U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTERAGENCY AUTISM COORDINATING COMMITTEE
AND NATIONAL VACCINE ADVISORY COMMITTEE
SAFETY WORKING GROUP
JOINT MEETING

WEDNESDAY, JULY 15, 2009

The Committees met in the Polaris Suite in the Ronald Reagan Building, 1300 Pennsylvania Avenue, N.W., Washington, D.C., at 8:30 a.m., Thomas Insel, Chair, presiding.

PRESENT:

DELLA HANN, Ph.D., Designated Federal Official, IACC Executive Secretary, Office of Autism Research Coordination, National Institute of Mental Health

IACC MEMBERS PRESENT:

THOMAS R. INSEL, M.D., IACC Chair, National Institute of Mental Health

DUANE F. ALEXANDER, M.D., National Institute of Child Health and Human Development

ELLEN W. BLACKWELL, M.S.W., Centers for Medicare and Medicaid Services (Via teleconference)

JUDITH COOPER, Ph.D., R.N., National Institute on Deafness and Other Communication Disorders (For Dr. James Battey)

LEE GROSSMAN, Autism Society of America

GAIL R. HOULE, Ph.D., Department of Education

LARKE N. HUANG, Ph.D., Substance Abuse and Mental Health Services Administration (via teleconference)

IACC MEMBERS PRESENT (continued):

STORY C. LANDIS, Ph.D., National Institute of Neurological Disorders and Stroke

CINDY LAWLER, Ph.D., National Institute of Environmental Health Sciences (For Dr. Linda Birnbaum)

CHRISTINE M. McKEE, J.D.

LYN REDWOOD, R.N., M.S.N., Coalition for SafeMinds

ALISON TEPPER-SINGER, M.B.A., Autism Science Foundation

EDWIN TREVATHAN, M.D., M.P.H., Centers for Disease Control and Prevention

PETER van DYCK, M.D., M.P.H., Health Resources and Services Administration

NVAC VACCINE SAFETY WORKING GROUP MEMBERS PRESENT:

GUTHRIE BIRKHEAD, M.D., M.P.H., NVAC Chair

BRUCE GELLIN, M.D., M.P.H., NVAC Executive Secretary

TAWNY BUCK, Co-Chair, NVAC Safety Working Group

MARIE McCORMICK, M.D., Sc.D., Co-Chair, NVAC Safety Working Group

ANDREW PAVIA, M.D., Co-Chair, NVAC Safety Working Group

ROBERT BECK, J.D.

CHRIS CARLSON, Ph.D.

VICKY DEBOLD, Ph.D., R.N.

NVAC VACCINE SAFETY WORKING GROUP MEMBERS PRESENT (continued):

CORNELIA DEKKER, M.D.

MARK FEINBERG, M.D.

LANCE GORDON, Ph.D.

JAMES MASON, M.D.

GERALD MEDOFF, M.D.

TRISH PARNELL

WILLIAM RAUB, Ph.D.

DANIEL SALMON, Ph.D., National Vaccine Policy Office Staff member

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PROCEEDINGS

Time: 8:32 a.m.

Dr. Insel: Good morning. Everyone has gotten quiet right on schedule.

I am Tom Insel, and I am the Chair of the Interagency Autism Coordinating Committee. I want to welcome all of you to a joint meeting of the National Vaccine Advisory Committee, as well as the IACC.

We've got an agenda in front of us that is shown here on the screen. I don't want to take a lot of time by way of introductions, but I think it would be helpful for everyone to know who is at the table. So let me start by asking people to introduce themselves. If you will press the microphone as you do so, because we are part of a webcast, and all of this is also being recorded. So we will start to my left.

Dr. Gellin: I am Bruce Gellin, the Director of the National Vaccine Program Office, and in that capacity ex officio of the

National Vaccine Advisory Committee.

Dr. Salmon: Dan Salmon, National Vaccine Program Office.

Dr. Pavia: Andrew Pavia, University of Utah, member of NVAC and Chair of the NVAC Working Group on Vaccine Safety.

Mr. Grossman: Hi. I am Lee Grossman. I am President and CEO of the Autism Society, the father of a 21-year-old son with autism, and a public member of the IACC.

Dr. McCormick: I am Marie McCormick. I am the Co-Chair of the Working Group on Vaccine Safety for NVAC and also at the Harvard School of Public Health.

Dr. Lawler: I am Cindy Lawler, a program director at the National Institute of Environmental Health Sciences, and I am representing our Institute here today on the IACC.

Dr. Raub: I am Bill Raub. I am a member of the NVAC Work Group and a former

science advisor for the Secretary of Health and Human Services.

Ms. Redwood: I am Lyn Redwood, Coalition for Safe Minds. I have a 15-year-old son who is vaccine injured.

Dr. Dekker: Corrie Dekker, NVAC member. I am at Stanford University where I direct the Stanford LBCH Vaccine Program. I am also a PI for the CSIS site there at Stanford.

Dr. Cooper: Good morning. I am Judith Cooper of the National Institute on Deafness and Other Communication Disorders at the NIH. I am representing our Institute, and I am on the IACC.

Dr. Gordon: Good morning. I am Lance Gordon. I am a member of the NVAC Vaccine Safety Working Group and a four-year alumni of NVAC.

Dr. Houle: Hello. I am Gail Houle, and I am with the U.S. Department of Education, Office of Special Education

Programs. I am an IACC member, and I am representing the Department of Education.

Dr. Medoff: I am Gerald Medoff. I am in the Working Group, NVAC Working Group. I am at Washington University in St. Louis, and I do infectious diseases.

Dr. Parnell: Trish Parnell. I am a member of NVAC, and I am the Director of PKID, Parents with Kids with Infectious Diseases.

Dr. van Dyck: Good morning. Peter van Dyck. I a member of IACC and the Director of Maternal and Child Health Bureau in Health Resources and Services Administration.

Dr. Carlson: I am Chris Carlson. I am from the Fred Hutchinson Cancer Research Center. I am a member of the NVAC Safety Working Group, and I happen to also be the parent of a child on the autism spectrum.

Dr. Mason: I am Jim Mason, member of NVAC and the Vaccine Safety Working Group.

I am retired, formerly Assistant Secretary for Health and Director of CDC.

Dr. Alexander: Good morning. I am Duane Alexander. I am the Director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development at the NIH and a member of the Autism Coordinating Committee.

Dr. Feinberg: My name is Mark Feinberg. I lead the Medical Affairs and Policy Group for Merck Vaccines and Infectious Diseases. I am a member of NVAC and a member of the NVAC Vaccine Safety Working Group.

Dr. Trevathan: I am Ed Trevathan, Director of the National Center on Birth Defects and Developmental Disabilities at CDC, and I represent CDC on the Interagency Coordinating Committee for Autism.

Dr. Debold: My name is Vicky Debold, and I am a new member of the Vaccine Safety Working Group. I was appointed because of my role as the FDA Consumer Rep on the

VRBAC committee. I have a 12-year-old son who is vaccine injured, and I serve as the volunteer director of patient safety for the National Vaccine Information Center.

Ms. McKee: Hi. I am Christine McKee. I am the mother of a nine-year-old girl with autism, and I am a public member of the IACC.

Dr. Birkhead: I am Gus Birkhead. I am at the New York State Department of Health and the current Chair of NVAC.

Dr. Landis: Story Landis, Director of the National Institute of Neurological Disorders and Stroke, one of the Institutes that supports research into autism.

Mr. Beck: I am Rob Beck. I am the public member on the IACP, and I am a new member of the NVAC Working Group.

Ms. Singer: I am Alison Singer. I am the founder and president of the Autism Science Foundation. I have a beautiful 12-year-old daughter with autism, and I also have

an older brother diagnosed with autism.

Ms. Buck: I am Tawny Buck. I am the Co-Chair also of the Vaccine Safety Working Group. I am the Consumer Representative on the ACCD. I am the volunteer Director of Government Relations for the National Vaccine Information Center, and I am the mother of a vaccine injured child.

Dr. Hann: Good morning. I am Della Hann. I am in the National Institute of Mental Health, and serve as the -- I believe it is called the ex officio officer for this committee for the IACC.

Dr. Insel: Very good. Well, welcome to all of you, and thanks in particular to the members of NVAC who have agreed to join the IACC meeting for the first couple of hours, as we understand you've got a lot of work to do today and tomorrow. So we appreciate your putting some time aside to help us in our task.

Before I introduce Andrew Pavia

from NVAC, let me just take a moment to say a little bit about what our task has been and how we got here.

I think you probably understand that we are a committee that was charged by Congress through the Combating Autism Act of 2006, and one of the things that we were asked to do was to put together a research strategic plan.

As part of that process, we brought together expert panels, beginning in January of 2008, and over the course of the following 12 months we created what I think, and I think the -- I hope the Committee agrees, is a really compelling and interesting document.

It is built around six fundamental questions, which were questions that we heard a lot from many communities as we collected information about putting the plan together. We had two RFIs. We had the -- Besides the expert panels, we had a number of other groups

where we got a chance to hear from many different stakeholders about what mattered.

The six questions we ended up with were: When should I be concerned? How can I understand what is happening? What caused this to happen? What interventions will help? Where can I turn for services? And what can I expect? So what does the future hold?

The plan was really created with those six as the sort of organizing issues, and for each of them we tried to summarize what do we know, where is the science currently, and what can we say with some assurance?

We have a section on each one that is what do we need, both where are the opportunities, where are the gaps, and what are the things that will be most important for a plan to address? Then we have a set of objectives, both short term and long term, that we thought would become targets for funding, both public and private funding,

because the IACC represents both the public agencies as well as, as you could hear today, some of the private groups that are involved with supporting research in autism.

In this process, there were many things that emerged as sort of -- I would either call them gaps or really important themes. One was it was clear that the needs of adults with autism needed more focus, and this whole issue about what can I expect and what does the future hold was a way of trying to capture that.

We also heard that there was much more -- there was a need for much more research on interventions, and a frustration that the treatments that we have were often not focused on core symptoms.

We also heard a lot about the need for more work on the environment. There was recognition that there had been a lot of progress on the genetic side, and yet on the environmental factors that, everyone agreed,

were very important in understanding the third question of what caused this to happen, we still were at a very early phase in the process.

As we unpacked that issue, one of the places where, I think, there was the most struggle within the IACC was around the issue of vaccines, and it really cut three ways. There were some people who said, been there, done that, there is a lot of research on this; this is the one thing we don't need to do more research about. We can conclusively say, based on the epidemiology that vaccines aren't involved.

Others who felt that, you know, there has been a lot of research, but none of it is perfect, and there still is a fundamental question about the vulnerability of either specific subpopulations or some aspects of autism, such as those children who show frank regression, that needs more exploration, and that not all the questions

have been answered.

Then there was a third group that said, well, you know, we don't think that this is a likely source, but there is so much public concern about it, we need to bring more science to the table to be able to allay the concerns of the public.

Initially, we had as a committee decided that there would be a couple of objectives in the plan, that we will actually look at this. One was going to be to launch an effort to study the feasibility of doing a study of vaccinated versus unvaccinated children, and the second was to look more at the mechanisms by which vaccine reactions could contribute. Those could be cellular studies, animal studies or finding a way to identify the subpopulation that was most at risk.

As the committee continued to discuss this and really kind of got wrapped around those two objectives, toward the end,

we really felt that maybe those weren't quite ready for prime time, and maybe what we ought to do is move them from the objectives category to the category of what do we need. We need more information about these two things before we actually identify what the studies would be that we would list as objectives.

What the committee asked for was an opportunity to bring in the expertise that wasn't present at our original expert panels and wasn't present on the IACC, because we hadn't been -- we had never included -- the Secretary didn't include people who were expert on vaccine safety or vulnerability to infectious disease or a number of other areas when we started to put together this project for autism.

So the discussion from the IACC and the decision from the majority of the committee was that the best thing for us to do at that point, which would have been back in

January, was to punt. That is, to take this issue and say let's meet with an expert group like the NVAC, find out what they can tell us about issues, particularly around feasibility, and see whether we can get enough direction from them to know how to move forward with those two issues, issues of feasibility and mechanism.

