whether or not the timing is right to do it, and whether or not we were rushing just for the sake of the fact that Rusty's retiring in a month; he's sort of the reason why we started pursuing this in the first place. But I think that there was a lot more to it than that. It wasn't just that Rusty's retiring.

I mean he has been a really strong advocate for this at the agency and we're sorry to lose him in that respect. But we also feel that we're at a critical point and people are recognizing that it's going to be a combination approach and people are moving to do it.

And as an advocate it's seeing the writing on the wall and knowing that there's going to have to be a lot of collaboration; now really is the right time to do this. Before we sort of move down a path of taking this approach within companies and maybe have it not lead to the success we could potentially have if we were identifying those partnerships now that can really feed into doing this successfully five, ten years down the line.

So that's my big observation. We're not looking to necessarily form a new consortium. If at the end of tomorrow we're saying that's what needs to happen, then maybe that happens but I think that a lot of what's been coming out in the discussions is that the infrastructure is already there and we're identifying those gaps, and

if we can find a way to organize ourselves in a different way, that might be the constructive way to approach it.

[Applause]

Chas Bountra: Can I just followup, Cynthia, I mean sort of – I agree that a lot of infrastructure's in place and there's a lot of willingness to do something. But you know, what crystallized in my mind yesterday in the session – I was in the session with Dian – I don't know what assets are available that we could potentially do combinations with.

I would just love to see a short list, because yesterday we were sort of talking about planning experiments in the absence of any tools to do the experiments with.

Tony Ware: Hi, I'm Tony Ware, I run product development for Lilly with several of our therapeutic areas, including Alzheimer's disease and cardiovascular, the psychiatry, and everything other than cancer, I guess is basically how I would summarize it at this point.

One of the good things about not know that much about Alzheimer's disease is that I get to learn a lot from you all, so I really appreciate it. But another good thing about coming from a different background is that you have ways to see how other therapeutic areas sometimes solve this.

And Reisa and I've had this discussion so many times that she's probably tired of me talking about it, but it's – but the field reminds me a lot of where cardiology was back just when the new therapies were starting to come out.

There wasn't a good way to prosecute them, everybody was arguing about what the right endpoints were and so forth – especially true with thrombolytics. So for those of you that were back in the thrombolytic era, nobody knew whether we were supposed to use two of these products together, no one knew what the right dose was, nobody knew how to balance the bleeding, and when the right time was and even if all of this was a good idea.

And the thing that made a difference – other than all these products were able to do this – is an academic infrastructure in clinical trials arose to support all this that let us turn the crank on these trials many, many times.

The first one was my boss at the time, Eugene Brownwald, started this at Harvard at the TMI Group – thrombophlebitis and myocardial ischemia – they were able to create a model which they were able to do many of these trials, and basically worked out everything that we know about thrombolytic drugs was either done by TMI or by the followup groups.

There is now the Duke Clinical Research Institute, Cleveland Clinic – now there really is no such thing as a major cardiovascular trial that is not done by one of these.

So one thing it does is that the organizing investigators, they put together groups of trial sites and they're all able to be done globally, so that some of this is a little bit of a plug and play model that you mentioned beforehand, which these trials are the same.

The other thing about this is the transparency that's involved in it. So what do these academic groups get for this? And every time that we do a contract with them I basically sign something that says, "We're going to give you a copy of the database; you publish it, you call it the way you see it. If you think the drug works; tell everybody about it. If you don't think it works, that's fine too. And this is basically the structure behind it; we'd like to see the paper before it appears in *The New England Journal* so we can answer questions from our customers but we aren't editing this," and so forth.

And this leads to the transparency that they can publish whichever pieces of all of this that they think is most newsworthy.

So I think as this arises – now so far there hasn't been a need for that. I mean the ADCS does this a little bit, but not to this sort of extent. I think that – with all of these different companies – that's the kind of infrastructure that will come up that will make, I think, a big difference in us being able to prosecute these and being able to take these on in an efficient fashion. So, thank you.

David Dilts: I have no idea of the timing.

Dan Perry: We're done.

David Dilts: Oh, we're done.

Dan Perry: Let me thank you, David Dilts, and Debra Hannah, Chas Bountra for a very eye-opening further discussion of the essence of today,

which is where do we go from here and what tools and who is to play. So thank you very much. And also for the previous talk by Debra and the opening by Maria Carrillo.

We are going to – yesterday having started you late for lunch and then giving you only 30 minutes, today we're going to start you early for lunch and still give you only 30 minutes. No rest for the weary.

At 12:00 noon we'd like you to be at your pre-selected concurrent working group session. Group number three will meet where group number one met yesterday, in the – whatever room that was – Foregut Square, I think – and that will be the group that will discuss opportunities to pursue through consortia and funding, or the possibilities of current infrastructure and so on.

And group four will meet in the adjacent room. That – oh, by the way – number one will be chaired by Enchi Liu of Jannsen and by Heather Snyder of The Alzheimer's Association.

The second group in the room to the left as you walk out of here, will be about data sharing, forming an affective partnership to pursue combination development, and that's chaired by our own Cynthia Bens and by Tony Ware.

So enjoy the lunch, it will be right out here. And please be prompt to your working group session. Thank you.

[Part 5]

Dan Perry: – summing up our working groups. If I may have you resume your chairs. Well, we've had another round of intense working groups. We've been given a good amount of time to air a lot of issues and now we're going to put the burden on the chairs and co-chairs to come forward and try to synthesis that down, or bring the highlights to your attention to give you access to the medians where you weren't, and maybe even gain some insights into the medians where you were.

So the first group, which was to talk about opportunities in consortia and partnerships in other arrangements and how to find funding to power these issues, chaired by Enchi Liu and by Heather Snyder – and I'll ask Enchi and Heather to come forward and give you a synopsis of that.

Heather Snyder: Great, thank you. We had a very lively discussion that started out with many different ideas flowing. I think at the end we came up with some concrete steps forward, or some ideas of how we can at least progress – and some of them are ideas of bringing stakeholders together to have additional ideas. Some of them are near-term and some of them are mid-term and some of them are more long-term or more field-based.

I think one of the things the group really agreed on overall is that calling our session 'Building Consortia Opportunities for Consortia' was sort of a misnomer; that this was really looking at ways of partnerships and collaborations and how we can bring folks together – bring different stakeholders together – for the right conversation and making sure that the right people are in the room – or the key experts or the technical experts, in some cases, are in the room for those different points and different discussion topics that we identified.

One of those that I think has come up a couple times – or multiple times over the last two days – was this idea of developing some type of inventory or resource list or opportunity of what is available; what are the targets that are being tested, what are the compounds that are being tested or available related to Alzheimer's disease, and developing really that resource inventory.

One of things though that we did identify is that, at least for those of us in the room, there were definitely key stakeholders not present that need to be part of that conversation to develop that resource or develop that inventory.
Part of that could also be leading to – or lending itself to understanding more mechanisms of what that targeted action is and what the compound is, and looking at the necessary levels of evidence to move forward; so what are those levels of evidence to make those types of decisions for combination therapies to move forward.

There was some discussion around trial design of combination versus individual at a very high level, so the idea of needing to take – and I think we heard this example this morning – needing to take a combination therapy forward and do you need to do that as well – or in parallel – with the individual therapies going forward. And there was some discussion around that and looking at further clarifying or further exploring that topic.

There was also the topic of looking at exploring existing infrastructure. So how can we really explore or expand on what exists today in the field. So the example that we really focused on was brought forward by Zaven and it was this idea of building on the ADCS infrastructure that already exists and bringing together those key stakeholders, the leadership of the ADCS, as well as other stakeholders in the field, to look at what that model might look like. How can there be an ADCS and a pharma-type model that would advance clinical trials in combination therapies?

Also looking at other models within the Federal government that exist in funding and mechanisms of taking forward clinical trials.

And then there was also a discussion about the funding mechanisms – and there are many funding mechanisms, whether they be venture philanthropy, private philanthropy, government or pharmaceutical companies support.

Although one of the things that we did hear from folks in the room is that if you had a plan and if you had a model that really had legs and would go forward and would drive the field forward and help de-risk the overall investment of pharmaceutical companies, that the funding would follow.

And so that was one of the discussion points that the group did address – or did at least share or lay on the table.

And probably the other two ideas – one that we saw as being more ongoing – is identifying forums for information sharing. So where are those forums that we're already – are coming together – key stakeholders are already coming together where there can be information sharing so that we're not continuously reinventing the wheel and continuously taking the time to look at the different necessary infrastructure for each individual clinical trial – not necessarily within the sponsor but for each clinical trial, and where can some of those types of forums of information sharing be garnered.

Things like – and one of those that was suggested was The Alzheimer's Association Research Roundtable as a possible forum for that type of information sharing. The CAMD forums might be another opportunity for information sharing.

And then the last and probably more long-term or long-term idea was the systematic review of understanding of what we know

about Alzheimer's disease. So really looking at what we know about Alzheimer's disease and rethinking what we understand about the disease, starting to drill down on the different targets and on the different mechanisms that might be playing a role.

There was the suggestion that the whole genome sequencing within ADNII may give light to new understanding within this concept and that that could also really help bridge to that addition conversation; and within that context being able to identify novel pathways and novel targets.

So invite Enchi and anyone in the group – because, as I said, it was quite a lively discussion to add-on to those talking points or to add-on to those different action items.

Enchi Liu: Heather, thanks for summarizing. I have just a couple of things to add on to what Heather said. In terms of having a work group of technical experts to inventory what available compounds are there is also – includes evaluation of whether combinations of these available compounds actually make sense to move forward. I think that was something that people – during the day-and-a-half – have also discussed.

And also in terms of the form for data sharing, the concept – just to add to what Heather said – is really to be able to learn from past mistakes so that we don't go into the same situation where individual companies are after the same targets, they use the same potential – very similar pathways for drug development and you end up having inefficient ways of utilizing your resources.

So the idea of the data sharing forum is to learn from each other so we don't reinvent the wheel and maybe have a more efficient path forward.

But I think that's a good summary. Thanks.

Heather Snyder: Are there others from the work group that want to comment on the discussion or other points that we may not have mentioned or that were brought up? Okay, thanks.

Enchi Liu: Thank you.

Dan Perry: Cynthia Bens and Tony Ware were the fourth working group in data sharing and forming effective partnerships.

Tony Ware: Cynthia was the working part of this group.

Cynthia Bens: I don't know about that. Let's see if I can earn my living today. So I think we actually came out in a very similar place to the other working group in terms of the need to sort of scale up in a step-wise way to actually getting at combination therapy.

We also had a very lively discussion, and I think in the very early stages a lot of the conversations that we had in our working groups yesterday – lack of a surrogate and some of the other iffy questions on where we are with the scientific rationale for combining two therapies were a bit of a hindrance I think before we hit the brake and came back and came back to former recommendations.

I think where we really came out was in addition to having this step-wise approach to forming the necessary partnerships, we decided t hat there actually should be a consortium to undertake a more adaptive-style approach to the early designs. And to do this the first step would be for the committee to go to the various companies to see if there are shelved drugs and collate an inventory – similar to what the first group recommended.

And then that the consortium would be the one that takes the early risk on and then eventually give the asset back to industry for further development.

And the regimen selection committee would also establish the procedures for data sharing and maybe even start with a single-agent approach and scale up to combinations – so that's another theme where there was overlap.

And then in addition some other tangible but really important issues came up with respect to other steps that can be taken around the same time as forming this consortium are something that Tony raised, which are having additional guidelines from the FDA on labeling of combination products – and this could potentially take a similar model to guidance that exist for drug and device labeling, because that would be an additional thing to tackle.

We also addressed the fact that it would be really important to address the payer aspect of combination therapy development in addition to bringing in US payers, and that it would also be import to bring in other European and other regulatory authorities who are responsible for actually – payers – I'm sorry – payers to address those issues.

But we did sort of stress the need for flexibility in this type of consortium, that there would be a need to adapt with the fact that data is becoming more publically available. Jannsen actually made the point that there is a lot of learnings that are going to be happening and so we need to be flexible, but also, with respect to funding, if any of this funding would come from the NIH, that there is a mandate that was brought up that the data needs to be made publically available.

So, did I leave anything out?

Tony Ware: No, I don't think so.

Cynthia Bens: Okay.

Tony Ware: Are there other people in the group who want to make other points?

Cynthia Bens: Great.

Rusty Katz: Maybe you said this and I just missed it, but Kun Jin, who's a statistician, at the agency – I don't know if you mentioned it –

Cynthia Bens: No, I didn't actually. Thanks.

Rusty Katz: He's undertaking – or presumably going to be undertaking this summer with an intern – looking at the data from the drugs that we have data on at least – at least the ones that have been approved – and trying to see if we can learn something about surrogates or biomarkers that were performed in these trials and how they might predict clinical outcomes.

So I think people thought that was a useful thing, and we may have to ask companies to – even though we have the data – to present it in a slightly different way, or even ask for more data that – put studies that they haven't been submitted – but I think there was some interest in that, and we're going to get back to the companies with a little more fleshed out idea of exactly what was planned.