So we sent those questions forward. We got some response. There were then additional questions that came from the committee, and in the course of thinking about this and discussions with Bruce and Dan, it became clear that probably the best way forward was, rather than to try to do this through an e-mail ping-pong, it might be better just to sit down together, have an opportunity for a conversation about this, and see whether we could get enough direction from NVAC that we would then be able to proceed as the IACC with a plan basically carrying on from where we had left off in January.

So that is, I hope, a quick and accurate summary of how we got here, and I would really like to turn this over now to the expertise that is here at the table to hear from Andy and others about where the NVAC process has gone and what would be the best advice for us.

Bruce, do you want to say anything by way of introduction?

Dr. Gellin: Thank you, Tom, and again I had an opportunity to meet with your group in this building in a different room earlier this year, and part of that was just to describe what NVAC was and wasn't and what the safety group was tasked to do and where it was.

It was at that point we talked about this plan right now. The only thing I will want to reinforce -- and this is my infomercial -- is that we have also in the works what is really the revision of the first draft of a national vaccine plan that came

with the statute of this office. There was a plan that was written in the mid-Nineties, and we are in the process of updating that.

There are five broad goals in the plan, and one of them is on safety. So I think that that -- There has been a number of activities around the plan.

The Institute of Medicine is working with us to review that plan, and they have had public meetings on each of the different goals, and they have had one on safety. They have had one on communications, and I know there have been several from your community who participated in those.

So there are a lot of moving pieces about this and some overlap. I think this is a good chance for us to sit down together and be specific about the questions at hand. Thank you for the opportunity.

Dr. Insel: So with that, maybe I can turn this over to Dr. Pavia, and you can tell us about recent activities and future

directions of the NVAC Safety Working Group.

Dr. Pavia: Well, that is an inauspicious start when your microphone fails on you. Good morning, and thanks for the invitation. I am Andy Pavia. As I earlier said, I started out as the solitary chair of the Vaccine Safety Working Group, and we now have three co-chairs. So we divide the responsibility equally between Tawny Buck, Marie McCormick and myself. So the early mistakes were my fault, and future successes are due to our troika.

Let's see. Do I have the slides keyed up here? Good. What I want to do is to bring you up to speed on what we have been charged with and what we are doing so far, and give you a better sense of what the Vaccine Safety Working Group has been working on and what we are able to work on.

The full committee formed the Working Group and thought about how to focus the efforts on vaccine safety into what could

be done and what was the most important things that needed to be done over the short term.

We came up with two charges to the Working Group. The first was really driven by a process that had been ongoing for several years, was the subject of an IOM report, and that was to help in the creation, review and vetting of a five-year or longer research agenda by the Immunization Safety Office at CDC. So that was our first charge.

Formally, it is to undertake and coordinate a scientific review of the draft ISO research agenda, and to advise on several specific questions: The content of the research agenda -- Are they appropriate topics? Are there gaps that need to be filled? -- to try and provide some effort at prioritization, realizing that resources were finite, and to provide, we thought, some pressure to provide additional resources where needed, and to identify scientific barriers to implementing that research agenda and

suggestions for addressing them.

So in our first task, therefore, we were focused on what CDC had proposed to do over five years and what CDC could do. You will notice that in many of the questions that Tom posed and that probably have been discussed before this committee, there are questions of basic science. That is not generally in CDC's purview. So those do not come up in the CDC agenda.

So in order to address this, we had to reach beyond the expertise and the time availability of the NVAC members, and we formed a working group with specific expertise. The names are all listed for you here, but I just want to mention the expertise.

I am an infectious disease specialist. My research area is HIV and influenza, not very closely related to vaccine safety, as you can imagine.

We had specific expertise in

neurology, genomics, in vaccine safety, immunology, epidemiology and public health, another immunologist. We had review by a well known ethicist and public health lawyer.

We have an expert in toxicology and environmental health, in maternal and child health, an immunologist vaccine developer, a member of the WHO's vaccine safety apparatus, a well known pharmacoepidemiologist, a biostatistician, and initially two public members who represented the consumer representatives from NVAC and ACCD. One also happens to be the parent of a child injured by a vaccine and the other a child at risk from a severe infectious disease.

As I will go over later, we have since added the consumer representatives of the two other relevant government advisory boards.

So in order to accomplish this fairly complex task, we divided up into four

working groups, sharing our topic expertise on that; read the agenda in detail; got more detail from CDC and others about what was within it; and started to develop draft comments and recommendations, and then underwent a process of internal review where we shared among the subgroups the initial recommendations.

We then drafted a report and began to work on prioritization criteria. Now during all of this, in parallel was a very extensive public engagement process that I am going to tell you about in a little bit more detail.

The first part of this that fed into the writing of the report was to convene a group of specific stakeholders who deal with vaccine safety issues all the time and to invite them to help us think about prioritization criteria and to think about gaps.

Then once the first draft was

done, there were several rounds of review. So this is just an outline of the public engagement activities in brief, and this is really ably orchestrated for us by the Keystone Institute.

There were three town hall style meetings in communities across the country. They were quite diverse. They don't represent a scientific sample, but they were Birmingham, Alabama; Ashland, Oregon; which has a very high proportion of vaccine hesitant families, and Indianapolis.

The writing group which I mentioned earlier was this group of additional stakeholders. We had then, once the draft was out, a broader stakeholder meeting held here in Washington, and there were two periods in which there were requests for written public comments. The first for public comments directly on the CDC-ISO report, and the second was when our first draft was available for review.

Then after the public comment period, after the conclusion of this public engagement process, we've redrafted the report and presented it to the full NVAC. This is a timeline, and just to give you a sense, again really in April of 2008 and was voted on in June of 2009 by the full NVAC and received the unanimous support of the full committee.

Now, hopefully, you have had a chance to look at the report and see some of the specifics, but I want to highlight just a few areas that overlap specifically with the things that your group is charged with, and these are those elements of the report on the ISO agenda that have to do with autism spectrum disorders.

So we noted that the public engagement process identified substantial concern related to thimerosal, particularly with respect to autism and autism spectrum disorders.

The NVAC is assured by the many

epidemiologic studies, the effects of mercury exposure done in a variety of populations which have demonstrated that thimerosal in vaccines is not associated with autism spectrum disorders in the general population, and that is a broad statement without regard to specific subgroups or additional areas for future research.

So we noted then that a small and specific subset of the general population, such as those with mitochondrial dysfunction, may be at elevated risk of reduced neurologic functioning, possibly including developing ASD subsequent to vaccination, and in the context of vaccination report, the ASD clinical subset of particular interest are those with regressive autism.

Vaccination almost certainly does not account for the recent rise in ASD diagnoses in the population as a whole. However, public concern regarding vaccines and autism, coupled with the prevalence and

severity of ASD, warrant additional study in well defined subpopulations.

So as you heard Tom lay out the three views of what could be done in response to the question of vaccines and autism, this probably spans all three of those.

The broad question of whether the changes in the epidemiology are due to vaccines, we also believe, is a settled question of science. However, there are areas where the science needs to be pushed farther to look at specific subgroups and specific biologically driven hypotheses.

Now the other area in which we spent a good deal of time was in considering how to approach the question that has generated a great deal of controversy and a great deal of discussion of how to compare outcomes in children who are unvaccinated with children who are vaccinated and those who are fully vaccinated according to the modern schedule with those who are vaccinated in a

more limited fashion.

Among ourselves with the expertise we brought to the table, there really was not full consensus. We had extensive discussion about it, but we felt that, really, the kinds of discussions that have happened so far have been heated, emotional, but have lacked some of the scientific discipline and care and rigor that was really necessary to explore the feasibility and what could be done and what should be done.

So we recommended that a study be undertaken under the auspices of an independent organization that brought together scientists of the highest academic credentials from across the spectrum to really look at the feasibility of this sort of study, and these are -- Let me read through the comments about what we thought about in terms of the feasibility study.

We recommended that an ad hoc committee be established with broad

methodologic design and ethical expertise to consider the strengths and weaknesses, ethical issues and feasibility, including timelines and the cost of various study designs, to examine outcomes in unvaccinated, vaccine delayed, and appropriately vaccinated children.

The process should be open and transparent, engaging individuals from a broad range of sectors. The committee will consider the strengths, weaknesses, ethical issues, and feasibility, including timeliness, cost, various study designs; consider broad biomedical research in this area, including laboratory studies, animal studies, and exploration into the basic science; and assess study designs comparing children vaccinated by the standard immunization schedule with unvaccinated children, as well as possibly partially vaccinated children or children vaccinated according to other immunization schedules.

The last recommendation was to assess the ability to include biomarkers of immunity and metabolic dysfunction outcomes, including but not limited to neurodevelopmental outcomes including autism, allergies, asthma, immune mediated diseases and other developmental disabilities such as epilepsy and electrodisability and learning disabilities.

You can see that one clear concern we had is that, if the fairly massive investment was going to be undertaken into looking at the feasibility and then conducting studies of this sort, that it not be focused on a single predetermined outcome, but that it really take advantage of the investment and look at all possible outcomes.

So that is what we have done so far. We have completed task one, review the CDC agenda. It is back in the hands of CDC, who is now revising their agenda in response both to changes in the last year, the recent

appointment of a new Director and our comments, probably in that order of importance, and then more will come from that. There will be a public announcement and revised agenda.

We are moving on and have moved on to charge two, which I think you will, I hope, agree with us is really both challenging and really one of great importance and kind of fun, if you will.

That is a broader charge to review the current Federal vaccine safety system and to develop a white paper describing the infrastructure needs for a Federal vaccine safety system to fully characterize the safety profile of vaccines in a timely manner, reduce adverse events whenever possible, and maintain an improved confidence in vaccine safety.

That is a somewhat bureaucratic way of saying that what we want to think about is new ways to bring 21st Century science to bear on the problem of vaccine safety, and to

take a system which has served us fairly well for the last 25 years and to bring it up to speed to really make it much more creative and much more in tune with the scientific capabilities that we have and that we are going to evolve over the next few years.

We have, as mentioned, three co-chairs. We have three new members who have introduced themselves, Vicki Debold, Robert Beck and Bill Raub, and we are beginning by trying to gather information and to think out of the box, if you will, to take experience from other areas of safety research.

Starting at 10:30 this morning, we are having our first meeting in this regard over at the Humphrey Building, and it is going to consist of five panel discussions with panelists from across a broad range of disciplines.

The panel discussions are arranged broadly around five topics. The first is the principles and policy alternatives for a

vaccine safety system. The second is to identify innovative ways of overcoming the gaps that exist in the current vaccine safety system and the science infrastructure.

The third panel will deal with an ideal system to meet the needs of the public, public health and health care professionals to have confidence and rapidly available information about vaccine safety.

The fourth is perhaps the most interesting, and that is to try and learn lessons from other safety arenas that we can apply, and the last is to enhance the adoption and the implementation of the NVAC white paper.

If you participated in advisory groups over the years or followed the path of advisory groups, many wonderful reports have been written, but far fewer have led to concrete action, either -- well, because of a number of roadblocks between the idea and the implementation, and we want to start out by

addressing those roadblocks and making sure that what we do has every chance of turning into policy and into science.

I think I will stop there and turn it back over to Tom to lead the discussion.

Dr. Insel: Great. Thanks, Andy. This is a perfect way to launch this conversation.

Let me just open it up here. I know that people from IACC have been looking forward to having a chance to talk to members of the NVAC, and what we had hoped to do was to take perhaps the next 45 minutes or so simply to lay out what you think are the major questions, and see if we can get some expert advise about how to proceed.

Dr. Huang: Tom, this is Larke Huang from SAMHSA.

Dr. Insel: Yes, we can hear you. Go ahead, Larke.

Dr. Huang: I just wanted to let you know I am on the phone.

Ms. Blackwell: And, Tom, this is also Ellen Blackwell from CMS. I am also on the phone.

Dr. Insel: Excellent. Anybody else on the phone joining us? Okay, thank you. Bill?

Dr. Raub: Tom, just as a background matter, some of the agency representatives might want to discuss this. Traditionally, the government has not had to tell the scientific community what to do. Especially, the strength of the NIH is the investigator initiated idea the morning mail.

To what extent in the ideas in the strategic plan are you indeed being peppered by the feel, as opposed to having silence with respect to initiatives from the scientific community?

Dr. Insel: One way we have tried to answer that is to do a very careful portfolio analysis. Actually, we will be going over that later this morning and, on the

one hand, starting with saying in the perfect world what are the questions we would like to have answered, and what is the science we need to have, then looking at what is actually being funded.

It is about a total of $184 million that is being spent in both government and private sources. For the first time, we have actually all of that. We have all the different players who have sent us information about what they are funding.

There is a clear mismatch. I mean, there is just no question when you start to map these that there are gaps where there is information that both the public and actually the scientific community would like to have, but as you remember from your days at NIH, scientists tend to go where the tools are best and the answers are quick, and some of these things are tough to get at.

We just thought that one of the things that a strategic plan and the IACC can

push is by identifying the gaps and saying to people this is where you need to go.

Now the advantage for us is that, having done that already, with the arrival of the American Recovery and Reinvestment Act, we actually had an opportunity to do some jumpstarts on some of those gaps. So we have committed about $60 million in the short term to be able to fund specifically research that was going to address those places in the plan that were opportunities that had not yet been fully explored. Yes?

Dr. Gellin: Can I just comment on that same question from the point of view of the NVAC Safety Working Group.

We didn't start with a blank piece of paper in developing our comments. We started with CDC's draft plan, and they constructed their plan by bringing together a broad range of scientists over a period of time to develop the ideas, the questions, where are the gaps in research around vaccine

safety, and put together a fairly comprehensive plan, draft plan, for us to then take and comment on.

So I don't think there are a lot of new ideas in our commenting back on the CDC plan and what Andy just presented. A lot of it is we tried to organize and make a little more sense of what CDC had put forward, and frame it more as a scientific agenda and try to push them.

In many areas they highlighted issues but didn't formulate research questions or hypotheses, and sort of pushed them in that direction. But I think the process from the beginning was very much driven by scientific input from the field and not a top down, government sort of approach.

Dr. Feinberg: I, obviously, agree with Gus's comments, but I guess one comment that might be helpful for those who are less familiar with the process is the NVAC specifically reviewed the CDC's Immunization

Safety Office's agenda, which is basically their conceptualization of what is appropriate for them to study, which is a small subset of the larger range of vaccine safety questions that might be explored, be they basic or larger scale studies that would be out of scope or beyond the expertise of the Immunization Safety Office itself.

So I do think it doesn't completely embrace the range of questions that one might want and need answers to.

Dr. Insel: Marie?

Dr. McCormick: If I could add to that, I hope Chris will join me. The people who reviewed some of the basic science and the biological mechanism part of that report felt that that was an area that required a great deal more effort in terms of formulating the questions.

So I think, in looking at some of the questions you have laid out here, that was an area of particular concern to the working

group that really needed much more elaboration.

Dr. Carlson: I will echo that comment. The ISO's agenda had a number of items that went beyond traditional epidemiology and got into questions of basic science, and we are not sure that the ISO is set up to do that science, and who are they supposed to hand those questions off to is a big question to us.

Dr. Gordon: I think that is part of what we are getting into this week with the Safety Working Group meeting. The ISO agenda -- The Immunization Safety Office is an office within the Centers for Disease Control, and internally within CDC really aren't set up to have those laboratory capabilities.

So we are looking more at the inter-relatedness between, say, the National Institutes of Health that has more laboratory capability, as well as the role of other agencies and assets to fully look at biologic

mechanisms and plausibility and approaches.

Dr. Insel: Dr. Birkhead.

Dr. Birkhead: I will just add that Andy didn't mention it in his presentation, but we spent quite a bit of time thinking about the National Children's Study, which is underway at NIH, as a possible vehicle to carry out some of what we were talking about in terms of the feasibility study.

I wonder if your group has looked at that as well, because in talking about designing large studies to answer questions about child health, I think that is going to be the gold standard study and, if we can't get on that train with some of the questions that we are asking, I don't think we are going to find comparable funding to do another study like that. At least, I don't see that in the cards.

So I wonder if your group has looked at that to try and help you.

Dr. Insel: Well, we have Dr. Alexander here, who may be able to respond to that question.

Dr. Alexander: Issues of vaccine safety and vaccination in relationship to developmental disorders or any other adverse events has clearly been one of the items included in the agenda for planning for the National Children's Study.

We do anticipate prospective gathering of information on immunization history of children, but the current plan has not been to do it in such great detail as to extend to examination of physician records. We did cost out a proposal to do that, and the cost was something like an additional $15 million-plus.

So that is beyond what we felt we could include in the basic study, but that is a possibility. Even with a 100,000 sample, as is projected for the National Children's Study, it still leaves you short of ability to

answer a lot of questions, particularly about subgroups, and even the question about nonimmunized or alternatively immunized children.

In 100,000 you may have 10,000 or so in that group, and that may not be large enough without some sort of a supplementing or additional methodology.

So basically, the answer is, yes, we have discussed it, yes, we have included it to a limited scale, but not to the fullest scale that it could be included for more detailed evaluation.

Dr. Birkhead: And I will just comment. I am aware that there is work with the National Vaccine Program Office staff meeting with the National Children's Study staff around this. There are other options other than looking at physician records. For example, immunization registries are available in some states to provide documentation of shot history.

So I think I am correct in saying it is an ongoing discussion.

Dr. Salmon: We have a small group that includes a representative from the Children's Study, FDA and CDC that is looking at these issues and considering what the current plan is, what the strengths and weaknesses are, and what additional approaches could be considered and might be worth giving greater consideration to.

Dr. Insel: Let me ask, to follow on this train of thought, whether looking at an enriched sample might be something that would improve the feasibility issue.

There has been at least this one project which has just been submitted for publication from a Canadian sample, small, but it is looking initially at 174 younger offspring of children with autism. In that case, in the Canadian sample only 56 -- well, I guess it was 56 percent of the sample did not receive either the full or the timely

vaccine schedule. So it was either incomplete or delayed in some way.

That is not large enough to look at the risk for autism. Obviously, if you've got a 10 percent recurrence risk, you can do the math. You can be well, well below where you want to be powered, but does that help in terms of the way that experts would think about this in terms of both the -- If you could take a sample like that and run it up tenfold where you would be closer to the power that you might need, does that help with the ethical questions? Does it help with the feasibility question?

Does it provide a way for us to think about collecting information on the relationship of vaccines to a whole series of health outcomes in a subsample of the population where there may be some of the genetic loading that would be important for vulnerability?

Dr. Pavia: Chris Carlson may want

to comment more about this, since he is the card carrying geneticist. But that is a discussion we had in the Working Group in terms of specific focus studies that could really address more specific areas, the study of siblings and of family members of index cases with ASD. Their response to a variety of exposures was one study methodology that we talked about.

That really didn't fall within the ISO agenda. So it is just mentioned in passing, but there are definitely some strengths to that approach, we thought.

Dr. Carlson: Actually, I am going to put on my epidemiologist hat rather than my geneticist hat. But one of the big challenges we have is simply the -- if it is self-selection into these categories.

If you did a generic study, I think at this point we can show pretty convincingly that there is a correlation between an incomplete vaccination schedule and

having autism, because it tends to be in children with older siblings who were affected that got 10 percent recurrence risk are much more likely to be incompletely or delayed schedule vaccinated.

It's this terrible confounding problem that we are really wrestling with the ethics of how one gets past that.

Dr. Insel: Well, that is exactly the conversation we have been having, because it is not randomized, obviously, and you are going to struggle with two things. One is the possibility that families that decide not to have the next child vaccinated are ones in which the loading may have been greater.

Second is the possibility that you've got -- you are looking at a multiplex family event when there is a second child affected, and whether that is the same as the simplex families that most of us have been focusing on.

If you put that aside and you say

let's just think about what families want to know -- You have a child, a four-year-old, with autism. You are pregnant, and you want to know what to do with the next child.

Would there be some value in providing data to families on a large scale -- so we are talking, you know, probably would need to be 2,000-plus, and it turns out we have about 2,000 children in our baby efforts already -- would it make sense to be able to look at this, not just for autism but for a whole range of health outcomes?

So asking whether the -- will the loss of herd immunity be such that these children could be the sentinels for being able to understand that? Will the other kinds of public health outcomes that are really going to be significant be detected here?

Would it make sense to have something like this just as a way of helping to advise families what is the best choice that they will need to make, or was it a sense

from the group that maybe even then you wouldn't have the power or you wouldn't have enough to be able to show whether it would really have the public health impact? Mark?

Dr. Feinberg: I just want to point out, the ethical issues are very complex, and I don't know that anyone around the table is an ethicist. Obviously, it deserves detailed investigation, but I think there is a difference between doing observational studies where people have self-selected what they want to do with respect to immunizing their children and actually recruiting people to participate in a study where you actually need to counsel people about the risks and benefits of not receiving vaccines.

Given that vaccines are known to prevent many serious, including many life threatening and life taking conditions, you know, the ethics of enabling people to not get the recommended vaccines is problematic from a

number of perspectives.

Dr. Insel: So, Mark, I think that is part of why I brought this up. If you have 56 percent of families choosing not to do this, then is there a way that -- essentially, it is an observational study. It is not randomized, but I guess what I am trying to get at from those of you who think about vaccine safety carefully: Could this be helpful or is this just going to be creating more confusion for the field, if it is done essentially as an observational study, the way the Canadian effort has been? Dr. Birkhead?

Dr. Birkhead: I think the group struggled with small studies of the type you are talking about. We didn't look specifically at that type of methodology, but a study of 2,000 is a very small study to try and show anything like that.

Just the other comment I will make: In our second charge, I think we are very interested to figure out how all the

various Federal efforts interlock and coordinate between the Federal agencies. In at least one NIH study a number of us weren't aware of this type looking at sibs, I think, was not -- we weren't really aware of on the NVAC.

So somehow the coordination of effort and reviewing what is going on and the strengths and weaknesses of existing methodologies could be part of what we should be doing in our second charge, but also part of what this independent body might do in looking at the feasibility of studies.

Dr. Carlson: And just to play further on that, one of the challenges we are dealing with is do we do the perfect study or do we use what is available? Is it worth investing resources?

This is a budgetary system. Is the value of doing an imperfect study high enough to justify it against other things one could do with that money?

I don't think that answer is settled, but it is something where doing the perfect study may be impossible. How imperfect of a study is worth our energy? That is really where the debate is.

Dr. Pavia: I think that we sometimes approach observational studies in this area differently than we do in other areas. In most infectious disease epidemiology, we use many observational studies. We are aware that they have unavoidable biases. We don't put too much weight on any single study, and we note the limitations, and we repeat with different methodologies until we have a weight of data.

In the area of vaccine safety, there is so much emotion and so much impact from a single study that is only a piece of the puzzle that sometimes I think we are afraid to do a study that contributes an important piece, because it will be misinterpreted as a stand-alone. Yet it is an

important piece that needs to be assembled.

I think, as we think broadly about the agenda, we need to consider that. A study such as a sib study is going to have built-in biases. It may give us some answers which are uninterpretable, but others which are very important.

I am not sure we should be afraid of doing it, simply because it won't tell the whole story.

Ms. Redwood: And, Tom, there was also a Congressional request several years ago to pull together an expert committee to look at the vaccine safety data link data that had been used previously for looking at links between thimerosal and autism.

I think NIEHS -- Cindy, you would know -- spearheaded that activity. They have a wonderful report, and they had recommendations about how that particular dataset that already exists with -- what? -- 200,000-300,000 children in it could be

utilized to look at this question again.

Now there would be questions and things that would need to be done to that particular administrative dataset, but even if you just took the Persantine study and took out the requirement that all the children in it needed to be vaccinated, which would then give you your zero exposure category, even though there were not a lot of children in there, when you looked at that early data they did not see outcomes in those children, and it was when those children were removed from the dataset where you were just comparing all children that were vaccinated that a lot of the statistically significant associations between ADD, ADHD, speech and language delays, neurodevelopmental delays in general went away.