Tony Ware: Yeah, I think that's right. I think – I mean I'd personally be supportive on it, but we'd like to see the proposal for that, but I think the idea of combining a bunch of data to see if we could inform something on the surrogate markers and understand a little

bit more about the variability with the large numbers, I think, could be very useful.

So thanks for bringing that up that we look forward to seeing more about the plan.

Steve Salloway: Just to add to what you said. Some of the partnerships are already – have begun, with public/private partnerships with sharing data with the ADCS, clinical trial data and having the ADCS analyze it, working collaboratively with assets for either prevention or for familial Alzheimer's disease – and in the Dian study there is a DIAN Pharma consortium and there is some form of data sharing and arrangements, and so I think we're in the – there's no combination arm yet, but I think we're at the beginning stages of – the formative stages – of this type of collaboration.

Cynthia Bens: Okay. Anything else?

Tony Ware: I think just to build on Steve's comment a little bit, we pointed out that there are of course – there are certain of these – for combinations and for other arrangements that can made anyway between the two companies. For instance, it's analogous to the process we go through to license a drug or to otherwise form a partnership with a company and the performing of diligence to share back the data, and there's some practical problems to solve on that, but that on an individual company basis that can be done. And of course the idea about taking shelved assets and bringing them forward in novel way is an – in addition to that.

Dan Perry: So we've budgeted a bit more time for open discussion and thought there'd be more back and forth on the reports of the working groups. If anyone has a point that has been sort of percolating over the last day-and-a-half, two days, and wants to raise it with the group – any issues that anyone wants to raise, this would be a good time to do it, and Chas, it looks like you have one.

Chas Bountra: I think what would be great is if we could put some timelines on these actions. You know, we've heard a lot about sort of, 'Okay, we want to get this inventory together, we want to troll the sort of mechanistic literature or whatever. But I think let's try and make some of these actions time-bound so that we get a sense of progress.

I don't know what people think. So I don't know who's going to take ownership of some of these actions but I think accountability and timelines might be useful.

Dan Perry: I think that's a good point, but it does go to the 'who' part. Who's going to take – who's going to convene the smaller group? There's been a lot of discussion about that; that's something that any number of the – either the patient groups or government groups could do. But I think when we have an actor then we want to know how long the play's going to run. So I think that's a good point.

Any other discussions or points? Because we have time. Sue Peschin.

Sue Peschin: So I'm going to actually take this because it's kind of weird with my back to all of you. I had a couple of thoughts – and this is just from my non-scientific observation – so please, understand I have no medical background and I've never run a clinical trial and my group does not fund clinical trials.

But I am, I guess, sort of disappointed by a lot of the resistance that I'm hearing. I know that this requires a big shift in thinking about how things have been done in the past. I do think that we've heard – and part of the purpose in inviting – I've also heard a lot of like, 'You don't have all the right people in the room,' and that might be true; there might be a lot of other people that we could have had here. But the people that we picked we picked for a specific reason and it's because they've sort of tread this path before. Granted, they've done it in other disease areas and with other types of compounds and – that have their own other types of barriers, but it's not like we're – this is being suggested for the first time ever. It is for – maybe for this disease – but not for the first time ever.

And it's been done successfully. And there is willingness I think on the part of some folks to start exploring this a little bit more. And I just want to invite those folks to sort of speak up and connect with each other; we're interested in pursuing this more.

I do agree – I mean I think the points that were made this morning about how you have to be thoughtful and all of that – I think that's important, and I don't think anyone disagrees with that. I don't think it's fair to say that unless you do it in a certain prescribed way that, you know, might have been suggested earlier, that it's not thoughtful. But I do think that there is a – I think, you know,

that – what the analogies that were used before about soccer and everybody convening around the ball and that's all been done a lot of times.

And as they mentioned before, a lot of time has been wasted, a lot of money has been wasted, and I – I – I am just frustrated: that's what I wanted to put out there. I feel like we can do better than what we're doing. And, you know, that the whole idea of the sort of low-hanging fruit and let's just work on sharing data and all of that – I feel like those are proximal goals – as David was speaking about before – that there are a lot of proximal goals along the way that I think could encourage us and help move the process along.

But in terms of getting to a bigger goal around combination therapy I think that we can aim a lot higher than what's being talked about here.

And I do think that there is a purpose in sort of upsetting the apple cart and having a lot of discussion where people are sort of frustrated and they express those frustrations and all of that: there's purpose in and of itself in that. But I hope that we come out of this – as Chas was mentioning – with some goals or some timelines or some ownership.

And I do feel like we do have at least some of the right people in this room to do some of that. So I would hate for everybody to just say, "Oh, wasn't the right group. Wasn't the right situation. Wasn't the right time."

And I do feel like – you know, Helen Lamont is here from HHS, representing the secretary's office, so we're sort of being watched on this. And it is a very important moment that we're in. And if we keep saying, "Well, we just need to keep having discussions and wait until all the planets align and all of that," I think the moment's going to pass us by.

And I am actually overwhelmed and grateful that the folks and the level of folks that are here from FDA have agreed to hang out here for two-and-half days. That's truly significant to me. And if we can come up with nothing better, you know, than what we've talked about so far then I think that would be a real missed opportunity.

So I appreciate – and them basically saying, "We will help you, we will work with you, we want to talk with you and dialogue with

you. We have all these great examples." I think I just want everybody to leave here tonight and think about if we could do whatever we wanted to do in an ideal world, what would it be? And then let's talk about tomorrow; how to make that happen, you know?

There is something I heard last night that I thought was kind of cute. This guy said, "It's a bit like the egg and bacon breakfast. And it's the difference between being involved and being committed. The chicken's involved in the breakfast; the pigs committed."

And I think that's the difference that we're talking about here. Do we want to just be involved and have lots of discussions, or do we actually want to make something happen and move this ball forward?

And I know my organization, The Alliance for Aging Research – and I know ACT-AD too – although we want to talk to our sponsors and get more feedback from all of you – we want to see something actually happen. So thanks.

Dan Perry: Great. Thank you Sue.
[Applause]

Dan Perry: Anyone else want to open up? Comment?

Reisa Sperling: Are we sharing now?

Dan Perry: This is sharing time. But any other observations? Truly. I mean we've been together a long time now – it seems like a long time – and let's hear from others as to where they think where we are and what we have to do. Reisa; I knew I could count on you.

Neil Buckholtz: We can do it now.

Reisa Sperling: Right. So actually that is one of the points. So I'm probably not as frustrated but I am worried that we're going to – if we don't come out with some real actionable items, that we're missing an opportunity. And I actually do agree with Neil that we have some of the key elements in place to make this happen fairly soon.

So I do think we have a good clinical trials consortium. I think we need to expand it, make it more adaptive, but mostly we need to resource it because we can't do all the trials we want.

And even if there are folks in here – very smart folks – who are not so excited about combination therapy yet, because we need to do single therapy – I think we should start planning for what it will take, because I can tell you with the A-4 trial it takes years to plan this, to get it going to the point where it will actually happen.

And so if we don't start really planning and making possible a combination trial today, it's not going to happen in the next two to three years: we really have to get started.

So I heard a lot of pushback and I think we should consider all the smart things that people have said about why we should be careful. But we must change the paradigm. We must fix something we're going in Alzheimer's disease. I think, yes, we need better drugs, but we also need more efficient clinical trial design – we can't waste a year every time we want to set it up – and we have to think now about when we do get a drug that works, or three drugs that work, can we see if putting them together will make them work better, and not wait for us to do that serially because, again, I don't want to be doing this in a decade.

So I'll just – again, I guess I am sharing more than I intended – I think we must be bold – Maria said that this morning – I really think we cannot let this opportunity pass us by where we do have the attention of HHS and other things, and figure out how, creatively between the public/private partnerships, we can move forward; because we've made a tremendous amount of progress in the past year on these exact issues. Why can't we extend that to thinking about how we would put two or three drugs together? Because every other disease where we've had success, that's what we do; we put the drugs together. So why is this so controversial to try to think about how we do it here?

Dan Perry: Thank you Reisa. Steven.

Steven Salloway: Tell me your name.

Sue Peschin: Sue.

Steven Salloway: So I want to thank Sue for opening the door so we can all ventilate a little bit. I just think this is a great opportunity. We do have wonderful people here and very, very talented people – and in our field – very, very talented people. And I do think we have the

resources; we need the will now to move forward and take advantage.

It's not going to be easy. We can enumerate many, many challenges that we face and how to structure the path forward. But I think we do have the ability; the need is great. We're talking about ourselves – and if you're in the baby boomer generation and our parents and grandparents – and so it's for people that we care about.

I'd like to see – if we're just keeping an open-minded approach – I think we should just build on the success of that we've had – I think I'm not alone – it's been a phenomenal success; beyond what we even imagined when it was created.

And we want to build on that as we move into the therapeutic area and create an ADNII-type model in the early stage clinical trial program. And I think we can do that; it's going to mean changing some of the ways we go about conducting trials and conducting business, but I think we're all going to benefit in the long run and we might get out of our comfort zone a little bit, about data sharing and about IP, and we've got to work out all these IP issues and so forth, but the need is so – it's compelling. I mean it's just – the urgency is really – we know what happens if we don't make progress.

We see it every day. Those of us who see patients or have family members you know what it's like. It's a devastating disease and we need to make progress.

And I think, the last point, is we haven't – I haven't heard from the secretary's office – but I think government has a real role beyond the NIH. I mean I think the people in the NIH in this room and the FDA are very committed and I think – I really compliment the NIH – Rusty, and your colleagues – about making the barriers low so that we can make progress and keeping an open mind, which is terrific, because that always hasn't been the case.

But I think the secretary's office should be really interested in this problem. This is a major public health problem, and actually taking the leap in saying, "Gee, how can we get these forces – our talent in the United States – together to make progress against Alzheimer's disease on the therapeutic side." So I think it's a huge role for government in being the catalyst – and you guys are being

catalysts for organizing this meeting, but I think the government can also be a very active catalyst and take a lead role. Thanks.

Dan Perry: Great. Thank you Steven. Anyone else want to share? This is the moment.

Chas Bountra: I just wanted to share something that Dan and I were chatting about last night over dinner and I conveyed this to Neil this morning.

A couple of years ago I met – or 18 months ago – I met Ezekiel Emanuel. He was giving a talk in Philadelphia at one of Garret Fitzgerald's meetings. And Ezekiel said, "Do you know how much we spend in the US on health care?" And the figure apparently was $2.6 trillion. And he said, "Do you know how much $2.6 trillion is?" And I forget all the details but he said it was something like – if it was 2.6 trillion seconds, that would be about 60,000 years; so that's before there was man on Earth.

Then he said, "If you had one-dollar bills and you stacked them up; 2.6 trillion would take you half-way to the moon." 2.6 trillion apparently is more than half the GDP of China, and it is the GDP of France.

So yesterday morning I asked Neil how much do we spend on dementia research in the US, and it was something like $450 million. So then Dan and I, having had a few glasses of wine, you know, we're thinking right, $450 million divided by $2.6 trillion – we're talking – this is less than 0.02 percent on Alzheimer's – or dementia research.

You know, to me – as you know, I don't live in the US – but this just sounds disproportionately low. I mean this is mad actually. I'm sort of – this is something that's going to cripple many societies.

And I said to Dan – I was in Japan earlier on this year – and in the UK the figure apparently is – so that in 2050 – 29 percent of people will be over the age of 65. In Japan that figure is 41 percent. And it's hard for me – I said this to my son – and I said it's hard for me to imagine going into the street and seeing one in three people over the age of 65 – and maybe even close to one in two.

But this is what we're heading towards actually. And I just echo all the comments that have been said. I honestly think that – you know, I think there's great stuff happening, I think there's great infrastructure, but I think we really need to get a bit more aggressive about timelines.

And somehow we need to get Neil some more money; otherwise he's going to go grey. Thank you.

Dan Perry: Actually, full disclosure, it was Chas that did the math, because, as Cynthia said, I don't do math. So I just nodded vigorously when he said, "0.02 – or 0.02."

Chas also said that for this to go forward and to have something that comes out of this meeting – and we still have a half-a-day tomorrow – you first have to start with people, and maybe only a few – and then you have to have plan, you have to have an idea; there has to be some group that sits down and begins to write the rules, 'How is this going to happen and what are company stakes going to be, and what's the role of government?' And if you have those things the resources will follow.

So I don't think that we should get particularly hung up on where is the funding going to come for some kind of an effort, how much of it is going to be government sharing the risk or private sector, not philanthropic sources or companies; it's the people, it's the idea, it's the plan. And I hope that we have something tangible in that direction before we're done.

Anyone else want to speak up? Say anything at all? Vent. If not tomorrow morning we're going to begin at 9:00 and we will get a recap from Diane Stephenson on all the things that we heard and exchanged and thought about today. And then we'll have a bit more granular recap because we'll hear presentations from all of the chairs of the now four working groups, and we'll have another moment like this to share and express ourselves and discuss, and then we'll wrap up and then we'll send you on your way by noon tomorrow. Trust that we will all be walking out of here feeling like this was a good investment of our time and that something happened in Washington on those two-and-a-half days that will carry us forward. Thank you.

[Applause]

[Part 6]

Diane Stephenson: And I thought maybe before I go into the highlights of the two work groups yesterday, I want to start with the end of the day, commend and thank Sue for getting up and being brave and saying we all have to challenge each other right now. But before I tell you, my long story is – I didn't get up yesterday to tell you this because I knew I would start off today – I have to tell you some personal things because the feeling we had from these last few days is something I've felt personally in several examples, one of which I want to share with you.

First of all, whenever you have game-changing ideas like this, there is always pushback. It's not surprising. What we're talking about today and what we started to talk about last fall is really transformational, not just for AD for any disease. This is tough. This is really hard. I just want to say that everybody came into this with tremendous hopes and ambitions, and we have accomplished a lot in the one-on-ones that I've had since yesterday. It's like people came to me and said, "Boy, I've been so impressed."

And I went back to my goal slide last night and thought, you know what? We did achieve the goals. I looked at identification of challenges and risks, and we've identified paths and ways to mitigate those risks in paving a path forward, so I want to thank everyone. This is what the goal was, to sit down together, try to create a roadmap. But the expectation around what it would take to form a consortium is where, I think, there was disconnect. And I think back to my recent several years; I was at Pfizer at a time where I was really struck by the progress in the field of autism-spectrum disorders. And I started this idea, with many people, with my friends and colleagues and leaders at Pfizer, and said, "This is going to sound crazy, but I think that genetics, and the science, and where things have evolved, everything has started with the science; it's a time where it's really prime for doing something. We have to do something in industry. There's a huge unmet need. The incidence is rising.

And people said, "Are you crazy? Go home. This is the most heterogenous condition on the planet; the genetics is not one or two genes; it's hundreds of genes; you're going to have to treat children, perhaps even in infancy." But things like biomarkers and imaging were coming along, and I kept trying to talk to people. And all those people who said "Are you kidding me? Go home." I just found those champions, like many of you in this room, who said, "It's not a crazy idea," and I partnered with two amazing

colleagues of mine, Howie Mayer and Larry Fitzgerald, who shared the same passion, and we went out, not just to our friends at Pfizer, but we went to world experts, Mark Bayer, Jackie Crawley. We went to the leaders in the field of autism, and we spent an entire year building the business strategy, the scientific rationale, what would be the targets, what are the genes, and we came back to Pfizer with a very solid plan, like what we heard at this meeting, "We need a plan. You need an action." And all those people who said, "Are you crazy?" went, "Boy, this is amazing. This is a huge opportunity."

And we, together with the experts and the leaders in the field, just like today, convinced Pfizer to be the first company to set up a fully dedicated unit for autism. Fifteen people worked with a huge investment from this company to be paving the way to be the first. And we also, at that same time, I wrote a proposal, a one-page proposal for the IMI that was seeking new projects, to say, "Autism is ripe. Not any companies are investing. We have to do something now." And that idea, when everyone said, "You're crazy," led to the formation of the first ever huge IMI $45 million funded project.

So I just look back to where we are today realizing that yes, there are challenges, but if there's a way, you're going to find the champions that many of you are in this room here. All of us are going to say, "Let's hear the issues, let's hear the risks, let's hear the challenges, and we'll find a way." I tell you this story, but I also tell you that what we heard from Chas Bountra, of his success story that he shared with his group. This is something he started in 2009. Deb Hanna was here and said the TB idea took a year-and-a-half to flush out the science.

I was in a meeting in Banbury, in Cold Spring Harbor, two weeks ago, with experts, many in this field, in areas of schizophrenia and psychosis, that were frustrated with all the challenges and the lack of drugs to treat schizophrenia, and they all got together and the same thing happened. All the people who organized it said, "We're going to form a consortium," and we spent three days in exactly the same challenges. You don't have the scientific rationale, the company's need the business proposal that they can sell to their leaders, what's the value proposition, are we ready, what are we going to get out of it?

So everything that's happened these past few days is happening in other areas, in other diseases. It takes time to do something that's

game changing, but we have passion, we have the people. I think we've heard the science is ready; this is already starting. There are companies already doing this internally. We have the amazing support of the regulators; we have the patient groups leading this, so the timing is right.

So I just start off with telling you these personal stories because I know all of us kind of came in and said, "Boy, oh my gosh, what happened?" But at the end of the day, this exactly is what it takes. It takes convening people; it's identifying what are the risks, the challenges, and how do we together learn so that when you come up with something this transformational that you identify is the science ready first. What are the rationale and scientific questions, and then the funding will come. So I start with that.

Now I'm going to have a chance to share with you the highlights from the two work groups from yesterday. I was in the work group three, led by Enchi Liu and Heather, and the focus of that work group was really on how to think through a consortium based approach for combination drug development, which was something that was kind of framed very early on in representing C-PATH. This is kind of why we came here. I'm not here representing really CAMD, but how C-PATH can help in terms of our consortium models and what that might be contributing.

But essentially, the ideas that were shared in that venue included having this idea of a working group, a think tank, to get through the issues on the scientific challenges, identification of the disease mechanism and the targets that match the different stages of disease.

We have a lot of knowledge already from ADNI and DIAN, and other initiatives. Zaven and Neil highlighted areas where this is already happening. The recent AlzForum webinar on systems biology approaches that are emerging, new targets based on the stage of the disease. We really want to capitalize on the science, to not convey that we have to wait another five or ten years to understand this disease; we actually know a lot. We're going to know even more when the ADNI genetics comes out very soon.

In an initiative, whether it's called consortia or not, we need to identify the rules of engagement, define what's in scope and what's out of scope. So it's not that you're trying to do everything all at once.

We heard in this session also that identification of short-term biomarkers of surrogates or efficacy is a key gap, but there are other initiatives, some of which didn't even come up in our meeting, about IMI, what they're doing, and how functional imaging and EEG and other global initiatives could be brought in because this is such a gap that can help advance any combination development forward.

It was also strongly recommended that we use existing platforms and infrastructure to accelerate a path forward, specifically, the round table, the ADCS, successes in place already, to assemble these think tanks and forums to help catalyze this program forward.

Many sessions, including session three, talked about the critical role coming up of the list of viable targets, the substrates, what are the assets to bring forward, and also to develop and map out a plan that will take these targets forward, and we talked about the ones that are already ready now, specifically around a-beta lowering, and that's already very doable.

Whatever combination we take forward, the first time ever, you're always going to learn. And so what we discussed as a group is in any initiatives where the companies are already taking to a-beta lowering targets forwards, we're going to learn a lot about what are the path and mechanisms to doing combination. How do you choose dose? How do you combine two drugs? What does the toxicity package look like? And all those things are already being augmented by having our Regulatory colleagues here today. And, of course, in all the sessions we talked about the key role of identifying creatively the funding mechanisms to go forward.

Any comments from those in work group three of things that I may not have captured?

Okay. So Work Group Four was really focused more on data sharing. And in that session – which I was not at, Cynthia helped bring me up to speed on it – there was really recognition that it's important to bring all the stakeholders in. We have a very diverse group here, as well, but it was recommended that it was important to hear the views of the payors in terms of their concepts around combination development and how that would be compensated. The role of the patient groups, and government groups in influencing the payors was raised.

And then the idea of concept of a consortium with a goal of combining assets early, and then bringing those to proof of concept, and then having that combined asset go back to the companies, was also raised as an opportunity for a platform in which the companies would actually contribute early on in a pretty competitive way, and then have the combined asset come out of it as something that they would own going forward.

It was also suggested that the model, many of the models already existed in terms of how to think about doing this, in terms of companies working together, specifically the DIAN Pharma consortium in which the companies are coming together to share in the common goal of advancing therapies, specifically with the goal of data sharing, in order to enable that to happen.

So it was strongly recommended in that work group that there be defined timelines and a plan for even just coming out from today, that we have a clear plan of timelines around defining the inventory of the assets, how long is it going to take the think tank and ad-hoc group that is going to own that, the mechanistic rationale, not starting from scratch, saying, "How do we capitalize on existing science that's emerging in this area?" And then how we as a group measure progress going forward.

And then it was insightful for Dr. Katz to get up yesterday and share that the regulators also, how they can help with this in terms of next steps and an action plan by suggesting already that they have resources within the Agency to have statisticians look at the existing data in the FDA on Alzheimer's trials to date and potentially search for biomarkers and surrogates for clinical efficacy.

I'll just comment on that note that the Critical Path Institute and our CAMD has been reaching out very aggressively to companies to contribute biomarker data to our database. At present, we have only clinical outcome measures. And that will also be aimed at how modeling simulation can ask how biomarkers track with the disease that will compliment with the richness of data from ADNI.

And then at the end of the day, it's essentially I want to communicate, again, kind of where I started in this summary, is that at the end of the day we heard that there's a tremendous sense of urgency. I also want to thank Reisa for pointing out that we have to start now and plan for the future. Now is now because in a

few years, it takes a while to plan these studies, and it's critical that we start these planning phases now.

We want to build upon the success of ADNI and continue to engage in our close dialogue and communications with the regulators, and again, identify a plan, the people, the roles and responsibilities, and an action plan forward. So those were the highlights that I captured from yesterday, but again, I'm here on behalf of Critical Path, a time where we continue to be brought into platforms around should we think about a consortium or not, because we do that, our whole game is consortia. But it was actually Marietta Anthony, who used to be at C-PATH, who came to Dan Morton and Sue early on when they raised this idea about combination drug development for Alzheimer's, to say, "Boy, you should be talking to C-PATH because we have another consortium, this tuberculosis consortium with the Gates Foundation, that's doing this."

And it's just really for me, a platform in which we want to learn across diseases, clearly AD isn't TB, but today, and this meeting, is clearly around sharing learnings to help catalyze a path and something that's transformational. So thanks to everyone, and I'm looking forward to our continued discussions today. Thanks.

Dan Perry: Thank you for the summary, Diane, and even more for your personal career experience in trying to bring about change and bring about collaboration in areas where it's always a challenge, and where often times you're told, "You're wrong," until you continue to press ahead, and eventually you're right, and you were right all along. So thank you for sharing that.

We're now going to hear from the co-chairs of the four working groups. I think we just as soon take them in order. So again, Diane, from working group one, and from working group two, I think Deb Hanna is not here, Yaning Wang, are they here?

Dan Perry: I can do a recap.

Dan Perry: You can recap that? Let me ask Diane and Cynthia Bens, and maybe Enchi also, to come forward. We'll capture all four.

Diane Stephenson: You go first.

Diane Stephenson: Okay, here we go again. I had the pleasure of leading Work Group One, which was really focused on what would be the viable targets or assets that might be considered for combination drug development, and we kind of covered a whole range of topics beyond that in all the sessions, but I'll try to share with you some of the highlights from that discussion that we came up with. We actually did come up with a plan.

It was clear that people felt that there were categories of targets. And initially, the discussion was, okay, there's hardly anything that's ready for Phase II or III, so why are we even having this discussion, but I think the team kind of came up with these categories. It was felt that there's already activity. We saw the presentation from Roche around taking two a-beta targets forward to augment and get the best approach at lowering a-beta because experience to date is that here is dose limiting challenges, and you may not be able to get the bang for the buck a-beta lowering that you want, and Reisa has been champion for this all along, and those would be probably most suitable further along, to catalyze the first and ever already happening within company's combination therapies.

But there was a lot of back and forth around what other viable targets could be there, there was a lot of back and forth around drug repositioning as an approach, and even what stage might even make it to the list. But I think that people in the room felt that there's a lot of things that we don't know. And I think there is a biotech investment in this, there are start-up companies that are doing really creative things, _____ and other approached, blood-brain barrier targeting for molecules that don't get in, and we felt that it would be worthwhile, in thinking through all potential assets that we, even come up with a global list of even early target ID, things come out in the media; it's like, "This company has this target that they're considering," and not just focus on AD, but we heard from John Trojanowski that things like TDP43 and alpha syncline, things that are being pursued for ALS, or Parkinson's Disease, may be viable considering the known pathology of AD.

So the group kind of came out with this recommendation that essentially we should be broad and encompassing in thinking about the viable targets that we would bring forward, and what stages they're at. If we can't get this information for proprietary reasons, we can at least go with what's been disclosed, what's out there, what we know about who's doing what in what target space and

that could be, essentially, a collection, a read-out, that would come from this subgroup, or ad-hoc team, that would say, "Here's all the potential viable target space that we know of."

We also talked about how to group the targets into classes around things like neuro-inflammation, or liver metabolism, really think hard about the viable targets that are linked to genetics. And Rachel – I don't know if she's here – but she talked about at Pfizer, we have very strict criteria for confidence and rationale that include human molecular genetics, apoe4, now we have Trem2 and other things that would really kind of be categorized into these classes, not just the known ones, a-beta, and tau, but classes of categories, and I think we came up with five different classes that could be kind of the overarching themes, here's the class, and under that could be therapeutic targets that belong to that class, apoe or liver metabolism, or trafficking, those types of themes.