So I think it would be very easy to go back into that dataset again and look at it. So that would be an existing data that is already available. You could link it with the

California data. There has already been recommendations put out by NIEHS in a government report as to how that could be done. So that is another opportunity.

Dr. Insel: Lee.

Mr. Grossman: This is Lee Grossman, for those of you in cyberspace.

I want to congratulate Bruce and Andy and the entire NVAC for your thoughtfulness and your attention to this matter. I think you are approaching it in a very methodical and scientific way.

The question I have is, because this is all proposal right now, proposal language, do any of you have a realistic time frame in which these studies will be conducted and concluded, and in the meantime what shall we be telling people?

Dr. Birkhead: I think from NVAC's point of view, we have commented back. The recommendations are going back to CDC. It is part of their five-year plan. So the

feasibility study, I think, is something we felt on the committee would be a year process, something like that. Then to actually begin new studies would take further time.

In the meantime, I think we are -- CDC in particular is trying to get the pulse of the concerns, develop answers to questions. It is not the ideal solution, since we don't have all the answers, but the practice of pediatrics and public health goes on, and we have materials to try and address these issues.

Dr. Pavia: The question, of course, deals with a lot of different types of studies. Some of the studies of children with mitochondria disorders, my understanding from CDC is that they are in the planning stage. Data are being collected. There is outreach. Bruce may want to comment more.

So some of those are much farther along than things like the National Children's Study, and then some of the reanalysis of

existing datasets, of course, can be accomplished in a reasonably timely manner.

Dr. Gellin: So, Lee, I guess I would be interested in some of the specifics behind your question, but I will point out that in these government advisory committee processes, the recommendations were voted on a month ago, and we have now come to really talk about that and think about a way forward.

In Andy's preamble he talked about the frustrations by sitting on the advisory committee and watching the implementation. So I think we are exactly at that point now of trying to see what is the path forward, which of these recommendations will be picked up, in what order, and how quickly.

So I think one of the things that we thought we would spend some more time about today is this feasibility study which was -- Again, I think that was probably the one piece that got the most discussion at the winter writing group. There was some language about

how to potentially move forward on that. But I think your question is the right one, and it couples with what Andy said earlier about here are recommendations, now what.

Dr. Insel: This is Tom Insel again. One of the things that I think the IACC is likely to struggle with is, as we see your recommendation, it looks mostly like what you are suggesting is that this question about feasibility be booted to another committee, to the IOM or to some group that would be convened.

I think what we will want to know is: Is that really the next step or is this something where we could go ahead and say, look, it's time to call the question? Let's actually see whether anybody could do such a study, have an RFP or something like that, that would allow us to find out whether the numbers are there and the people are available to be able to at least look within the younger sibs.

As I said, we already have a fairly large network that is going on. Is that -- Is the sense of the group that we are really not ready to do that, that it really would be essential to have another panel or another group dig into the feasibility and to run the statistical modeling and all of that before we do it? Story?

Dr. Landis: So in listening to that discussion, it seemed to me that you all took a very broad approach to vaccine injury, including asthma, immune disorders, a whole variety of things, and that to design -- we are back to the ideal versus the doable -- that embarking, as Tom has suggested, on a pilot looking at sibs might be a useful strategy just tracking neurological effects, while a bigger, broader, potentially better study could be planned.

There is something attractive about moving ahead with what may not be the perfect study but is certainly doable and

might provide good data, even though there is selection of parents who will have kids vaccinated versus parents who won't.

Dr. Insel: I guess it comes back to what the study would be for. So it is the perfect versus the doable, in a sense.

If the goal here is to be able to provide information for families who have the question now that we can't currently answer, I'm just worried that spending another year or two in panels discussing feasibility may not be the right way forward. But let me turn this to Jim Mason.

Dr. Mason: I can readily understand the desire to get some information quick. If I were a parent with a child with ASD, I would want to have that answer, but I think there has to be a warning here that sometimes we encounter unintended consequences.

I could readily see a bias if you are comparing the siblings of a person with

ASD who hasn't been vaccinated or had delayed vaccinated with vaccinated people, and then following them forward. If there were genetic or other factors involved in ASD, you might come out with results erroneous but reassuring.

That is why I think you really need to convene an expert committee as rapidly as possible that includes epidemiologists and geneticists and people that really can crunch the numbers in terms of how many you are going to need to get a specific result, because if you avoid that and try to do a quick and dirty, simple study, you can come out with erroneous results that can mislead people.

I would rather give no advice than to give the wrong advice, and I think, without having a specific endpoint and a study population that you are assured will give you valid results, I think it is a mistake to go forward.

CHAIRMAN INSEL: Mark?

Dr. Feinberg: And I think all of us agree that addressing parental concerns is a really important thing to do, and I think everybody would like to provide the answers to those questions as soon as possible.

One of the challenges, though, is that parents don't have one question. They have multiple questions, and the questions change over time. Yet studies need specific hypotheses in order to be designed and powered and conducted.

I think some questions may be within the realm of scientific resolution, and others will be well beyond it. So I think talking about this as a nebulous sort of study like doing some study is not going to get either the scientific answers people want or the answers to questions that parents might have, I do think that a rigorous analysis of what is possible and what is not feasible is important.

Dr. Carlson: So one of the -- The

question you seem to be asking is: Is it possible to get started? I think there are two answers there. The first is it is absolutely possible for an investigator initiated study to be funded. That is, we don't need a panel for someone to propose to do such a study. You simply have to find the funding agency that is willing to say this is a valid study design.

That is, if you could find the right institute to go into, an institute that cares about -- and this translation across boundaries becomes a challenge. Is it vaccines? Is it autism? Is it both?

Just looking at siblings -- that seems like something that is economically feasible within something that is not mandated, that it could be done within a RO1 scale research.

If that could be done, you don't need to wait for a committee to do that. You simply have to be able to put it together

in such a way that it is convincing that what you could learn is of value to the community, and sell it to the appropriate institute. There is nothing to stop that.

The bigger scale is the question of sort of this top down stuff. The CDC's, the ISO's agenda is not about putting money into a pot for investigators to apply to. It is about what questions do we consider really important to answer right now that we can as an institute tackle.

That is a different question, and that is going to take a lot longer. It is much harder to steer and, frankly, it is much slower and more deliberate an investment.

So there are two answers, I think.

Dr. Insel: Vicky.

Dr. Debold: I make this remark as a member of the Writing Group and a parent who has a number of different questions and frequently in a position of responding to a lot of parent questions.

The work that we did in Salt Lake City fundamentally approached this question from a different perspective than what IACC is looking at it. We were looking at broad vaccine injury questions, not just ASD.

So when we put together that recommendation on vaccinated, unvaccinated, differently vaccinated, we specifically addressed the issue of timeliness. We also addressed the issue that there was a broad array of studies that needed to be done.

We were clear about this, because we were afraid that people wouldn't want to focus on the perfect study versus the imperfect study.

In fact, there is an array of studies that need to be done, both in vitro, in vivo, animal models as well as human studies. There's options for looking at things retrospectively, prospectively. There are a number of things that could be carved out looking at specific kinds of questions.

With respect to certain types of studies, I agree with Dr. Mason that we probably do need an expert committee to look at some types of issues. There are other types of questions and studies that have bearing on this issue that don't require that type of expertise and oversight.

As Chris mentioned, all we need to do is have a willing funding agency, an agency that is willing to supervise and shepherd in and make it possible for people who want to do vaccine safety studies.

So there is fundamentally a difference in perspectives in how we are dealing with this topic, but I think that there is every reason that we could go forward with beginning to chip away at some of the issue.

Dr. Insel: Bill Raub.

Dr. Raub: If we put aside funding issues for the moment, it is not a matter of either/or, and I certainly cannot muster a

good argument against thinking through a well designed, robust study that might be for the top down, so to speak. But the RFP -- or the RFA is a wonderful, pragmatic tool, and in my experience relatively low risk in the sense if some money is set aside and the solicitation is made in the scientific community, the worst case scenario is nothing good comes in. You have an answer, at least at that time.

On the other hand, there are extraordinarily clever people out there in the world who, for a relatively small amount of money, can sometimes shed very important insights on these problems, and it is a way of moving forward without having to table in any sense the pursuit of the more robust and larger scale activity.

Dr. Birkhead: Just in response to that, I think one of the discussions on the work group was that this independent panel that would meet to look at the design could actually solicit proposals from the research

community for how people would do this and evaluate them as part of the process of looking at the feasibility.

Dr. Insel: Lee Grossman.

Mr. Grossman: Yes. The reason for my question about what are we going to say in the meantime was to solicit a response to convince me that, above and beyond the science that is being considered, which I think is given full consideration here and looks very, very good, is the fact that just the very nature of bringing up this question and thinking about how we are going to proceed, and then eventually when the studies are developed and run through, that there is going to be questions from the community, by the media, by others about why are you doing this now.

It seemed as though in the past there was a -- that the vaccine program was almost sacrosanct in that it was so well run and was beyond question, and now all these

questions are coming up.

The reason I am bringing this up is because there should be this openness and this transparency, which I'm convinced that you will be doing, but there also needs to be a campaign to assure the public and the media to get in front of this so it doesn't become a greater problem than it is.

Primarily, the reason I am bringing this up from a personal nature is because my agency will get the calls from parents and from the community and from the media asking what is going on, and there should be as part of your plan, as part of your program, a coordinated effort to roll this out in a way that you are in front of it so that all of us working in partnership can bring forward the information that is correct, right, and will calm the fears of the listening public.

Dr. Insel: Thanks. Since this is -- Go ahead. Tawny Buck.

Ms. Buck: I think that, building on what you said, it is really important to remember that the Vaccine Safety Working Group is looking at adverse events, not including just autism but across the board.

My vaccine injured daughter was a pertussis injury 14 years ago. I have two other children since then, and I am still seeking answers to these questions.

So it is not -- Although for you all, it is about autism, but for us it is about a host of adverse events, and I think that is certainly an important factor to keep in mind when you are answering those questions.

Ms. Redwood: Along those same lines, Tom, since the IACC did receive -- what? -- 50 or 60 public comments with people requesting specifically that we look at the issue of vaccines and autism, and since we do have money available and we did have that in our strategic plan, I would think that

restoring those initiatives in our strategic plan -- It seems as though there is consensus among the scientific community that these studies need to be done, that there is a gap in the information that we have about vaccine safety.

So I would think it would be the responsibility of the Interagency Autism Coordinating Committee and NIH to try to fill some of those gaps, and we do have funding; whereas, from what I understand, several of these other entities don't have funding, and they don't have the specific infrastructure that NIH has.

For example, CDC doesn't have the laboratory to be able to do these types of mechanistic studies. So I really think we should strongly consider taking on these issues as they relate directly to autism.

Dr. Insel: We will have a chance as an IACC to figure out how we want to revise the plan, as we are required to do

by law each year.

We only have about five minutes before we go into public comment, and I want to -- Since this is a unique opportunity for the IACC to hear from NVAC, are there other questions that you as a committee want to pose to NVAC or other issues that you want to get some feedback about?

Most of what we have been talking about here is this feasibility issue, but as I understand from your report, Andy, you are mostly oriented toward CDC. So the questions around mechanisms are questions you felt were much more in the NIH domain. Is that fair to say?

Dr. Pavia: I think it is fair to say that throughout our deliberations we were very concerned about a number of mechanistic questions that needed to be answered, and about the coordination and scope of the basic science, but that wasn't our charge.

It was very clear that those

questions, by and large, could not be answered by the researchers of CDC, and they fell to NIH and the network investigators, yes.

Dr. Insel: Marie McCormick.

Dr. McCormick: As part of that discussion, though, I would say that as we are moving forward, one of the issues that we are going to have to face when we are doing this large safety plan is what are the potential mechanisms for addressing those issues.

If they can't be done at CDC, where can they can they be done, and by what mechanism can they be identified, because there are a lot of very interesting questions that were identified in our discussions about some of these mechanisms and what we might need to do about them, but at that juncture responding to that report, that was off the table. But it is very much on the table right now.

Dr. Insel: Yes? Sorry, I can't see your name. If you could just identify

yourself.

Dr. Gordon: Lance Gordon. Yes, I think you've really gotten to the essential difference between charge 1 and charge 2 of the NVAC Safety Working Group.

Charge 1 was limited to a review of the Center for Disease Control's Immunization Safety Office research agenda. Charge 2 was really looking at the broader enterprise.

So now we can take on the questions of what are the mechanisms for doing laboratory studies, to looking at genetic susceptibility, to going well beyond the CDC by itself; and how do they interact with the other assets?

Dr. Insel: So hearing that, again for the IACC, what we are trying to figure out is what is the piece of this that we need to do? What are the pieces of it that others will be doing? As you have heard from others, this is a multi-faceted problem.

Can we assume from your comment that this issue around laying out the agenda for mechanisms of injury related to vaccine will be done over the next year or so, and that that piece of it we could look to you for guidance on?

Dr. Pavia: I think that will be part of the white paper. We are going to have to address the issue of how broader scientific agendas are created, about how coordination between agencies are achieved, and to the important issue that you touched on and Bill Raub touched on, which is how do you balance the model of totally investigator initiated, what comes over the transom research, with trying to think through what are the questions that need to be answered and soliciting the best science to do that.

We are going to try and tackle that. I don't expect that we are going to be able to solve that in a year, when the best minds in the country have worked on that for

40 years.

Dr. Mason: I do think that we should give consideration to the funding aspects of this, though, and is there -- We get this expert committee together, and they make recommendations. Is there going to be a pot of gold so that they can be carried out? Is there money set aside that could be used to fund investigator initiated?

Let's not leave money altogether, because it is going to be important at some point, and we hope sooner than later.

Dr. Insel: Chris brought up the comment before that these are all decisions, that if you decide to fund X, you are not going to be able to fund Y. Mark Feinberg?

Dr. Feinberg: Just to address -- follow up on Lee Grossman's point, one of the risks here is by focusing attention on the issue, you raise concerns which may be beyond the level that concerns actually should exist, which is not to say that this discussion

shouldn't take place. It's just the discussions should be balanced, and included in that balance is the substantial weight of evidence suggesting that vaccines are not associated with autism.

So while there remain some questions that need to be explored in more detail, I do hope that the positive message about the safety of vaccines overall, what goes into assuring vaccine safety, and the available scientific evidence suggesting that there is not an association between vaccines and autism in the general population, as was stated in the NVAC report, needs to be emphasized as well; because otherwise I think people could come away from this discussion or others like it thinking that, by focusing on vaccine safety, what you are really talking about is vaccine risk. And I think that would be problematic from many levels.

Dr. Insel: Chris and then Vicky.

Dr. Carlson: Following onto that,

it is really important in many contexts, even if you were doing the younger siblings study. We have had a lot of discussions around, if you were to do that, is vaccine the only exposure you measure in that study? We would very much hope it is not.

That is, we would rather solve autism, not only look at autism and vaccines. So to the extent one can broaden the number of exposures one looks at in these studies, you can make them much more valuable than focusing on one single endpoint.

Dr. Insel: I mentioned this. It is a really important point, Chris, because we are already doing so much of this, and actually to exclude medical records about vaccines, it is almost a conspicuous absence here. So if you have 19 or 20 things you are looking at, to add that one is maybe not the huge effort. Vicky Debold?

Dr. Debold: A question and a point, the point being that in terms of the

communication about vaccine safety and autism, the question is going to come up about what do you mean by they have been demonstrated safe in the general population? What does general population mean when you are talking about my child or the child that I am carrying?

So that is a big deal, and how that is answered and dealt with, with the public, is very, very important.

The question is: Isn't there an existing, open RFA or RFP at NIAID on vaccine safety that people could -- investigators could submit proposals to, to begin doing some of these studies, or no? Am I wrong about that?

Dr. Insel: My sense is that there is not -- RFA or RFP means set aside, which I don't believe exists currently. There is a program announcement, which means that they are open for business, but it is not committed for that particular topic. Duane?

Dr. Debold: I was just going to

say, so what does that mean? Does it mean that there needs to be money put there or -- I mean, how can you kind of get that program going? What will it take to make that operational?

Dr. Insel: Let Dr. Alexander answer that question.

Dr. Alexander: I really wasn't about to answer that question. I really wanted to comment on what Chris said just a minute ago about looking not at autism just in relationship to vaccines, but in relationship to other things, too.

That is the advantage of the National Children's Study, because you would be looking at autism in relationship to hundreds of variables, hundreds of influences on the child's development, and not just vaccines.

So there is the advantage of doing it in that kind of a context.

Dr. Insel: So to answer Vicky,

your question about how do you get it done, mechanically at NIH I can tell you what we do. If there is an area that we think needs to be addressed and we have a program announcement, and there are no applications coming in, then we create an RFA, request for applications, request for proposals, if it is a contract, to stimulate interest.

That works pretty well most of the time. If you put money into something, people usually do apply. Cornelia Dekker?

Dr. Dekker: Vicky, we applied in October, and we are resubmitting today. So there are some investigators who are trying to take advantage of that. It is sort of a first, actually, to have something for vaccine safety specifically, but the type of study that we have proposed is something that was too expensive, frankly, to do within the context of CISA, which is the other group that looks at studies.

So we are looking particularly at

biomarkers and very specific immune response markers and safety evaluations. So it is a nice mechanism. We will see how useful it is and whether any of us get any funding from it.

Dr. Insel: So we are invading our public comment time. I want to be careful about the schedule. Marie, do you want to make a final comment?

Dr. McCormick: Just one comment. When we are thinking about vaccines and adverse events, we've talked a lot about getting information on the vaccines. I think the other half of that is getting standardized information on the outcomes that we may be interested in.

In the National Children's Study there is an instrument for looking at autism in particular, but not necessarily some of the other outcomes that we would be interested in looking at.

So I think, when you are thinking about these studies, there is a balance both

on getting the immunization information and the standardized measures of the outcome and adverse events.

Dr. Insel: That is a great point, which we will back to, I think, at the very end.

So we have one request for public comment from this morning's session. We have another public comment session this afternoon for the IACC.

I wanted to invite Dr. Geraldine Dawson from Autism Speaks to join us. Gerri, thanks for coming.

Dr. Dawson: As Tom said, I am the Chief Science Officer at Autism Speaks and on the faculty at UNC Chapel Hill and Columbia University and former Director of the University of Washington Autism Center.

I just want to make a couple of comments about the discussion this morning, which I really appreciated. It has been, I think, a great discussion.

First, in terms of Autism Speaks' kind of general position on this issue, the landscape positions that Tom outlined at the beginning of the session: Our scientific review from our Scientific Advisory Committee has concluded that there really is no compelling evidence for a connection between thimerosal or MMR and autism, particularly in terms of the general increases that we see in prevalence of autism. But we do feel that the question of whether there might be genetically or immune medically vulnerable subgroups is a question that still warrants some investigation.

So that has been kind of our position on it, and that has been our funding strategy.

We currently are heading up the Advisory Panel to the National Children's Study with respect to studying autism as an outcome. So that panel is headed by Marshalyn Yeargin-Allsopp and also Craig Newschaffer and

Irva Hertz-Picciotto, and they have been systematically reviewing the National Children's Study working with the people that are working on the National Children's Study, and looking at how we can optimize that platform for studying autism as an outcome.

Currently, actually there is only a screening measure for autism and really hasn't been looked at very carefully.

One of their conclusions as a major limitation is the fact that there is no collection of medical records, and this not only limits looking at vaccine as a risk factor but, really, a wide range of other really important potential risk factors related to prenatal and postnatal period.

So we are going to be recommending that perhaps as an adjunct study, if not on a larger scale, that that component be added.

In addition, Autism Speaks funded a feasibility study last year to look at whether the Baby Sibs Research Consortium,

which is a consortium that Autism Speaks oversees along with the NIH of 19 different investigators who are following infant siblings who are at risk for autism prospectively, and so we commissioned a feasibility study to see whether that particular platform would be useful for addressing the questions of vaccines as well as other questions like mitochondrial disorder and several others.

So in that report, which we are happy to share, we have polled all of the different groups and found out how many samples they have, how many have accessed medical records and actually conducted a power analysis around the feasibility of that.

Unfortunately, we concluded at a Board of Directors meeting last spring -- concluded that it was underpowered. So we are reticent to invest more money. However, we are investing and have put supplementary funding into two Autism Center of Excellence

network studies that are looking at infant sibs.

So this is Craig Newschaffer's early study, as well as Joe Piven's study of infant sibs where he is collecting detailed neuroimaging data as well as outcomes.

So that together those two samples will be about 1700 infant sibs. So that if we combine those with the other sample, you know, now we are looking at about 3700. So we have provided supplementary funding to those studies in order to collect genetic information, because they are already looking at environmental exposure data, a wide range, and this will allow us to potentially look at gene/environment interactions.

So there is -- I think there are lots of opportunities here, but I wanted to make sure that people knew about the work that we have been doing, and we would be very happy to share that information with the group in terms of some of the decision making.

Thank you so much for your time on the topic.

Dr. Insel: Thank you. Gerri, don't go away. Alison?

Ms. Singer: Could you talk a little bit about the response from the clinicians who are involved in the Baby Siblings Consortium at the 19 sites with regard to did they have any input, being on the ground and the ones who would actually implement, with regard to the ethics of collecting prospective data or the practicality of collecting prospective data or did they address that issue?

Dr. Dawson: So, well, first of all, with respect to the National Children's Study, I failed to mention we also have a third subgroup that is looking specifically at ethical issues, not only related to collecting information about vaccines, but issues related to if you do detect an infant who is at risk, you know, what are our obligations; how do we

handle that ethically?

So within that subgroup they are looking very carefully at those questions, and I think there was a very lively discussion at the last meeting of the Baby Sibs Research Consortium about those issues, because, clearly, there are issues that have to be addressed.

They are not insurmountable, certainly, but I do think that the other group that we have convened is a group on risk communication, because we feel like this whole question about how do you both collect information about a question of interest and yet not alarm people is very, very important.

I certainly think people are capable of understanding that, and that most people probably feel reassured by the fact that we have a very aggressive program looking at vaccine safety.

So we have been thinking about how we can do a better job on risk communication,

and we feel like that is kind of part and parcel of this whole effort.

Dr. Insel: Thank you very much, Gerri. That is very helpful to know. Actually, I guess if you add up the numbers between the 2,000 that are in the current 19 sites and 1700 more that will be coming on with the early study and with the additional study, you know, it is probably getting into some very large numbers for baby sibs who are being followed anyway for some environmental exposures. So there may be an opportunity there that the IACC could revisit.

Any other comments before we close? Bruce?

Dr. Gellin: This is a long awaited opportunity. So I want to make sure that we get the most out of the time that we have together.

Again, as you have heard in our discussions and you heard in Andy's presentations, the issue that, I think, has

consumed the most of our time and the most of our discussion is this one about the feasibility study, and Gerri also mentioned a different set of feasibility studies. But you saw the language in Andy's presentation about what the NVAC Vaccine Safety Working Group came up with, and it was unanimously voted on by NVAC.

I guess I would like to take the pulse of -- it's not quite this side of the table, but the IACC, because we need to have a pretty clear path forward in the sense of whether or not this is something that the IACC feels is worth doing, it needs some other molding to try to move forward.

In the language of the recommendation, I believe we said the Institute of Medicine or some organization like that. So maybe we could have just a quick discussion about those IOM-like organizations or how we might proceed with this; because now, as I said, six weeks ago

this was voted on unanimously by the committee. It is in the lap of HHS, and as we begin to move forward, I want to engage with you about getting your advice on how best to do that.

Dr. Insel: IACC, you have been asked a question. So what do you think? Alison?