That was the recommendation in terms of the path for defining the target space for combinations, and I think that could be a work product that could be very viable and doable in a really short period of time. The other topics probably, I'm not going to get into in detail because they were things that came up over and over again in all the subgroups. The critical need for defining biomarkers as readouts, and short-term efficacy for any combination that you bring forward, the need for better biomarkers of synaptic function, even looking more carefully at FDG PET data to date, that's been gathered to date, to ask how does one track with a biomarker that clearly does have some component that looks at synaptic function.

Those were the themes that were continued to be emphasized when we kept talking about targets, but came back to a lot of the themes, again, were emphasized in the other forums. Hopefully, that helps.

Dan Perry: Yes.

Diane Stephenson: Questions, comments, for those who were there, not there, anything around the targets?

Dan Perry: I just want to think about each of these summaries in terms of what can actually be done, and you were saying something about that there can be a work group formed around identifying targets, and you said that there's a lot of things in existence right now that are kind of happening with that, is there any suggestion that you can

make in terms of overseeing that, how it would fit into some type of a structure, and you said you could set up a timeline for it, can you expand on that a little bit more?

DianeStephenson: Yes, we honestly, as a work group, didn't really talk through the logistics of how that could really be done. Enchi, do you have ideas?

Enchi Liu: I may have addressed it a little bit in Work Group Three, because we were talking about infrastructure, but I think from Work Group One, just a comment from Work Group One; I think you spoke about the near-term and longer-term goals. I think the nearer term goals are to identify the agents who are already available and take an inventory, and do a feasibility of whether a combination is actually a good idea, whether the existing compounds that might be either shelved, or in company hands, could be used in combinations. So there needs to be a feasibility of inventory and a catalogue, and an assessment.

The future, longer-term goals, I think what I heard from Work Group One, is to look at additional, or novel targets, and then identify what are some early compounds are in development that we could foster and combine down the road.

Enchi Liu: And then the infrastructure, I think none of the work groups really talked about that, but work with _____ a little bit by saying that we need to form a technical committee, smaller group, where they can do the assessment. Not that we don't know a lot about science, but this forum wasn't really convened to dig deep into the technical detail. And I don't know which forum, and people can speak up and make suggestions.

Diane Stephenson: I think it would be good, if people have suggestions here. I don't know. Neil, are you raising your hand or are you just …

Neil Buckholtz: I think simplistically about this, but it seems reasonable just to set up a work group that would combine academic expertise, expertise from the companies, look and see, do an inventory. As we've all said, do an inventory of what's currently available. As Enchi said, also, there are available, lots of small biotechs.

Actually, we've fostered a number of them that have compounds that are going into Phase I, II, clinical trials; we're funding through the program that Laurie manages, a number of Phase II clinical trials. So there are actually a lot of things out there and many of

these are actually not focused specifically on beta amyloids. So it makes a lot of sense to me just to do this, to set up this kind of work group.

That's sort of what we did before ADNI was funded, we set up a number of work groups to look at a number of different areas, combining expertise from academia and industry, and it worked out pretty well. So that would be one work group, and we can talk about other work groups as well, that would make sense coming out of this area.

Enchi Liu: And we'll do an inventory of, of course, publicly known things, and then maybe if companies, later on we could cajole to volunteer other things.

Don Berry: I agree with the work group. We have to do something. People ask me, "How did you do it in ISPY 2?" And I said, "I didn't do it in ISPY 2. I followed three dynamic women who drove absolutely, refused to say "no", who plowed through all kinds of barriers, and I followed.

Laura Esserman, of course, the PI, who's completely uninhibited, who calls me at 3:00 a.m. Sunday morning, and say's "You've got to talk to me." Janet Woodcock, who continues to be involved in ISPY 2 and facilitated the pathway, the registration pathway, for drugs, pathologic complete response was not part of the registration pathway when we started, we sort of gambled. And Janet pushed it and pushed it and got it through Rick Padzur and others so that now there's a Guidance that establishes pathologic complete response for accelerated approval.

It takes somebody who is driven. It's all about women. Of course, breast cancer is about women. You talk about urgency, Maria Wetzel, who was one of the original members of the Data Safety Monitoring Board, a young woman in her 40s, has metastatic breast cancer, two weeks ago, said she has to step down because the breast cancer was winning. Two days ago, she died of her breast cancer. And she knew that ISPY 2 could have helped her.

The other woman in this troika was Anna Barker, who she knew what David Dilts put up the other day, of the 360, whatever it is, places that you have to visit. And that's the cooperative group. She knew; we knew that we couldn't have done this through the cooperative groups. She said, "Let's do it through the Foundation for the NIH." She was Co-Chair of the Biomarker Consortium. I

was a member. We got them to sign on, and they did it; I think, enthusiastically. Lot's of hype. Anna, at one meeting with the FDA, said that "We had to come here to prepare you for the on slot of reporters who are going to ask you about this study." Sort of, "The onus is on you."

Nobody's asked me about ICE 1. ICE 1 with not randomizing, had two focuses; one was biomarkers to, of course, build the infrastructure for doing this. Standard therapy, look at biomarkers, look at longitudinal modeling, imaging, so the two main things were imaging and biomarkers, and we built the infrastructure; we built the IT; we built the network that would eventually become expanded into ISPY 2, but formed the core of the main sites that were doing this.

And it takes somebody, that "Little Engine Who Could", or "The Little Woman That Will." It really takes somebody who is committed, whether it's the pig and the pork and the ham, the ham and eggs, but it takes somebody who's committed, who's driven. And if you just have working groups that come and meet and talk, it doesn't do it. You've got to drive. You've got to say, "I hear you, but the answer is no; we're not slowing down. We're going."

So I'm willing to help, but I'm not a dynamic woman. And I don't know that – obviously there are dynamic men, and we need men too – but we need people who want to change the world. And you can change the world. Here, as I've said several times in this meeting, it's ripe for change. It's a disaster. When it's a disaster, and talk about baseball, you fire the manager. You get rid of the team. We did it in Houston. Of course, we ended up with a lousy team, but. So you've got to change, and you can't just talk. You've got to do and you've got to push, and you can't say "no."

Cynthia Bens: So Don, I don't think you're going to like what came out of Working Group Two. That was the group that was focused on modeling and simulation, which followed the talk that you gave about the critical role that modeling and simulation played in ISPY 2 both for learning across adaptive designs, but also for CPTR and allowing for early decision making. The group was Co-Chaired by Deborah Hanna, who runs the Critical Path for Tuberculosis from the Critical Path Institute and Yaning Wang, from the FDA.

And really, there were two short-term goals that came out of it. One was that there needs to be a smaller working group solely

focused on pulling together data experts and modeling experts to see what data really exists and what's out there and what we can realistically get access to. I think toward the end of the group one of the things that came out is the lack of access right now for the consortium to company biomarker data. So that's something that I think that we'll need to explore moving forward. And also to create an inventory of what models currently exist through consortium, but also within the companies, that they may be developing themselves. That is what we're looking to convene in the short term.

And Don, I'd just like to address your point. I may not be a dynamic woman, but I am very committed to seeing this through to the point to where I know that it may not be something that we create as a new consortium, but I'm really committed to shaking things up a bit. And I think that we've been working fairly collaborativly with the Association and with the Critical Path Institute, and I think that one of the major things that came out of the last two-and-a-half days is I went home and cried a little bit at night. But with some love from my husband and dogs, came to show me that the planning that went into this meeting for the last six months was not a complete and total waste, and the fact that I woke up in the morning and dusted myself off and came in was a sign that I am truly committed to seeing this through. So I could be part of the triumvirate that hopefully leads us to where we need to be.

And anyone else who's still here, I think Gary; you were part of Working Group Two with me, and modeling and simulation. Steve, I think you might have been part of that as well, so if there's anything that you can add that I may have left out, please let me know. No? Great.

Diane Stephenson: I actually have one more comment about modeling and simulation. Something we're thinking about a lot at Critical Path Institute, both, Deborah and myself, across the consortium. In the recent past, actually there's been several start-up companies that their whole focus is modeling and simulation. Some of them have the core focus on genetics. It's this bottoms-up approach. But they're actually very engaged and very interested in this.

We have a handful of at least seven, and I'm so thrilled to have had dinner with Don Berry, and Lauren, of Berry and Associates. This is a very rich group of very talented, mostly young, really creative, bright, young people that are using bioinformatics to create

models. I think that we should reach out to those folks because they are really doing this. Hugo Geertz, I invited him here for that purpose.

I'll say in September of this year C-PATH is going to be cosponsoring a meeting with FDA and ISOP, International Society of Pharmacometrics, to showcase examples of how modeling and simulation is used for decision making and drug development of all phases of drug development, not just for AD, but for all disease. So this is kind of innovative, and I think that we want to use this as a platform to expand what we're thinking and modeling beyond what came from the workgroup perhaps.

Enchi Liu: Is that a specific conference?

Diane Stephenson: Yes. We're just doing a "save the date." It's just going out on September 26.

Enchi Liu: Because I was thinking that would be a good thing to do because most people in the work groups are talking about testing on a combination of agents in animal models, but let's take a look at modeling simulation and the avatar type of modeling that Hugo Geertz – I'd like to see a presentation of that.

Diane Stephenson: Sure.

Rachel Schindler: And just another comment about that work group. I think one of the things that we also talked about was looking at the landscape of what was in the field, but also making sure that when we're looking at that landscape, and we're pulling the different data pieces together that we assess the quality of the data that we're bringing together. And I know Diane's group has done a lot of work in looking at making sure that that data is speaking a common language, and one of the things that was also discussed was that there's some ongoing activity in mining the FDA database right now, and that they've been able to just change some of the parameters and bring that data together to look at different questions within that database. But if we're looking at bringing a larger set of data, or continuing to combine that, looking at making sure we're speaking the same language, and having a set standard of what is quality data; that's, then being looked at when we're assessing the landscape.

Enchi Liu: Heather, did you want to help summarize what Work Group Three?

Heather Snyder: Sure. So to summarize Work Group Three, and this was looking at consortia and different models of partnership, I think one of the things that we first did, or that came out of the discussion, was that we changed the name, and that it was really looking at collaborations and partnerships, and going off of what Work Group One talked about, that there are some existing framework, so where we are already convening these types of work groups. CAMD has some of those things, the Alzheimer's Association does some of those things, and those were two of the examples that were really discussed, at least in our work group, where those types of work groups have convened and come together, both bringing industry experts and academic experts, and had an output as well as a driving force forward and been able to change various aspects of the field.

We also came up with one of our short-term goals was this idea of developing an inventory, which I think was a theme that we heard over the last two-and-a-half days, pretty consistently, to be able to look at how combination therapies can be used or what types of combinations should come together. We really need to understand what is out there and also understand the underlying mechanism that may be for the target.

One of the other things that was discussed, although we didn't go into great detail about it, was really looking at, or having identified rules of engagement of what was a necessary level of evidence to move forward with a combination therapy, and that was not something that we really delved into with great detail.

One of the – and I think this was identified previously – is that this really was a very specific technical expertise to have this type of conversation and to look at what is that inventory and what is available and being able to pull those resources together. So the idea of maybe not so much of a work group, but a task force, which implies more of an action. That would be one item that came out of our work group that could be in near-term format.

One of the other near-term goals was the idea of enhancing existing infrastructure and exploring some of the existing models that exist. There was the idea of ADCS and maybe pulling together ADCS leadership with some other thought leaders and having that discussion of how can we enhance what is already existing in the ADCS as a way to explore partnership to help de-risk some of these combination therapy models from

pharmaceutical companies and encourage maybe their support another way within that model, within that framework.

And I think one of the things that we discussed within that were different funding mechanisms that may be able to be applied. One could be like a model that we've seen in some of the more recent trials, where there are submission ideas that then get evaluated by a group, or a counsel, and then the best one goes forward and then there's some type of financial structure that's built in. That was one that was discussed at least. And those we identified as two of the near-term goals that could be tackled in the very near future.

And looking more at the long-term, there was really a discussion about – and I think we went back to Work Group One and some of those discussions – that there really was a lot that we still didn't understand about the different targets that are being explored, and maybe there needs to be a systematic review of the disease and where we are in the understanding of Alzheimer's Disease, and looking at being able to really drill down into what are the different mechanisms that play.

There was a suggestion that the whole genome sequencing, when that data is available, would actually be able to shed some new light on some of these different mechanisms that are playing a role and maybe interacting with one another and that this also could lead to the identification of new targets and so really looking at that systematic review. We're doing a systematic review of our understanding of the disease. And that wouldn't be an immediate goal. The feeling really was that that was a much more long-term goal of really evaluating and looking at the field. And, of course, this would be technical expertise across the field to really bring that together.