Ms. Singer: I think the discussion that we started to have earlier about whether or not it was worthwhile to go through the process of having the independent committee -- I think that is critical because of some of the issues that were raised today and some of the issues that have come up at the NVAC meetings and at the Working Group meetings.

It is not just a question of can we sufficiently power these studies, and how would we power the studies, but it is also really an ethically charged question that really warrants some further discussion with

regard to the fact that, even within the Baby Siblings, if you used the Baby Siblings model, you are looking at a group that is already at increased risk for autism, and now they could be at increased risk for infectious diseases.

So I think it does warrant taking a little bit of extra time to make sure that all of the parameters, not just is it sufficiently powered, are considered.

Dr. Insel: Duane?

Dr. Alexander: I have been a proponent for doing such a study for sometime, through the Institute of Medicine or some other group. I can't think of a better group than IOM, but there are other possibilities.

I think that the time has come to recognize some of the shortcomings of the existing programs, the vaccine adverse event reporting system and some of the others that we have in place.

We know what the shortcomings are, and we know things that need to be done to try

and correct those. I think that the mechanism of an IOM expert panel or something akin to that is what we need, and that it needs to address not just autism but that it needs to address the whole system of how we evaluate vaccine safety.

There are better ways to do it than what we have now. They are not cheaper than what we have now, but they are going to pay off in the long run, and I think in the interest of protecting children, we need to invest in this kind of an effort, and the starting point is to pick up on this recommendation from this panel, get to the Institute of Medicine or some other comparable group, and ask them to tackle this head on and give us the best advice that they can for how to fix this problem.

Dr. Insel: Ed Trevathan?

Dr. Trevathan: Thanks. First, I just want to thank all of you on the NVAC for being here today. This has been, I think, a

very productive discussion. This is exactly the type of meeting of the minds and exchange that many of us thought was essential several months ago, and we know this has been a real extra effort on your part. We really appreciate you being here.

I have to say, I personally agree with, I think, what has been said by Duane and, I think, Dr. Mason as well, that this is a critically important issue, and yet we know that there is a price to be paid if it is done incorrectly or if we go too quickly without carefully considering all the ramifications.

Yet there is a need to move as quickly as possible. So I would think convening the type of group that Andy suggested -- certainly, there are a lot of different organizations. IOM would be the one that I think many of us know the best -- and to do it as quickly as possible, I think, would be perhaps the wisest move at this point.

Dr. Insel: Does that answer the question, Bruce? You were also asking whether there is another organization or another way to do this, and I don't know whether the group has a sense of that. IOM often gets the task. They are not always the most efficient or economical, but they do get it done, and the question is whether there is another way. We may want to think about it.

Okay. We are just at ten o'clock. Lyn Redwood.

Ms. Redwood: Yes, just a quick question, Tom, to get to the issue of the sense of urgency. I think there's things that we could do now that could help fill some of the gaps that we have, I think, using animal models, doing primate studies, those types of things. You don't really need an expert panel to be convened to design them.

NIH has done them before with Burbacher. I think that, you know, if we put out an RFA and put money there and we review

the applications, we could go ahead and move forward with some of these mechanistic studies and animal models now, versus waiting for another panel and another report to come out.

Dr. Insel: And by the "we," when you say if we put out money, since IACC doesn't have its own budget for this, you are thinking NIH. Okay. Dr. Landis, last word.

Dr. Landis: So I understood that the recommendation was to have an expert panel to look at the feasibility of a large study that would look at vaccine safety, and that a second charge that you are now addressing is how to, I think you said, bring 21st Century science prospectively to looking at vaccine safety studies. But I kind of had the sense that Duane's suggestion of an IOM panel was actually putting those two things together, and that you have a charge to do the 21st Century science thing and that the panel will probably be most effective and most expeditious -- the expert panel -- if it just

focuses on the feasibility study.

Am I correct in my parsing those two things?

Dr. Pavia: Yes, and in reference to your comment, the expert panel is expected really to look at the feasibility of a large human epidemiologic study, in whatever form that might take, and would not preclude other mechanisms to get at basic science. That is a different question.

Dr. Insel: I guess, if I were going to try to summarize this very useful conversation, it sounds to me like NVAC has a very important and broad agenda of which autism is a very tiny piece, and yet something that has, fortunately, caught your attention, and we have been able to get some good thoughts about what you would recommend.

IACC also has a very broad agenda of which vaccines are at best a small piece, and there seems to be a place now where there is some overlap.

If we are going to go ahead and as an organization, as Lyn was just suggesting, if we begin to think about how we can put some things in more urgently, at the same time that we think about convening a panel to help on the feasibility question, I am hoping that we can turn to NVAC again for some of the expertise, and maybe not for the committee but for individuals and for suggestions about who could help us with some of the science.

Similarly, as you go forward into Phase 2 that you talked about, Andy, if there is any way we can inform what you are doing from the perspective of all these other health outcomes, we would love to know that autism will still be in your discussions, and that this isn't the last time you will hear the word and that we could expect that some of what you will be developing and thinking about will also inform what we do down the road. That would be extremely helpful.

Dr. Pavia: Thanks. We will

definitely take you up on that offer. I have a little list I have started on scientists we need to hear from.

Dr. Insel: Okay. Well, with that as an agreement, let me just second Ed Trevathan's comments of how much all of us appreciate your willingness to spend the first hour and a half or your very busy agenda here.

I know you have to run back over to the Humphrey Building to do the rest of your work, and it means a lot to us that you were willing to sit down with us initially and help us address this incredibly important problem.

So thanks to all of you, and best of luck with the rest of your deliberations. You've got such an important job.

We will take a break, and reconvene in about 10 minutes.

Time: 10:20 a.m.

Dr. Insel: We wanted to devote some time at today's meeting -- and we will, hopefully, do this on a regular basis at the IACC -- to getting updates on major projects that are already out in the field.

One of them is the NIH Autism Centers of Excellence. The other one we thought you should hear about today is NDAR, the National Database for Autism Research.

So it is a pleasure to introduce Dr. Alice Kau from the NICHD, who will take us through an overview on the Autism Centers of Excellence, and then follow that with presentations by Dr. Ed Cook who leads one such center, and from Dr. Mike Huerta, who is going to talk to us about NDAR. Alice, take it away.

Dr. Kau: Thank you. So I am here to give you a brief overview of the Autism Centers of Excellence or ACE program.

First of all, ACE is a trans-NIH

collaboration involving five funding Institutes. The first one is the Institute that I work under, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NICHD; National Institute on Deafness and Other Communication Disorders, NIDCD; National Institute of Environmental Health Sciences, NIEHS; National Institute of Mental Health, NIMH; and National Institute of Neurological Disorders and Stroke.

ACE also represents NIH's effort to consolidate two previous NIH funded large programs. The first one is CPEA, Collaborative Programs of Excellence in Autism, which was funded by NICHD and NIDCD for 10 years from 1997 to 2007, and then the second program is STAART, Studies to Advance Autism Research and Treatment, which was mandated by the Children's Health Act of 2000 and funded by the five ACE funding Institutes, and STAART was funded for five years.

There are two types of sites

within ACE. One is centers, and the other is networks. Centers are just like CPEA and STAART. They tend to be located in one institution, multi-disciplinary, and involving some projects that are interdependent, interrelated.

In addition to centers, ACE also funds the networks. These are sort of mini-networks, and so we have many networks or projects. So ACE is not a huge network, but we fund networks. They are all multi-site projects, focusing on specific topical research, and there is always reason why they use network as a mechanism rather than centers. One obvious reason is to facilitate subject participant recruitment, such as in a drug trial.

There are common requirements for all the ACE centers and networks. The first one and the most important one is data sharing using National Database for Autism Research. All the sites are required to submit data

twice a year, even when a study is ongoing.

When a study is ongoing, they only need to submit common measures, and I will give you a list of the common measures later. The Director of NDAR, National Database for Autism Research you see here, will give you more information about NDAR. Also we have built in annual meetings for ACE grantees.

Here is the list of all the common measures that ACE investigators rare required to collect unless there are reasons why they are not suitable for a particular study.

For IQ assessment, we do not specify which measure to use, because of a wide range of ages involved in different projects, but we do require them to have verbal and nonverbal components.

So here a summary of what I said so far. The ACE program was started funding in Fiscal Year 2007 and 2008. So here are where the centers and networks we have funded -- We funded six centers and five networks.

The six centers are University of Washington, and you heard from Gerri Dawson, who was the PI when the grants were funded, and now the new PI is Dr. Bryan King.

We have University of California at Los Angeles, and we also have a change of PI there. Dr. Mary Ann Sigmund was ill and had to retire, and the new PI is Dr. Susan Bookheimer.

Another center located on the West Coast is University of California at San Diego, and Eric Christian is the PI.

On the east coast, we have Yale University. The PI is Ami Klin. We have University of Pittsburgh. The PI is Nancy Minshew, and the one who is the most close to the center part of the country is University of Illinois at Chicago, and I am very happy that the PI of that site, Dr. Ed Cook, is here with us, and he will tell you more about the research that are being conducted at his site.

There are five networks. On the

West Coast we have University of California at Davis. Dr. Sally Rogers is the PI. UCLA has also a network, in addition to the center, but they have different PIs. University of North Carolina, Chapel Hill, Dr. Joe Piven is the PI; and we have Wayne State University in Detroit with Diane Chugani as the PI.

So these are the centers, and they do different kinds of projects. As I said before, centers tend to have multiple projects focusing on a specific topic and involving scientists from different disciplines. and usually projects are interrelated. The hypotheses are interrelated, and some of the participants go through more than one project.

Dr. Nancy Minshew's center focuses on information processing and learning, Dr. Susan Bookheimer at UCLA focuses on communication, the core communication deficits of autism spectrum disorders, and that site also involves a very innovative communication intervention involving training parents to

implement intervention.

At Yale site Ami Klin studies brain behavioral and molecular studies, and he is also involved in identifying biomarkers for early diagnosis. If I may add, that though the ACEs were funded before the IACC strategic plan was finalized, many of the projects actually are addressing the objectives of the IACC strategic plan, and Dr. Ed Cook will give you more information about his center, focuses on translation studies on insistence on sameness.

Brian King from University of Washington has a theme looking at protective versus risk factors for developing autism.

Dr. Courchesne's center at UC-San Diego focuses on identifying early brain development and other physical characteristics that may predispose the children to develop autism, and the subject of his project came from physician referred infants.

Here is the networks. We have

five networks. Dr. Joe Piven's studies also focus on early brain development of infant siblings with autism. So which will complement Dr. Courchesne's study, and we will be able to integrate both sides of study and draw broader conclusions.

Dr. Dan Geschwind's study, genetic studies, identify autism risk genes. Dr. Chugani's is a psychopharmacology trial for children younger than six. Oh, let me take it back. Dr. Chugani's studies focus on safety and feasibility study at this point.

Dr. Sally Rogers at UC-Davis is comparing two types of interventions. One is intensive behavioral treatment compared with standard community based intervention.

Craig Newschaffer's network was mentioned earlier by Gerri Dawson, which is the early study, early autism risk longitudinal investigation, focusing on genetics and environmental risk factors.

This is my NIH colleagues on the

ACE program team. Thank you.

Dr. Insel: Thank you, Alice. Let's see if there are any questions about the whole project before we move into the specifics of Dr. Cook's. Any issues from the committee?

Okay. Well, it is a pleasure to introduce Dr. Ed Cook, who some of you saw at IMFAR, since he was an organizer this year of that August event. Ed runs, as you heard, this project on the insistence of sameness, and though he is identified as being at University of Illinois at Chicago, in fact, this is one of those ACE centers that crosses several institutions, including Vanderbilt and University of Chicago.

Ed, thanks for joining us, and we are looking forward to hearing about this center.

Dr. Cook: Thank you very much, Tom, and to the full Committee, for the opportunity to speak.

Just as Alice was speaking, I was reminded of two things I thought I would just throw in there. First of all, she had to summarize in one sentence or two a nine-pound application.

The other thought is one thing that was not in the application was I withheld a letter from then Senator Obama which, I just realized, I have to go back and frame now.