And then probably the last particular action item that we talked about was – and I think this reiterates some of what came out of Work Group One in particular – but this idea, and this was not identified in near-term, short-term or mid-term, but more as an ongoing, something that we could start today, tomorrow – and it was just identifying different forms for information sharing, that there needs to be leaders that come forward to share that information, to share lessons learned, and I think we've seen some of that in the different work group discussions, but continuing to foster that type of environment and identify forums where that can then have a home, and not just one particular form but across the field, to really encourage that type of collaboration.

The idea was that we could share lessons learned so that rather than -- I think there were several examples of folks that talked about reinventing the wheel for every clinical trial, and I think we heard that a little bit in the presentation yesterday morning, and that this really, in order to be successful in this, really to provide consistent and unique platforms that would engage and enhance the sharing of knowledge. So I think that was kind of a summary of our near-term, long-term and our more immediate-terms.

Enchi Liu: I just wanted to add that for me, I think the premise of November's meeting and today's meeting is that there have been negative results coming out of Phase III trials over the last, I don't know, six years, and I guess the group wanted to get together – maybe instigated by Rusty Katz and others last year – that are there alternative pathways to drug development that could ensure success in Alzheimer's Disease?

I mean the companies are going to march their own way in their own programs, but is there something in the community that we could do in addition, or in parallel, to those development programs? And I think that's why we're all gathered here. But I think some of the resistance that Diane had referred to over the last couple of days comes from maybe – I think you guys know what they could be – but one that's really the technical feasibility and an assessment of whether really combination therapy would be an alternative pathway. So I think it's a good thing if we could convene a technical group to assess that.

The other things would be the legal, contractual, and IP considerations for companies and different models. And I know that NIH, NIA and other folks have experiences that I think could be shared more widely. Not everyone understands how things have marched through, so sort of inventory of how those models might work could make it more attractive to companies to want to volunteer compounds that they've shelved in addition to what are some other de-risking factors for companies to be willing to volunteer the compounds? Could it be shared funding or some kind of risk sharing? Those are things I've heard over the last few days.

So for me, I think there's the spirit of combination therapy in the community to continue this workflow is there, but I think for companies to really all join in, get more participation, I think we

need to show them some data or some models that make them more comfortable to step up.

And then I also hear some of the discussions about whether we need to first go in to get evidence in pre-clinical models or should we build the infrastructure and get funding first. So I think these need to be resolved, maybe they should go in parallel. I'm not sure. But I really like the idea of the ICE 1 and 2 because it paves a way get some knowledge and then be experimental. So Reisa?

Reisa Sperling: I think that's encouraging in breaking down the pieces. You have to do an – I can't speak to the lawyers and the IP nor to the pre-clinical models, but I think after last night I really went home and thought well, can we come out with an action item on the middle piece which is how would we create a protocol that would allow us to do multiple combinations, but start with one, build it and see. I think we've done ICE x1; it's called ADNI. And I think we need to now translate the advances from ADNI and the other work that's been going on at the ADCS into a protocol for combination therapy.

And I very much would like to get a man involved and really think about whether we are ready for adaptive components to this or not because I do agree with everything that was said in the work groups about the concerns that we don't have great surrogate markers yet, but they are coming, and we're going to learn a lot over the next year or two to continue through ADNI and through some of these prevention trials.

So there is one specific action item. There is an NIH clinical trial planning grant. I did look it up last night, Neil and Laurie. It actually is for Phase III studies so I'm not sure how adaptable that would be to say we want to build a Phase II or Phase II, III kind of program, but we can find out about that. There's nothing that gets academic investigators actually moving like an NIH grant deadline, so I think we should consider something like that.

I would like to see us at least talk with the ADCS about this because I do think they have much of the infrastructure we already need, it's already funded, and I think there are some actually terrific folks that are very interested in adaptive designs such as Ron Thomas, as I mentioned. And I think although Paul has some concerns about this, rightly so, I think he's very supportive of combination therapies with more traditional factorial designs and

maybe part of this actual planning grant would be to look at the relative merits of those two designs with the data we have now.

So that's it.

Neil Buckholtz: I just want to build on that. I thought there was, Diane, there's a general consensus out of the Working Group One that we do have combinations that could be deployed in the very near future. The first ones probably would be two different mechanisms of a-beta, and we have to decide which phase of disease to focus on. But I think we need a model to do our first test case. A lot of these issues will come up, the protocol design, IP – if it's two different companies – IP issue, data sharing, all the different challenges that come up. So I think it's important to move forward.

I think Sue's been very helpful by challenging us not to just leave here with sharing ideas, but actually having an action plan. I think that's something that we can do and at least start planning for because it's not going to happen overnight, it's going to take you a year, a year-and-a-half in the planning stage before we even deploy that trial. So I'd like to see us have a plan to move forward.

Reisa Sperling: Thank you so much. We did really discuss that in Work Group One quite in detail. And I actually have a question to this group in relation to that. Because we know that individual companies are taking two different agents that lower a-beta through different mechanisms through in a combination path. We saw some pre-clinical data for this at ADPD. We're going to learn a lot no matter who's doing this about the first time you really do it because there's so many challenges. How do you pick the dose? How do you do this?

There's also the example of catalyzing this discussion to get buy in on the value of taking the best guy, agent, from two companies to say they take their best base inhibitor, and they figure out which one it is and they do it.

What incentives could be provided to an organization that's not here? For example, Roche, for a company that is paving the way to do this on their own, to share somehow the learnings of how did they actually do it so that the next company, or as parallels trying to figure this out on their own, doesn't have to reinvent the wheel. Is there any incentive that could be created for that?

I actually, these companies even, again, I can't say specifically because I have CDAs with them, but several companies are in this position, and they're already talking at least to the ADCS and several of us about how to do it because they realize there are some issues as well, especially in working with regulators and others to make sure that this is a smooth pathway. I can also say that even some of the companies who have both assets, or multiple a-beta assets are wondering whether it might make more sense to have different combinations than they currently have. So I think building this and facilitating the possibility of combining across those is really key. Even if we ultimately decide to do it within company, there still would be.

So again, I listed this the first day, but I think the assets on the clinical side are to say we have a ready to go clinical trial network with lots of patients ready to go and have worked out a lot of the issues around outcomes and statistical models to do this. Of course, companies have this on their own but they frequently go out to expertise in academia to get it, and we could offer that.

And I think they also believe, and maybe I'm wrong about this, but that academic investigators can help them trail blaze on this. So they're risk averse, academics are crazy, and not risk averse, and that partnership, I think, has worked well in moving the prevention trials forward in ADNI, and I think it would be a really good partnership for combination therapy even if it's done in company.

Diane Stephenson: That's a good suggestion, Reisa. Thank you for that.

Dan Perry: We want to continue to the questions of this panel, but I wanted to ask one of my own. One of the things that was brought up by John Allam yesterday was there are all of these older drugs that are now being identified by the National Center for Advancing Translational Science, some 50 combinations, we're not sure if any of those are relevant to Alzheimer's, but within that larger library of older drugs that are no longer being pursued under their own because they seem to be underpowered for whatever it is they're trying to do.

There may be some that could be combined with other drugs under development that could be very beneficial in this field in terms of hitting the inflammation targets or whatever it might be. And John Allam particular said he thinks that this is an area that is more right for exploitation by the patient groups and by academia. A little bit less interest by industry but industry would have some interest in it

if it's their own already approved and tested drug that might have a new life as an adjunctive therapy. So I throw that out to the panel and to the group, and please continue your questions.

Enchi Liu: I think, Dan, we do include those 58 compounds that NCATS has as part of the inventory, but it might take more investigation on what the mechanism of action and what the combinations might be. We might have to do modeling on whether it's feasible to do combinations. So I think that will be part of the inventory in the feasibility assessment.

Dan Perry: Okay, fine.

Reisa Sperling: And I think, to add on to that, I think that goes into the discussion that we had about what is the level of evidence that is needed or necessary or is even available within those different combinations or within the compounds that are available and being able to assess that in order to make a decision or even identify what could be the next steps. And that was something that came out of actually both in the modeling discussion but also in yesterday's work group as well.

Diane Stephenson: Perhaps I can comment. In some of the one-on-one's I had with our industry colleagues not everyone was completely on board with this idea. What I'd like to say is I think it's worth engaging those who may not be in the room right now – I don't know if I see Suzanna – but the NCATS folks who came last fall. I did talk with John McKew since then, and he said that at least the RFP duration right now for any new funding proposals around those compounds has ended at least for now. But to get into this a little bit further, the people that aren't here probably would need to be engaged on whether or not this really makes sense to do more.

Enchi Liu: I also – Rusty, please. No, go ahead. Ask your question.

Rusty Katz: I don't have a question for the panel, but I just wanted to add my voice, mostly my personal view for what they're worth, about the meeting, the issue that we're talking about. So it's not really a question, and I don't know if it's the right time, but I'm up already.

And by the way, I'm Rusty Katz. You might have heard my name. I want to just give you my view of the meeting. One of my favorite quotes in all of literature was written by W. C. Fields. So that tells you the kinds of things I read, but also the older I get the younger the audience gets so there may be people who don't know

who that it is. Just ask an older person sitting next to you if you don't know who that is.

But he wrote an essay about benefit performances. These are performances for charities. And he said, "Now they're all for worthy causes, and I'm sure some of them are." So I go to a lot of meetings, and they're all very important, and some of them are. And this one, most definitely, in my view, is among the most important meetings that I've been to. Not just because everybody seems to be attributing to the reason of the meeting, to me. If that were true, I would consider it a great legacy actually.

But it's sort of obvious, I think, that this is the next step. Not just because our attempts so far have failed. Maybe they've failed because we were ___ population. Maybe we still have the right targets, but for some reason, it's not working. But when you become aware of how much is wrong in the Alzheimer's brain, it just seems to follow logically that it makes sense to treat as best we can these other abnormal pathways.

It's not going to be easy as everyone has said, and I don't think I'll have really anything here to say on a personal level that's different from what anybody else has said. But it's not going to be easy. We don't have surrogates, and that would be very useful to have. We will eventually have them, but I don't think we can wait to learn everything that there is possibly to learn before we forge ahead.

There was some, I think, early in the meeting. There was some sort of conflating of various issues that arise. I think, in particular, there was some sort of confusion about some of the things we were talking about like identifying new targets and consortia related to that effort and doing a trial, and consortia related to that effort. I think those are very different things although ultimately, they're going to be very linked.

And I think the effort to identify targets is extremely important. I think that goes without saying. And I think actually even contemplating the prospect of using combination therapies, it just leads, almost logically, to the effort to identify new targets. Even though you can have a combination, and we've contemplated doing a study and using a combination just that one target, still, I think the larger issue of identifying the targets is critical, but I don't think the field can wait to identify all these new targets.

There are plenty of targets, there are plenty of things that are wrong in the brain that we know about already, and I'm not particularly discouraged by what has been called "push back" from various people. I think I hear and have heard over the course of several days, a gathering consensus that it's time to do trials. It's time to identify drugs that might be on the shelf in drug companies, and to try to make the effort to go and identify what they are and to set up a small group of people who will make the decision about what drugs to study, what targets to look at.

I think there is a consensus for doing this, and as I say, it's not going to be easy. There's money involved obviously, I don't even know what the problems are, but it just takes the will to do it. And I think the will is there, at least with the people in this room, and we even heard from someone in the pharmaceutical industry that what I would consider the potentially very thorny issue of IP and sharing data is a tractable problem. So I don't think that's really a problem.

A couple of things from sort of the FDAs point of view. Steve Saloway has praised us for lowering the bar. I get a little nervous when I hear that phrase. I'm always wondering if they're taping this so they can take it back to my bosses.

Cynthia Bens: We tape it because it's being transcribed.

Rusty Katz: I don't really see us as "lowering the bar." I do think there is the potential for considerable flexibility in the rules. And we are committed to trying to be as flexible as possible. That doesn't mean that in a particular case, you may not have to do a full factorial study, or in a particular case, the non-clinical toxicology might not have to be fairly extensive, looking at the individual components first and then looking at the combinations. I don't know. These, more than most, have to be taken on a case-by-case basis. But we can be flexible when it's appropriate to do so.

I think the main point I want to make from the point-of-view of the Agency, is that we are committed to working with the community very closely. I would say the initial evidence of that is that we've been here, Nick and I have been here for about two-and-a-half days, Laurie Burke was here for two days, Yaning Wang not only co-chaired a session but has obviously been very involved in the efforts to model and simulation to look at disease progress.

We heard that Kun Jin is going to take the summer and try to look at the entire FDA database that we have for at least the approved drugs and see what we know about the relationship between surrogates, or potential surrogates, biomarkers, and clinical outcome. And Don Berry mentioned Janet Woodcock who's been involved in initiatives not only in other diseases, but actually in Alzheimer's Disease as well.

So I hope you get the sense that we are committed to working with the community. And even though I will be gone soon, I think it's fair to say that I'm quite confident that the folks that will still be there, including Nick, who is our team leader for Alzheimer's drugs, will be committed to the same level. And even though I won't be there, I will be watching.

Thank you.