So the theme is insistence on sameness, one of the two main features that Kanner first described in '43, and serotonin which just happens to be a circumscribed interest in our laboratory for 46 years -- actually, 48. I don't know where I came up -- Oh, 46 when the application when in. It is now 48.

Dan Freedman with pediatrician Ben Schain in '61 first found this elevated blood serotonin in autism. It is a biomarker that has been subjected to actually a couple of decades of looking for artifact, has withheld

the standards of time, but we still don't know exactly what it means.

The co-PI is John Sweeney, and there is a lot of translation in our center and in the other centers. I can't say enough about John's involvement in this center. If you ask me too much about neuroimaging and neurocognitive parts, you are going to see me quickly slip up, but that is the whole point of our translational work.

I like the neurochemical and genetic and pharmacology questions better. But the to and fro that actually started before we even knew the RFA would come out thinking about it, as we merged our two sites of the CPA, John was subcontract to Pittsburgh and Nancy Minshew, and we were to Yale and Fred Volkmar, just -- I can't say enough about even the process of planning even before the RFA came out.

So we have three cores. I will say a little bit about them. I know they are

often not the most exciting things, but they are essential.

We submitted four projects, neurochemistry and genetics, project 1; neurocognitive and neuroimaging, which has human and rodent subsections that are integrated, a pharmacogenetic component; and the last, which actually with Lee Grossman here. I remember talking about finding variants in humans and making mouse models and presenting that concept actually as the CPA was being conceptualized at the ASA meeting in '95, and talking about we would one day do that.

So with the publication of the group down in Dallas with the neuroligin mutation, it was quite exciting to see that for the first time, I believe, within about the last year.

Well, the fourth project didn't make it. As much as you can tell, it didn't, and we move on, happy to have put in four

projects so we could survive.

The administrative core: The main thing I want to emphasize here besides, it is obvious the central role, is the Midwest Autism Consortium, a series of seminars ranging from presentations by clinical programs around the Chicagoland area to clinical research, including having had people come from Michigan and up from St. Louis. We have actually referred down people who could participate in their participation in the Piven network on very young brain development, and then all the way to molecular genetic research, including mouse models.

The goal is to get people to think across disciplines, to teach students to be translational, and to also, as far as recruitment, explain to all the clinical sites why the work is important.

So from the beginning and in the application, this was meant to provide a wide net for recruiting subjects, but I can't say

enough about how much I have learned about resources in the area and translation back and forth.

Assessment core: Obviously, this includes not only the common measures. It includes drawing of blood. All our blood is sent to our major genetics repository for transformation of cell lines and sharing with other approved researchers, and also we have blood from platelet and genetic studies, and they will be shared.

So you already heard about the core measures. We have additional clinical measures for our site, the restrictive repetitive behavior scale, revised from Joe Piven's group; the childhood routines inventory; the aberrant behavior checklist, and parental broader autism phenotype questionnaires. As far as translation, a couple of our items come from Joe Piven in North Carolina, a collaboration.

This one is one that we are

particularly excited about, and Robert Gibbons at UIC is quite an expert and shares a lot of his resources and analysis of longitudinal data. He also had been doing very interesting work with John Sweeney on analysis of imaging and neurocognitive data.

They have developed event related fMRI similar to event related EEG to use at our studies, what I would say sort of classic epidemiological analysis, classic statistical analysis, and then we have Nancy Cox, long time collaborator, involved in the analysis of the genetic data, and her junior colleague.

What I am really excited about is trying to get the two worlds to talk to each other, because sort of living in both worlds and more traditional statistical analysis and genetic data analysis, there are, I think, opportunities to integrate those that I hope that our dataset and also the larger NDAR dataset will lead to development of methodology not only essential to us but to

share.

So, oh, boy, I glossed over that. The other function is data entry and sharing through NDAR. We will say more later.

So Project 1 I direct, although the interactions with Jim are in real time. Literally, he will respond to my e-mail before I respond to his and, yes, we study autism for a reason, as a social reference.

Ghanshyam Pandey is an outstanding and essential person. It turns out some of what we were doing was interrupted by the untimely death of Hermesh Aurora over a decade ago, and we have brought that back with Ghanshyam Pandey who many of you know at NIMH and his work in the serotonin area with post-mortem studies and platelet studies.

Basically, I must say, some of this is a sort of my bad. We went from our neurochemical findings, realizing that they indicated heterogeneity, and then I made a shift to genetics, sort of ignoring that we

had markers of heterogeneity to start with. You know, it would have been nice to have bridged earlier, but in some sense we now have the opportunity to go back and say we started with markers that indicate heterogeneity; why did they then go to genetics, assuming that those markers were irrelevant to looking at the genetic studies. So we are trying to, in a sense, right that wrong now.

The problem with this is that you have to go the best measure that we can get, because we can't get in vivo brain studies of serotonin transporter function actual uptake. Then the uptake is a more relevant physiological feature than binding, for interesting reasons.

So that we have to get fresh platelet studies. The study has to be completed within hours of the blood draw, and so that is an important area here.

So our hypothesis is that there would be higher serotonin -- There is only

high blood serotonin in a third. So why would we be taking that and looking at -- assuming that that is going to hit everyone in terms of the genetics.

So now we will get that measure. We think it will be higher in the high IS group compared to the low IS group, and then we want to identify the group with high blood 5HT and study mechanism, which is really our drive, is to understand mechanism to lead to eventually developing better treatment.

We expect increased serotonin transporter function based on a previous study, decreased 5HT-2A binding, and/or altered integrin beta 3 function.

Integrin beta 3 is something we found to be related to serotonin transporter function in collaboration with Randy Blakely and genome scan collaborating with Carol over who doesn't have autism or psychiatric disorders at all. It was just a good genome-wide scan of our marker.

So anyway, many studies of serotonin transporter gene, and it is heterogeneous. The most remarkable thing is the heterogeneity test is positive, but the largest sample and the meta analysis -- that includes the largest sample done by Bernie Devlin is positive, but the main thing to take away from it is heterogeneous.

You know, you say the relative risk is small. Well, that is what we are left with, if we look across large samples.

Heterogeneity may be related to phenotype, which has been an interesting thing that we have already started doing from Camille Brune in our lab's paper, and also to neurochemical subtypes, which we haven't been able to look at other than some preliminary studies.

So -- and obviously, Project 1 is responsible for genotyping common variants and identifying rare variants that will inform the other two projects, which is a key to shift to

the second project, John Sweeney and Mike Ragozzino.

This is a translational project within itself. John -- We happen to have a west campus and an east campus, a medical campus and a more basic campus separated by a mile. But John had bridged that with Mike Ragozzino, and Mike had been studying set-shifting in rodents and not realizing its relationship to autism.

So John and I have helped him understand its relevance, and basically Project 2 has a set of neurocognitive and neuroimaging studies of set-shifting in which the human paradigms correspondent to the rodent paradigms, which I think is a particular strength, again something they worked on for years but is applied to this center.

I think another interesting piece that I am appreciating more now that I, frankly, didn't appreciate enough when this

went in was that there is a component related to emotional processing -- so not just looking at, in a sense, set-shifting or flexibility, but that in relationship to emotional processing at the same time.

This may be related to what I think has emerged as a very important distinction between repetitive sensory motor behaviors versus insistence on sameness, which has a little bit more of an implication that there is distress by the individual. So I think this makes the emotional processing component important.

The rodent pharmacology studies are related to the neurochemistry of project 1 and some of our earlier findings in serotonin II receptor and the pharmacology of Project 3.

Project 3 is Alex Naijar. Tom just followed his wife to New York City. So Fadi Naijar has started this to be the PI takeover, and we are looking at variability in

response to escitalopram in terms of several candidate genes, but we will also have other genetics to look at.

This is an interesting question, because many of you may -- probably do -- know about a negative Citalopram trial of repetitive behavior. We do have previous positive studies, including clomipramine which has the same mechanism in terms of its therapeutic mechanism of action, from the intramural program at NIH, at least two other well controlled studies.

One question is the nature of the repetitive behavior. So we come back to this distinction between repetitive sensory motor behaviors versus insistence on sameness. My own view from the clinic and using these compounds for 20 years is that, if there is not distress of the individual, not those around them, and then that is not really what we would expect to treat.

So I think what is very

interesting here is how this study, in a sense, was started before this repetitive sensory motor behavior versus insistence on sameness sort of factor analyses were done, some of these being done by the geneticists looking at -- Anybody can do factor analyses of the structure of these symptoms, but it has tended to come from those sorts of people with those sorts of interests, and the IS is looking more OCD-like, but it is not as simple to just call it OCD in this situation.

With that said, I don't want to imply that things that people do over and over again that don't bother them at the moment are not a problem in autism. Even though I have never found drugs like this are helpful for those particular kinds of behaviors, they are still problematic.

So that a child that doesn't care about the streetlights but how they get from point A to point B in a particular routine, and they are not conflicted about it, is still

a particular risk. I have lots of other stories that I don't have time for.

Project 4: I need to make it clear, we are not spending money on Project 4. I think I know what -- However, Project 4 is trying to proceed. We are collaborating. We can't have our center fund it, but we certainly can talk to each other.

We are staying in active contact, and there is some funding through a K award to Veenstra-VanderWeele at Vanderbilt mentored by Blakely and a pending recovery grant. As far as I know, it is still pending. It made it, I think, through the first cut, and we were pretty tough on things.

Developing junior college: Just one example. Suma Jacob is also an NIMH K awardee studying oxytocin, vasopressin and related receptors and their genes, and we are particularly interested in the interaction of this with the serotonin system.

There's even been preliminary data

come out in the last year suggesting this is more important than we would have even thought, although Tom will probably tell me we should have thought of that a long time ago.

She is doing a very -- she is able to do a very interesting study with limited funding from the K Award, because it can be built on the center.

NDAR update: There are two big days for ACE centers and networks, January 15th and July 15th. Today is July 15th. So we are not restricted to the six-week window of data uploading, but basically for core measure collected by June 1st they have to be uploaded by June 15th.

Most of us have figured out it is better to do it as you go along, rather than to think about deadlines, but the deadlines are important. So I checked, and we are up to date with many of the core measures, including karyotype type, which I updated -- made sure was updated yesterday. That one, actually,

there was some delay in the way that we do karyotyping.

By the way, I have a clarification about waiting for NDAR to be ready for Vineland-2 survey edition. As it turns out, we have a lot of them uploaded, but our current up-to-dateness is affected, because they are doing what is necessary, is maintenance upgrades.

So DAS-II is a bigger complication, and if you were following Alice saying that it makes sense that we have different cognitive measures, you can imagine that with item level data entry, the database has a big problem to have so many tests set up, and DAS-II, although from Cathy Lord, and continuing sort of to follow her lead, we feel it is a very good test, but yet it is not the most widely used test. So it didn't necessarily was the one to first get up, but we'll catch up fairly quickly.

I have actually been impressed

with the timeline of NDAR, how quickly they have been able to get things running. You know, there is always the first few months, you sort of wonder, and now things seem to be flowing rapidly.

So a few sort of general thoughts: The main is heterogeneity, and some of it has to do with -- I spent a lot of time thinking about this in terms of common and rare variants in genetic heterogeneity.

The only thing I am sure about, absolutely without a doubt, is that having used the title to papers maybe 5-10 years ago, something like the complex genetic heterogeneity of autism, I'm sure that was the right choice.

There is still this -- I think we are moving beyond common versus rare variants to yes instead of versus. In fact, I think we are getting more evidence that common variants are affecting rare variants.

So then the interesting thing is

in the approach to heterogeneity, and with our study and with data starting to come in, you know, in a sense a common variant approach to heterogeneity we can handle with correlations, we can handle with subgrouping, high IS, low IS, different forms of genetic variants. But then the question is what about the fact that, from the beginning, our work on serotonin has pointed to basically outliers?

We start with outliers for high serotonin within the outliers for high serotonin. We have subgroups of outliers for serotonin transporter and low outliers for 5-HT2A.

So thinking about approach, what I am most interested in, which may not show up, but we have to look for, is what if our rare genetic variants end up as outliers in any of our other measures. Absolutely, we may not have power for this, but it may give us some clues, if we at least keep our wits about us. So we will be looking for that.