Diane Stephenson: Rachel?

Rachel Schindler: I don't want to reiterate things that have already been said, but I do want to try to put some more concrete lines around some of the things that were said over the last couple of days. And I think one of the issues that is very implicit in all of these discussions, particularly for the scientists, is that this suggestion of combination therapy and the way it's being suggested and the way it was depicted, for example, in the TB and the I Spy examples, is that it is counter, not just counter-intuitive, but actually, it's what becomes intuitive, but it's counter to what we were originally all taught which is that in science you isolate each factor in order to understand the problem.

And we learn that in the clinic too, that if you start two medicines at once and the patient gets better, you don't really know why they got better, and if they get a side effect, you don't know which one it was, and then you've got to stop everything, and so we learn, and particularly in high school chemistry, to isolate one factor at a time. So this is very counter-intuitive to that.

But I'm intrigued particularly, by the way that it was done in I Spy and the factorials and the way of using the modeling and the factorials to facilitate that, and I think that's a very important thing to stress when this gets presented. Because otherwise, it's so, as I said, counter to the scientific method. So that's a very important point to stress.

The second thing was, and I might have even been the first to use the word “incentive," and maybe that’s really not the right word. Incentive sounds, to some extent, like there has to be something in it for me, there has to be gain. Maybe a better way, and particular with drug companies who are really big and bad and only for profit and don’t care otherwise, maybe a better way to talk about it is to breaking down the barriers and the obstacles.

So for example, we’ve all talked about IP and the complications with that. So I think there were more policy and advocacy people here than science people. And I look straight at Dan who’s been at this for –

Dan Perry: Longer than you want to know.

Rachel Schindler: Way longer than I’ve been born or something like that, which was just yesterday. But also tied in to the parallel thing to this is not just the terminology like “Incentive," but terminology like “things on the shelf," or “low-hanging fruit."

As was said yesterday, or the day before yesterday, I certainly wouldn’t want to take – if I were a patient – I really wouldn’t be so thrilled about the “low-hanging fruit," or “something that was shelved," that doesn’t sound so very much appealing. But maybe another way to think of it is for the things that have been aside for the moment.

One of the key issues, for example, and we can sit and break all of these things down, and this is where I want to get there in the end, but say something like that one of the issues is patent life and IP. And so for those things where the clock has already ticked, and it’s practically out, why can’t we – and again, now I’m looking at Dan. This is your bailiwick – but that would be something extremely tangible and doable, to talk about extending patent lives or invigorating them, or again, I’m not an attorney, so I don’t know what the possibilities are or how you describe them.

There are so many things I have on my list, but I’m not going to go through them. But that’s, for example, one very specific thing that could be done.

Cynthia Bens: I think it would be very helpful to know what that incentive would be. Yes, because I tried to bring up the issue in Working Group Four, what sort of incentives or what would be attractive to

companies to get them to participate in any sort of a consortium type effort that leads to I Spy II. Because I know that even in Chas's model, when the assets given back for further development, I think that the years that he gave that the company would still have at the end, it was pretty short. I think eight was the longest.

Rachel Schindler: Right. And again, it's not coming from what is, I think, the largest pharmaceutical company I can tell you people really want to help and do things. It's not that, really that we're so evil, it's that it's a business, and the stakeholder, and the shareholder, and the stock price. There's responsibility that always comes back to us. But again, even with that, I want to point out that the amount – our company was the first to be involved with ADNI and donated $2 million the first year. I could give you a thousand examples, but we're not all so big and bad, but it's times of terrible constraint in every sector not just in health or pharmaceuticals, or whatever. Everybody knows that we're just all restrictive right now.

So anything that could be done. People want to do something, but also will have to have jobs, so to take things like that into consideration, for example, extension of patent and of IP. I think in terms of action items, I spoke yesterday about parallel paths and that not just to save time rather than working in series, which, by the way, is the whole concept of what's being discussed here in combination. It's saying we can't wait to test one drug at a time; we're going to have to kind of throw them all in together because we just can't wait anymore.

We have to make clear that's not at the expense of the science. But those parallel paths are number one, things in the infrastructure. And an example is, how would you carry this out? Reisa has been frequently bringing up our favorite, ADCS. Other things in the infrastructure, how would you do this consortium or now? But again, we have to be really careful not to put the cart before the horse. So it's sort of a question taking each step kind of then relates back to the others and all the levels kind of rise at once. I don't think it's so much a consortium or not at this point, but it will be.

I think we need to really collaborate with the science. It's sort of you start with your wish list out here, your theoretical, which is what would we want to do? And I do think in en deference to everyone here and everyone who has been here the last couple of days, there are fabulous technical efforts. I mean I consider myself

a very good clinical scientist, but there are some smoking Alzheimer's scientists and pre-clinical.

And by the way, if they have the answer, we wouldn't even be here. I'm not saying that, but there has to be, as – I can't remember who said it the other day – but there has to be clear scientific rationale. And even if we all don't agree on which mechanism it's going to be, whether it's going to be a-beta, and whether it's going to be all antibodies because some do antibodies, and some do fibular, or whether it's going to be one antibody and one small, one large, whatever.

I think, again, we need the technical expertise to really sort out a very good work plan that is very scientifically driven. So you start there, with your wish list, and then on the other end you start with, okay, I've got my fantasy, on the other side is what's available, what can I do? And then inventory was discussed. What is really available? And then you start to marry them up. Those are science parts that can be done in parallel.

And again, I'm elaborating that reality of what's available and can be done. The modeling is critical. We have some, I know Dr. Berry was here, and he's obviously greatly experienced at that. We also all know some just unbelievable modelers who we can bring to ____. And I think one of the really key things is bringing the best people together, not necessarily the people who were here, but really getting the best people together.

We talked a little bit about the policy issues. So extending patent life, I think we're ready, we've already started on the Regulatory path. That's been well elaborated. We haven't actually talked about the specific of that, but again, I leave that to the experts.

I have more of a list over there, but this is sort of the short because I didn't want to monopolize the time up here, which I think I've already done. But we can talk about it more. I think the key is really to separate this into digestible, workable, doable problems and really get the right people. And I think we also need some legal expertise on this. And there is wonderful precedence. That stuff doesn't bother me at all because those are very attackable problems, but we should do that in order to keep the momentum.

I think the hardest part here is the science, particularly when you're talking about putting molecules together that so little is known about. The TB example, which is so beautiful, is very different.

These are drugs that may not have been advanced enough, and I think the bottom line is patient safety. And so a lot of what we're talking about, or a lot of what was mentioned, cannot be done in the way that it's been mentioned because of patient safety.

We can do the DDI work, drug/drug interaction work. But it's more than that. Particularly, people talk about putting two antibodies together, for example, and we know the issues with vasogenic edema. So we can sit down in a small group and articulate some of these problems and then begin to work on all of them simultaneously.

Enchi Liu: Thank you Rachel, for your insight and also reiterating and tying up a lot of the discussion that we've had over the last two days. Thanks for that. And I want to also echo what Rusty said earlier, that I actually feel like doing this meeting, there was a lot of consensus. I felt like the discussions points were more people struggling with what is the right path forward, rather than a real negative attitude about combination therapy and going forward. I think what I heard were more people trying to figure out what the right pathway is. And one of them could be also including how to de-risk for companies to be more willing to volunteer their compounds, not the "low-hanging fruit," but maybe their best ones. So thanks for tying up the discussion points.

Rachel Schindler: Regarding that I would, there's a number of things I would look at. As I mentioned in a work group the other day, I would speak with Don Berry.

Reisa Sperling: I think he's here actually.

Rachel Schindler: Was he here? I didn't see him. You're in the corner.

Don Berry: It's all those dynamic women.

Rachel Schindler: This is fabulous. It's a first.

Rachel Schindler: But that would be really a great example and one of my take homes is I'm going to speak to my Oncology counterparts about it as well, in addition to your perspective, to get the opposite side of the same perspective, something that has worked. That was another thing on my list from two days ago.

Reisa Sperling: What were you going to say about Don Berry?

Rachel Schindler: Just the other day in the work group I said that one of the things that I think, certainly that I would do immediately, is I said that, in the work group two days ago, I said that I would want to talk to Don, more specifically about some of the questions that I have about the various companies, what phases of development the drugs were in, specifically in terms of what kind of data were available. Some of the examples would actually be – and I'm not talking about best practices and learnings or anything like that – but I'm talking about if we knew where some of these drugs were and some of the specifics around them, then we have, I have a list of questions ready, if it was done at certain stages and with certain information and lack thereof, that would tell me a tremendous amount about either why it was doable or what was surmounted.

Don Berry: So we have a particular policy that's doable, that's working that everybody buys into. But that doesn't mean that can't be modified and still be found acceptable.

Rachel Schindler: Oh no, of course. I just mean that if we sat down and talked about some of the individual compounds, for example, and I would have a list of questions to ask you; I would ask you very specific questions about some of those compounds, and depending upon your answers; it would make sense because right now, I'm having trouble seeing it, but if I got the answers to those questions, I would have a big "aha," or "oh, of course. That's why you were able to do it. You found a way around "x" and "y," and that's kind of what I would need to know to figure out how to go forward.

Don Berry: I can provide that. The one thing I can't provide is the data.

Rachel Schindler: I'm not talking about that at all. It's theoretical. I'm not even talking about the specific drugs. I'm talking about some very specific things about the exact drugs that have been used.

Reisa: Thanks Rachel. The other thing I also heard, I'm sorry, is that we're forming these actionable work groups and whatnot, but I think I also heard from Don and then Maria yesterday that we really need to have a leadership to drive this. We can't just have silo'd work groups, but there's an organization to that. So, go ahead.

Diane Stephenson: On that note, I actually, when I see it – if I can perhaps put Diana, from New York Academy, a little bit on the spot here. In two weeks, there will be a meeting. Many of you know or are already invited to participate in those catalyzed by Mike Krams, who was

in our fall meeting who is not here today, around how to really get into a deep dive around I Spy II for Alzheimer's Disease, very focused on prevention. But Diana, perhaps you can get up and talk a little bit about that meeting? Because it's very much aligned with some of the actions that we're thinking, it will have similar but not identical people, so there could be additional experts that we could tap into in terms of next steps for actions. Diana?

Diane Van de Hoef: Hi. I'm Diana Van de Heof from the New York Academy of Science. It's just a pleasure to be here, so I just thank you for inviting us. Our next meeting is in a couple of weeks. That's June 10 and 11. And I think the purpose for that is just to take on a more broad on combination therapy, but to dive deeper into how do we identify patients, how do we engage them in the clinical trials?

I'm really nervous. Sorry. I don't know why. I always get nervous the first time I speak to people, and then I'm like, "Okay."

But yes, I just find this very interesting to talk about the patient engagement story because I think that's something that came out of this meeting. Thirty-nine percent of the clinical trials have less than five people engaged, and I'm really surprised to hear that. So let's talk about that.

Diane Van de Hoef: Okay.

Neil Buckholtz: Well actually, to answer, 60 percent of Phase III clinical trials do not include ____ approvals.

Diane Van de Hoef: That's crazy. So let's talk about this. Because I mean that's probably a bottle neck, a true bottle neck, right? So that's one of our working group sessions. The other one is to talk about how do we look at clinical efficacy, or the endpoints? What are we missing here? And I think that is a really great discussion that came out of this meeting, that the biomarkers, how do we identify them, surrogate endpoints? I think we really want to dive deep on that.

And then I was really interested in what people were talking about with the business models of how we're going to fund this type of work, so we want to bring Chas Bountra into that discussion. He's going to Chair that session for us, and Laura Esserman's part of that. She can just really – this is my first time meeting her – I'm

anticipating that she's going to give us a lot of key insights into successes and how we can create a robust business model going forward.

So I think that's going to be one day. It's very ambitious for one day, but we're going to get a lot of work done. And the next day we're going to try to come up with a roadmap to get some very clear, defined action steps. If you can't make it in person, maybe we'll have some remote access. Please talk to me afterwards if you're interested in attending that remotely.

Diane Stephenson: Great. Thank you so much, Diana. I brought this up today because I think a lot of what we're talking about, next steps, maybe we could even help to engage some of those folks to help us in this plan. It's not identical. The meetings are not the same. Our focus is really on combination and especially around the Regulatory path. Their focus is somewhat distinct, but I think we can share some of the insights from that meeting as well. Thanks.

Sue Peschin: And I just wanted to follow up on what Enchi brought up about leadership. I agree and I think that it seems like, at least from this session, that there's a lot of great work group ideas, or task force ideas, about the pieces that need to be tackled and can be tackled in either the short-term or the slightly longer term. I do want to put out that the Alliance for Aging Research and also ACT-AD would love to be a part of a group, I think, makes sense, whether it's Critical Path and the Alzheimer's Association, Don Berry, Dave, Chas. If we can get a leadership group together that would sort of look at this, and not being about a crown and a sceptor here, to you know, to be any type of power grab, but really about doing the grunt work that's going to be necessary to kind of organize some of these task force and work groups, and kind of keep things in line, and keep things going. So I did just want to cap that off.

I know that one of the goals of this event is to do a publication, and that's always very important to memorialize it. That will happen, but just to sort of put out there that we'll be reaching out to all of you and please feel free to reach out to us, to give us more of your feedback and what you got out of this and what you'd be interested in participating in because we are committed, and we are planning to move this forward.

Cynthia Bens: Thanks Sue. And just a quick comment on the idea of publication, I'll let everyone know where that's at. We actually, thanks to Lisa Bain, who's here with us today and also came to the meeting last

fall, have a draft, a paper, Reisa and actually the authors who presented at the meeting last fall were sent that draft. We put it on hold in terms of submission until we kind of got a sense of what this meeting was about and whether or not we should be revised, but I'm actually very eager, very much, to hear what people's thoughts are after this meeting.

And it's pretty ready to go, and the plan would be to submit that to Alzheimer's eventually. It would be a great way to show that we really had convening of diverse people to really make the case of the rationale for why we would think to do this now, and I'm happy to share that draft with anyone here.

Dan Perry: Cynthia?

Cynthia Bens: Yes?

Dan Perry: Can you do –

Cynthia Bens: Working Group Four? Sure. And I think that Rusty actually did a really great job of summing up what came out of Working Group Four, because I think that while it started with what seemed like a jagged pill to swallow, which was sort of the, I think, realization that came from some of the discussion the first two days about their not being enough articulated scientific rationale for combining the therapies and how necessary that would be for companies to take on the prospect of partnering together. And I think that there is an understanding on my part. I tend to be sort of pushy and impatient advocate, but I think that I've came to the realization that it's a very pragmatic process. Not to use _____ words is "to do drug development," and that what we're asking of you is a pretty tall order to consider without really doing our due diligence in establishing that scientific rationale.

But I think we all came to some, I think, tentative agreement that there needs to be a Committee established, a committee of the willing as I'm calling them, who would be willing to really have serious conversations with some of the companies about whether or not they would be willing to make available some of their assets that are for this type of testing.

And I think that I got a little bit of encouragement during the break of the work group from Don Berry saying that "You just need to get started." I think that we're at that point where, you know; we've now had two major conversations and while I think that we

need to take a stepwise approach, we just need to get started in doing this even if it's just starting with working groups and putting together the small committee to see if this is possible. I think now is the time that we really need to start doing it because I think while everybody agrees that it's a good hypothesis that we need to get down to brass tax on how to make it happen.

One of the other really interesting things that came out of the working group is the work that's being done by FDA that Kun Jin brought up. And there's a three-month pilot that they're going to be doing over the summer with a fellowship to really comb over the data and make some sense of where the connections are with clinical endpoints, and I think that would be helpful for us to have a follow-up conversation, to the extent that we can on what sort of the plans are for that and any sort of information that can be gleaned from that can provide a little bit more certainty on how to move forward.

And one of the things that came to mind, both during the group and then also afterwards, there have been several conversations, and Sue and I have had them separately, about the role for advocacy, really, and providing a more constructive environment for fostering the type of environment that you'll need at your companies to try to pave this path in. We, I think, are willing to not only be helpful with any way that we can weigh in with the senior leadership of your companies to really show how serious we are about being committed to this, but also to have some of those conversations for identifying how the structures can really provide some more incentives to pursuing this.

So two other things that came up, and I think Diane brought one of them up in her opening remarks, is the issue of payors. And it didn't only come up in terms of how the payors would pay for the combinations, but also what types of data would need to be provided in addition to the data that FDA required to approve it. So we are committed to exploring that, not just nationally but internationally, because we know that's critically important as well.

And Diane also mentioned that there are other global efforts that are going on to analyze this data on biomarkers and endpoints, and that whatever we do should be aligned with those as well.

I think that's it unless anybody else from Working Group Four has anything else to add?

Thank you, Steven.

Steven Salloway: I just have a comment about infrastructure and leadership, not so much about Working Group Four. I think we should look at the infrastructure we currently have with ADNI, where there is a scientific leadership, plus there's an allied ADNI Pharma scientific committee that's been very involved. There's the NIH Foundation that's a very important part of the ADNI infrastructure. Looking at ADCS, looking at the DIAN Pharma consortium, looking into models that we already have and see what we can take from those, each of those, in constructing a functioning organization here for early stage clinical trials that are going to foster combination therapy among other things and see what we can use directly from those – because we may be able to use a good part of ADCS – we can just take in terms of modeling from the others to see how we would want to construct the infrastructure for this group.

Enchi Liu: So in comment to that, could ADNI III be the combination therapy?

Heather Snyder: So in ADNI , I'll just say Enchi, you've done such a terrific job of leading this new Clinical Translational Working Group for the PPSB.

Well, you are clearly already doing a lot. And I remember last year, being at one of the ADNI PPSB meetings, where that concept came up of having an additional work group. So perhaps this is an idea that they take on another, that there's another extension of PPSB.

Enchi Liu: We could try, but it's all gratis. Because PPSB, if people don't know what that is, it's the private partners who fund a third or fifty percent of ADNI. But we're all volunteers. There's no money. And ADNI too, is a very specific protocol and grant, so the work groups that are initiated are in-kind contributions from the companies. So I'm not sure that's the right forum. I mean it's a think tank, but we always have to ask money or incoming contributions.

Reisa Sperling: Okay. So maybe that tempers what I was going to say. But I think it's a good suggestion. So again, the ADCS is the clinical infrastructure for ADNI. So that's already there. We may need to expand it, and maybe it's too; it's not nimble enough for all the adaptive things, and we should make it more nimble. But I think that part we've built, and we should – I actually was thinking that

the PPSB would be a good potential forum to say how would you take what's in ADNI and now apply it to clinical trials, because I think ADNIs been unbelievably great, but now the question is how do you actually take that into clinical trials rather than having it be in parallel?

I think we need to do more biomarker development in the setting of trials. I already said that. So is it that you think that there wouldn't be people interested or could it be if we had other funding to somehow capitalize on the people who are already involved in the PPSB and some of these groups because you're already there, or is it just overwhelming working on other things?

Enchi Liu: I think I would prefer, if Mike Weiner initiated an idea to the group. I don't mind coming and talking, but I think you know some of the pharma groups that belong to the PPSB are not here. So I think that Mike Weiner might be the person to broach first.

Reisa Sperling: So we could get Paul to talk to Mike, right, to _____.

Enchi Liu: Dean? Please?

Conrad Wong: My name is Conrad Wong.

Sue Peschin: Oh Conrad, I'm so sorry.

Conrad Wong: I just had a couple of thoughts after having been at this meeting for the last couple of days.

Sue Peschin: Raise your microphone up.

Conrad Wong: Whatever initiative that's put together with regards to clinical trials, I really appreciate the FDA being here. And you know, one concept I'd like for this group to be thinking about is as we're studying these combinations in patients, that we work with the FDA so that potentially we can make every patient count that participates in our trials because if we find that we have a good effect in these early trials, we're going to want to move these –

We're going to want to move these to Phase III and to the market as quickly as possible to patients. So working closely with the Agency to ensure that whatever data that's generated in these clinical trials early on could potentially count, and I think that would be really helpful.

And then, you know, I hear the urgency, but at the same time it takes time. So there are studies ongoing to enable combination therapies to be developed. And you know, the first thing that we have to be conscious of is the safety of the patients, and that it takes time to generate that data and that database to ensure that whatever combination we're going to be putting together, especially given that we're thinking about going earlier into the patient population, we don't only want to slow the progression of this disease, we want to stop it and ensure that people continue to have healthy and good quality of life. And so that really takes time.

And I think still too, in really important ways, how the community can be partnering with industry is in developing our clinical programs, helping us get consensus on who the patient is and how to identify the patient. But that's still, there's a lot of discussion about that and there's no clear consensus.

And then the other big thing that we need partnering with is really identifying and developing the outcomes, whether they're biomarkers or patient reported outcomes, whatever those outcomes are because currently, the outcomes that we're using apparently are not sensitive enough to demonstrate an effect with whatever treatment, and I'm afraid if we continue using the current endpoints, that we'll continue to fail. So I think we could really use – and that's a huge effort. That's no small task. Those are some of the thoughts that I had.

And then I guess one last personal comment, and I know I work for Lilly, but I'm not representing Lilly in this perspective, and that is we're working hard. We're working really hard. I spend a lot of my time thinking about this, ruminating about this. And this is my first time to come to a meeting where it's a lot of advocacy groups, and it's been tough to hear, but I need to let you all know that there are thousands of people working hard, every day, dedicated, to coming up with a cure for this disease.

Enchi Liu: Thank you, Conrad.

Don Berry: I want to comment on the safety issue. Obviously, it's a concern. It was a concern in ISPY 2, which I indicated. We're giving experimental therapies to patients who are potentially curable. The FDA is certainly worried about it. We worry about it. The standard in cancer is that you introduce experimental therapies in

the metastatic setting, not in the so-called curable setting. And we were doing the opposite.

As I indicated, we had some Phase I data. We acquired some Phase I data of the combinations that we were using, but a minimal amount. And we proceeded slowly, early on, and we have, name another trial that has a DSMV monthly. And it meets monthly because we want to follow diligently the safety. So you can in combinations, and in whatever combinations you need, some data in the clinic, but not a lot in the Phase I setting. And in the trial in question, we would proceed slowly. We could even put a governor on the accrual rate, the recruitment rate, to assess safety as we're going with an intimately involved DSMV following the patients, individual patients, seeing how they're doing, and ensuring that they're not put at undue risk.

So it's completely doable. I hear these barriers, but the barriers are not insurmountable and there is a way around every barrier.

Cynthia Bens: Thank you. Mike?

Mike Simmons: So I'm going to offer kind of a different perspective. As I've listened to the discussion this morning, there's a tremendous amount of passion in the room. And I think if we look at where we're at today and the amount of resources that we have, we're operating certainly in an environment where there are constrained resources.

If you go back to one of the slides that Dave Dilts showed, he showed a process map, and I would encourage us, as we think about this, to plot this out on a process map, to really look at this whole entire process, to be able to understand right now, where do we have good information, where do we have gaps, where are there strategic questions that still need to be answered in order for us to be able to move forward.

And as we do that, for us also to think about the various groups who are already involved, because one of the things that I think when we bring passion to the table, and one of the things that we all want to do is we all want to be part of the solution, but it can be really easy to actually end up doing work that's already been done or that is already in process. And I think if we can look at this from a process map perspective, we plot the process out, what needs to be done, where are there gaps today, what do we already know, and then we think about who's already involved; I think it

will help us make sure that we use the resources that we have most efficiently.

And I think it allows us not to do this in a serial fashion, because I think there is certainly a risk in not being able to deliver something quick enough to people who are already suffering today, but it does allow us to do something in a more sequential fashion and not miss steps that we absolutely have to be able to address.

One of the things that I brought up in work group, I believe was Work Group One, that is a huge issue, and it's an issue, whether we do combination therapy, or whether we're looking at individual agents. If we look at what's happening, we're looking to try to engage patients at a much earlier point in the disease.

Primary Care Physicians who are already in the trenches, who are seeing these patients every day, are not making a diagnosis. So we could have combination therapy trials, we could have everything in place, but yet – and again, using the cancer example that Dave showed earlier where one of the biggest issue was sites never actually enrolling patients – we could suffer from a very similar thing because that's an issue.

And I think if we can look at this from a process perspective, we're going to be able to tease those kinds of things out, and it doesn't mean that you try to solve that first and get that right before you move on, but at least we're working on those steps so that we don't look back and we don't expend a lot of energy and say, "Wow. We weren't successful. Why weren't we?" and we find that one lever that we probably should have addressed early on. Just a thought.

Cynthia Bens: Thanks, Mike. I appreciate that. And I'd just point out, again, we do not want to create yet another entity. I think that if you look around the room, I mean all of the people who are involved in all of the efforts that we've been talking about leveraging, they're basically represented here. So I think that was part of the goal was really to highlight what's already being done and how we build on those things even right down to the New York Academy of Sciences meeting where they're going to talk a little bit more broadly about implementing an ISPY trial.

But again, it's a clinical trial issue. I think that's one of the things that is the beauty of I Spy is when you can get down to having a

smaller patient population that you're studying, hopefully that will help a bit with the trial recruitment, but also with reducing costs.

And I think I brought that up as well, we need help identifying those areas where we can bring value and pooling the resources to help reduce the cost of clinical trials, because we all know you're spending a lot of money, and we certainly appreciate it, but we know that's just not a sustainable model.

Rusty Katz: I just want to point out what, which I thought I've seen over the course of the last couple of days, this sort of perception of what I would call a false dichotomy. Some people want to be bold. We've heard a lot about we should be bold. But we've also heard a lot about will we have to worry about patient safety, and we don't have all the information we need to have. I don't think being thoughtful and thinking through the problems and being bold are mutually exclusive.

So I completely agree with Don, there will be problems, but these are imminently soluble. It won't be necessarily easy, and it won't happen overnight, but these can be solved. And of course, we're worried about patient safety. I haven't said anything from the FDAs point of view about that, but of course, we're worried about patient safety. But there are ways to ensure to the extent possible that we protect patient even as we move into a bolder approach. So these things are imminently doable, and they're not mutually exclusive.

Cynthia Bens: Thank you for that comment. David? Yes?

David Dilts: Yes. I look at this historically, okay, if you haven't figured that out yet. As Thomas Alva Edison was experimenting on incandescent bulbs, he was simultaneously building a power system. It took him years to figure out how to make an incandescent bulb that lasted a long time, but once he had it; he had the first electrified city in 18 months because he built the system betting on the calm, that the science of the incandescent bulb would be there.

So when you talk about looking at an inventory and the state of the science, you also need to parallel look at the state of the infrastructure system. I mean ISPY 2 is a great thing, but you know what, there are a lot of other people that have done cooperative relationships; they've figured out intellectual property, there's this thing they call the CEO Roundtable on Cancer.

They've figured out how to have a safe harbor that pharmaceutical companies can do things they never could do before. So look at inventory on that at the same time you looking at the other side. So that's one.

Second thing, in manufacturing there's a thing called, it's a Goosey loss function. The Goosey loss function basically says you can be too fast, and you can be too slow. So if you're too fast, patients get harmed and all kinds of evil occur, and if you're too slow, nobody cares. It's too late. That's the problem that happens in clinical trials. It takes too long, and you're indifferent. So there's two sides of a loss. So you need to be safe, but you also can't study and think and study and think.

So the thing I would strongly encourage you to do, which I haven't heard so far, timelines. I mean it's all well and good, we're going to do an inventory of this, and we're going to find out about that, we're going to have another meeting. When is something going to happen? When are you going to pull the trigger?

When I teach my students I say, "Listen folks, it's wonderful you have the very best Christmas toy on December 30, nobody cares." My son is a lawyer. All trial lawyers care about is what happens before the jury goes out. After the jury goes out, they don't care about how smart you are because it's all about timing. So when is the time that you're going to say, "We've done enough, we're going to pull the trigger?" When is it time to say, "It's time to go forward, we have enough safety information, we have enough knowledge, and we know the new knowledge is going to be generated without question," when are you going to have something ready to go, and you're going to say, "Now's the time to go?"

I'll leave that to the panel to decide.

Cynthia Bens: Ian?

Ian Kremer: So I've been sitting at this meeting for two-and-a-half days being far quieter than I usually am at meetings, and we'll see if I should have stayed quiet longer. I'll let others judge that. So I think I'm up to five points, and I might lose them all.

First is a movement start with "can't" and "won't" and "not yet." And it's the job of the movement to push back against those. And the success of a movement is defined, not only by what are the

achieves at the end, but what assets it brings to bear to build itself to be able to resist those sort of natural forces of "can't" and "won't" and "not yet." And I think it relates to Dave's point that you have to know what it is that you want to achieve, and you have to know by when you want to achieve it.

And we actually sort of already have that. It may not be the right target, but 2025 is the one that the government, in this country has staked out. Others have staked out other dates and lots of folks have said 2025 is completely unrealistic, and they've said it from two directions. I've heard lots of people say, "We can't get to 2025 by 2025 because scientifically it's just too soon, and the process doesn't enable it."

And I've heard a whole lot of patients and their families saying 2025 is completely unrealistic because the person with the disease that I am, or we are caring for, will be long since dead. So maybe 2025 is right, and maybe it's wrong for a variety of reasons, but government, which is not generally in this country seen as a risk taking entity, has been willing to put it's on ____ on a date. And that's a starting point. If we happen to get there sooner, that's great for a lot of those families and individuals. And if we happen to miss it by a couple of years, and we only get to an effective disease modifying intervention or prevention by 2027, I think there are going to be a whole lot of people that are glad we got there by 2027 because we at least aimed for 2025.

So it's not bad to miss even though it's better to miss on the early side than the late side. The real problem is, as Dave said, not having a goal that is measurable and quantifiable and hopefully attainable, and you push toward it.

In terms of the advocacy side, because I know nothing about the science side, and I hope I know a little about the advocacy side, that too has to be collaborative. So probably the most important actors in effective advocacy are all the folks or organizations who don't think of themselves as advocates but who can come to join those of us who think of ourselves as advocates, and give us the resources we need to be effective advocates.

Part of what they bring, and can add, are material resources. It's the scientific know-how to explain to us what it is we need to explain to members of Congress or Regulatory Agencies, or other decision makers. Part of it is just their own voice to come with us and add their voice in a very literal sense to those conversations.

So it's not always us being the middle person trying to find our way through a reasonably, not horribly inactive version of explaining this science.

But we need to translate it, but someone's got to be there to say, "You got that slightly wrong. Let me just clarify." Because the worst thing you can do in a meeting with a regulator or with a member of Congress, or with their staff, or another decision maker, is be wrong. And we do our best as advocates to be right about the facts, but at some point if we are wrong it's going to come out. And it won't be because we meant to be wrong, it's because nobody with greater expertise than us was there to save us from ourselves. Despite our best intentions to be right, we were wrong about something that mattered. So we need scientific community to be there with us literally and figuratively to keep us on point, emphasizing the most important details, and getting all the facts right.

But we also need – this is truly a collaborative process if we're going to get it done. If the ___ large advocacy community is going to call for sometimes revolutionary changes in the way things are done from a governmental perspective, we are going to need more assets than we've got, and by that I mean money.

Some of the organizations that are willing to step forward and be the lead advocates don't always have the number of staff or the dollars to create the collateral materials or what have you, so I'm not saying this all has to be financed by industry, but I'm saying be a partner for us. And if we, in the non-profit advocacy community come to industry and say, "We need a grant." Well, this is for the greater good and it's one of the little practical steps that has to be achieved. A lot of the advocacy groups are dealing with the bad economy too, and we don't all have the assets we would like to have to be able to convey the message that we all need to have conveyed to the decision makers.

The next point is about de-risk. I think we all agree that industry needs help de-risking this process. But I do want those who are asking the advocacy community to help create the mechanisms of de-risking understand that you are asking the advocacy community to take on more risk, and you are asking the government decision makers who have to create a de-risked environment for you to take on new risk. And it's about their credibility. If they take the steps, for instance, extending IP, they have other constituencies that are going to be really angry at them and not understand why it's being

done. So it doesn't require industry to take a different position on it, but it does mean you've got to have the backs of the people you are asking to assume more risk. That's just kind of a reality check that I won't belabor, but I'm happy to discuss with folks separately.

Two last points, one is that we have to keep our eye on the end game, and the end game is not coming up with the drug intervention, with the effective intervention, it's not even getting reimbursement approved by CMS or other payors, it's getting doctors and patients and patient's families to adopt the intervention. And we all know, and those in industry probably know far better than I do, the catalogue of effective interventions that have been developed that don't have 100 percent adoption yet despite all the safety and efficacy information and history, and great case examples from their neighbors and other people that they know that can say, "This one works." They're still lots of people that don't use it.

So when we think about not leaving any patient behind, let's include those that we need to help adopt what you all will come up with for them in this process.

And then the last is when we get full adoption of an effective intervention. I want to reengage Sue about this question of whether there will be scepters or not.

Sue Peschin: Thank you Ian, for your comments and insight. Any other comments?

Cynthia Bens: I would just add, Ian, that from my perspective, everybody I know or have been exposed to that has Alzheimer's is dead, but I actually contemplated that if what it takes is quitting my job to make this happen, because I think, it really is a transformational moment, and somebody needs to devote a lot of time to it, I actually contemplated that last night, because somebody needs to devote a lot of resources to doing it. And it's probably the most spontaneous thing I've ever done in my life. My husband told me to go to bed and get some sleep. He's like, "You've been too overworked for the past six months." But no, I just think that it's going to take that much commitment on behalf of somebody to do this, and I think that I'm not the only person in this room that's committed to giving it a lot more effort than we have, quite frankly, not just with the resources to do it.

I told Diane this morning that I'm probably supposed spend about five percent of my time to the workday doing Alzheimer's Disease, and it's far more than that. Its nights, and weekends, and everything in between.

Dan Perry: Well, it behooves me to throw out some boquets. First of all, are there any other comments that anyone wants to make? We're running a little bit ahead. We have time. Anyone? Thank you very much.

First of all, I want to thank the panel and the co-chairs of the four working session, Enchi, Diane, Cynthia, Heather, thank you very much for the hard work that you did in riding hard on those working groups and bringing forward good summaries that help us gather together our thoughts at the close of these two-and-a-half days. So let's give the co-chairs a big hand.

I also want to, let me actually tee off something that Ian just said. A lot of the advocacy organizations, none of us are only in one silo, and a lot of the advocacy groups do consist of the scientists, the clinicians, industry; we work very closely with the regulators. So already, a lot of this is being interdigitated within some of those advocacy groups.

Let me begin by thanking sincerely our two cohosting organizations, Critical Path Initiative, Diane and Deb Hanna; you have dug into this; you have been real leaders, and you joined us last November, and you brought it forward beautifully today. So I really thank Critical Path Initiative.

I also thank the Alzheimer's Association, Maria Carrillo, Heather Snyder, for joining us to create a united front of advocacy, patient organizations, that are part of this.

We had five companies with big global footprints all represented, and we know they are working very diligently; they're scientists; they're regulatory specialists; they're business development people, and I heard John Allam say yesterday in response to my saying one of the things that we wanted to see come out of this was to have companies talking to one another, the beginnings of some recognition that there is common purpose in sharing information and moving ahead on combination therapies, and he said, "You've already done that. It's happened." So we do not know all the conversations that are happening, but I'm very grateful to the five companies that have had representatives here throughout our

session. And we trust that through the publication and through external communications, that word will get to other companies as well.

I want to thank the visionaries among us. And many of you are visionaries, but I believe we were particularly blessed to have Reisa Sperling, Chas Butra, David Deiltz, Don Berry, show us their vision of what can be, to take us beyond where we've been, to take us beyond failed Phase III clinical trials, to look at and see a future and describe it, and in many cases show us parallels where in other diseases and even other industries, in the automotive and computer chips, even real rocket science, people have faced similar hurdles and have found their way to working in common purpose toward goals.

So while we really do need the hard nuts and bolts work of the scientists, the business development people, the clinical trialists, we really need those visionaries. Otherwise, we are too easily discouraged, and we're too easily stuck in what we can see right in front of us because they see something further than that. And I think those and the others of you who are visionaries; Anna brought that to the discussion; we owe a great deal of debt.

The FDA. David Dilts asked me yesterday, "What's the secret sauce of this meeting? What is it that you guys are doing, what is it that's happening here that doesn't happen dozens of times a year?" And the secret sauce is you, Dr. Katz, your colleagues, Laurie Burke, Nick Kozauer, Kun Jin –

Cynthia Bens: Yaning.

Dan Perry: Yaning Wang, who have been here throughout for I think has got to be some kind of a record setter to have two-and-a-half days of this kind of presence and openness and willingness to be accessible and to help us all work through these problems. And that's what has really made this special. At the same time, we have had the National Institute on Aging. We've had Neil Buckholtz and Tony Phelps. We've had Helen Lamont from HHS. If there's one thing that I'm ready to argue anyone that says that the problem with too slow drug development in Alzheimer's and some other area, is that ____ FDA, they just go too slow, they're too bureaucratic, boy, do I have an answer for them.

The Regulatory Agencies are not the problem. The NIH is not the problem. The government is not holding us back. The

government is paying the bills for people with Alzheimer's Disease as well as paying the bills for developing the drugs like the pig and the breakfast; they are committed as are the companies, as is everyone here. And even your FDA colleagues, Bob Temple and Janet Woodcock, we know that we have willing allies, even outside of this room that are going to make sure that we don't stop here.

Change is hard. It's always hard. Doing something new is always hard. And while there's elements of this that have been done for a long time not in this space, not in this way and not at this level. And that's what we have started to do today.

And lastly, the bouquets that I want to hand out if I may be allowed, is to my own colleagues, The Alliance for Aging Research. Sue Peschin our new CEO, who came to us a year-and-a-half ago from the Alzheimer's Foundation of America, and you saw very well her willingness to stand up and not only say what is expected to be said, but what needs to be said and to somewhat open the windows, let the airs come in, identify where we are and what needs to be said.

And to Cynthia Bens, who is the most committed, most passionate, most effective, the heart, brain and muscle of the ACT-AD coalition, and I thank her husband and her dogs.

Cynthia Bens: Dan, I want Gerber Daisies.

Dan Perry: What?

Cynthia Bens: I want Gerber Dasies in my bouquet.
[Laughter]

Dan Perry: Okay. I'll just leave you with this; a huge thank you to all of you for participating with open minds and open hearts, open hands, and I am willing to promise you right now that this meeting is not going to be forgotten. This will be talked about. This will go forward in other iterations. But we've done something here that will be remembered, and it has to be that way. So thank you all.

[*End Audio*]