So that cues us for copy number variation prediction. I talked this over with Alice, and basically said G band and karyotypes basically were put in the grant to be safe, but the reality is we know from the AGP paper with the 10 K data that even 10 K data will pick up interstitial 15q11, q13 duplications that the best G band and karyotypes will miss.

So we would like to do this by chip. So we are doing 1M chips for our karyotypes, also recognizing that you may miss translocations, but you will miss much more by lower resolution G banding than you will pick up translocations.

So that is basically our paradigm, and you have that in your folders. So I don't need to go through those unless somebody really wants to go into the details.

So, you know, the question is -- and this is, obviously, an active topic; David Leadbetter is working with a very large

cytogenetics labs consortium to try to help us sort all this out. So we are considering basically about a 1 megabase threshold, well below G banding, which is 4 or 5 megabases, or a known syndrome.

So I have checked, and since manually for 16p11.2. We can debate how much that is a known syndrome, but it would be something that we would want to upload to NDAR, and not in controls. There are large things that are, obviously, polymorphism.

So this is hot off the presses. We got the data Friday, or analyzed it first Friday after getting it maybe Monday, putting it through the protocols, and not surprisingly found a 15q11-q13 interstitial duplication.

Our paper in '97 suggested 2 out of 140. This is after about 85 sent for karyotyping.

Well known region: The Prader-Willi/Angelman Syndrome region. For those that know it, we can tell from the chip that this

is between break point 2 and break point 3. Given a lot of interest in break point 1 to break point 2 and CYFIP-1, it is notable that this and many other interstitial duplications that contribute to autism do not include that region or regions distal to it.

So we pick one of these up, and it is already uploaded. Obviously, it will take time for the cell lines to be available, but they might be relatively soon. This is about a two month collected case.

Did not stand out. In other words, we are certainly -- We have a geneticist/peds neurologist doing our dysmorphology exams. Nothing stands out. The thing that does stand out is she fits our high insistence on sameness phenotype, as I would expect from the other patients I have seen with this duplication.

So without knowledge of the -- Everything has been done blind to the duplication. She was entered into the

pharmacogenetic study, the Escitalopram trial, where she had what would be considered a good response in repetitive behaviors and reduction in her irritability score. That was good, certainly not perfect.

Nothing remarkable about the 5HT lab measures. Obviously, that was the first thing to look at: Is this one of our high outliers for serotonin uptake, high or low, and for the other measures?

So progress: We got it running. We are keeping the momentum of data entry and collection, and then we are going to be starting to look at preliminary data. Obviously, we have to do that a little bit thinking about next steps.

Goal beyond the specific aims: Want to work more to connect with those involved in novel medication development, especially that may relate to 5HT drugs, and insistence on sameness.

Our center beyond this mechanism

is working. We are still waiting for, for example, one of the MgluR5 antagonists to be available to C sites, so we can start those studies. We are not restricting ourselves to one neurotransmitter.

Possible connection and novel treatment: Escitalopram is improving switching in the rat task, Mike Ragozzino. 5HT6 antagonist and the 5HT2A antagonists have a similar effect. 2C does not. We know that risperidone has some 5HT2A and 6 antagonist effects in vitro from a fairly old study by Roth, and one of the things that I would like is something that might have some of the positive effects of risperidone without the -- It really is toxicity -- of D2 antagonist effects, even if it just not having teenage boys with -- or women with breast discharge from the prolactin effects.

There is much work to be done, and I am going to end on a -- It is not really meant to be provocative, but maybe for Tom it

is, because he is used to people like me going, no, I won't share, I won't share, and I am going to say maybe we are not going far enough in thinking about this.

So this just came up two days ago. I was seeing a child for the Project III pharmacogenetic visit, and she asked about her six-year-old: Will this be useful to him if he has children some day, which is a very positive question and, frankly, he is high functioning and, you know, it is a reasonable thought.

The interesting thing is maybe 20 years ago I was real confident and I'm like, well, just call me up. And now I'm a little older, and I'm like, well, what if there is data in the repository that may be useful to them in guiding the next steps?

It's a little bit hypothetical, but the idea is with access and understanding that the important thing is sort of how you help people understand things. Is this

something at some point that the NDAR should allow someone to have access under certain situations?

So, you know, again, my concern is, you know, boy, for the next few years, as long as we are up and running, as long as I am kicking, God willing, great. But should there be some mechanism to allow people to access now that we have karyotype data there?

Obviously, the karyotype data, by the way, our consent forms say, if we find something, we will tell you. Being well trained by David Leadbetter and the CLIA Act, I have to say we have research data that suggests a clinical test may have a high yield, and we have done that and will do that, but the issue is someone may be working on -- We have signed agreements, gone through the process of allowing medical sequencing to be done. I suspect many of these samples will be some of the first complete genome sequences done.

Somebody may find something later that we can't feed back today, and that has already happened with one of our families of the 15 q11-q13 duplication where it was decided it was negative, and 10 years later using repository samples something was found. We had contact.

We could feed back to them. So I'm not sure I need to derail us on that, but it's just to say sharing is good, and I understand all the challenges, but --

So we have very specific aims. We are very excited about them, but I also think that I am excited that things will be found at the broader level and at the more even subject level that will be useful to the field.

So thank you all.

Dr. Insel: Thank you very much, Ed.

(Applause.)

Dr. Insel: I think, rather than take questions now, let's go on and hear about

NDAR, since you are likely to have raised some questions about NDAR yourself, and then maybe you and Mike can respond to the Committee thereafter.

So I will introduce Mike Huerta, who is at the NIMH working in the Division of Neuroscience and Basic Behavioral Science Research where he is involved with many of our large scale database efforts. Mike is also the head of our neuro-technology program as well. So, Dr. Huerta, take it away.

Dr. Huerta: All right. Thanks a lot, Tom.

Good morning, everybody. Thanks for this opportunity to talk about NDAR and how it adds or will add value to autism spectrum disorder research. As you probably know, NDAR is supported by NIMH, NINDS, NICHD, NIEHS and the NIH Center for Information Technology.

I am Mike Huerta, but I would also like to acknowledge key members of the NDAR

team: Dan Hall, Matt McAuliffe, and Gretchen Navidi, who bring not only considerable expertise to this project but also, as parents of children with autism, bring a sense of urgency and devotion that has benefitted this project.

So how can a database like NDAR add value to scientific research? Well, when you are in the weeds, there are lots of answers to that question, but I think the big answer to that question is by supporting new ways of doing that research.

So in the last 10 or 15 years of the 20th Century, several paradigms started emerging in scientific research that have actually transformed entire fields. These are interrelated paradigms, and here I call them high volume or high throughput data collection. Obviously, getting data from 30,000 subjects is better than getting data from 30 subjects.

The next is computation and

informatics. Of course, when you have data from 30,000 subjects, you need some serious number crunching ability, and this paradigm allows you to do that. But computation and informatics approaches are a lot more powerful than just number crunching.

They allow scientists to visualize and organize their data and to understand their data in ways they couldn't otherwise do, and this in turn results in them having insights into their data and the disorders they study that they wouldn't otherwise have.

The third interrelated paradigm is this notion of collaborating laboratories. So rather than having five or six different labs working on essentially the same subject -- question, that is -- in isolation of each other, the notion that you have heard today, both this morning and from Ed's presentation and Alice's presentation, is gee, wouldn't it be a good idea if these five or six labs worked together prospectively and jointly?

That is the notion of a collaborating laboratory or, as I summarize these shorthand -- these topics here, these paradigms -- collection, computation and the notion of a collaboratory.

So as I mentioned, these are very powerful paradigms, and they have transformed entire fields of science, including but not limited to astronomy, physics and, in biology, genetics and genomics.

NDAR supports these paradigms and, I think, can help transform ASD research across multiple data types and disciplines. As I mentioned, genetics and genomics is, of course, already in the midst of using these paradigms on a regular basis, but other data types such as imaging are also amenable to these.

So I am going to go through some features of NDAR now cast in these paradigms, starting with high volume data collection and starting with the types of data that we have n

NDAR.

As was mentioned, we have genetic and genomic data that we accept. We accept rich phenotypic data, including the common measures that were mentioned, but also a number of other clinical assessment measures. We also have the ability to accept a variety of imaging data.

In addition to these three broad classes of data, NDAR also accepts information that is associated with particular datasets. So this could be the details of the research methodology. It could be data analytic tools that would be useful in analyzing a particular dataset, the publications that are relevant to a particular dataset, and in the context of the IACC, even the relationship of particular datasets to strategic plans.

Most importantly, though, NDAR is extensible to include other data types. So if five years from now there is an entirely new data type that doesn't fall easily into one of

these three classes, NDAR can easily accommodate that.

In terms of the sources of data that are coming into NDAR, as was mentioned, the ACEs are a group of investigators that are essentially required to submit their data to NDAR. In addition, another group of investigators, those who will be funded by the NIH American Recovery and Reinvestment Act funded grants that came in response to the heterogeneity RFA, will also be required to submit their data into NDAR.

I think, in terms of the number of dollars, I think these two categories are maybe about equal. So it would be essentially doubling the amount of data coming in, if you look at it that way.

Well, of course, there are hundreds and hundreds of projects in autism research going on around the country beyond just those here, and in fact, we have encouraged the entire field through an NIH

guide notice to share their data, submit their data to NDAR and share it, whether they are funded by NIH or private foundations or whatever.

So we have encouraged that actively, and finally -- So what we would like to see is all of these pertinent data types entered into NDAR for sharing.

Importantly -- and you will hear this a couple of times in the talk -- NDAR also has the ability -- it's built this way -- to deeply link with other data resources. Right now -- and we call this confederation. What that means is, if you've got two data resources confederated, you can ask for data, and the data will come not just from the source that you are in but from the other source with which you are linked.

We are in the process right now of confederating NDAR with the NIH pediatric MRI data repository, and for those of you who don't know about that, that is a data

repository of some 500 subjects. These are magnetic resonance imaging scans, basically looking at typical development of children from ages two weeks to age 19, I believe, and these are longitudinal -- staggered longitudinal design.

You can imagine that those kinds of data would be very interesting to those studying ASD.

We also have -- Since the ARRA funds became available, we have solicited grant applications to support the confederation of other ASD data resources with NDAR, and those grant applications will be reviewed next week. The bottom line is we have this ability to deeply link across different resources.

In terms of computation, the tools and capabilities in NDAR include your standard things like data submission, access, sharing, and we have quality assurance and control procedures and policies and tools.

We also have some pretty robust ways to search and study the data that are in NDAR, allowing not only hypothesis generation but also hypothesis testing, and allowing things like corroboration and validation across studies, or not, as it turns out.

Another capability we have is something we call the data dictionary, which sounds pretty simple, but in reality it provides a platform for community based conventions and standards to be developed, and this does a couple of things.

Of course, once you have standards, that allows one to compare rigorously and to share rigorously data across labs, but by making this a community based effort, it invests the community in those standards and, therefore, it increases the likelihood that they will be adopted and used. And of course, a standard is useless if it isn't used.

Other tools and capabilities in

NDAR include the ability for researchers to use NDAR as a private collaborative space before they share their data with the research community. So if there are investigators in Chicago and Michigan and California, they can work jointly, collecting data from their subjects in their respective communities, can deposit the data into NDAR, can use the tools in NDAR and share the data in NDAR just amongst themselves until they reach their primary research objectives, at which time the expectation would be that the data would be shared. This has been a very attractive feature to the community.

As I mentioned, we also have this ability to confederate with other data resources, and e have the capability to move large files around, which is necessary for our current operation, but is also necessary for cloud computing which -- pardon the pun -- is right on the horizon. So we are forward leaning.

In terms of collaboratories, these are encouraged by NDAR in a number of ways, and I just put it this way to organize the ideas.

One is to attract investigators, because we offer data and tools that are of interest to them, and those data and tools not only are those residing in NDAR but, as I mentioned, also reside in resources that are linked with NDAR.

After attracting investigators to NDAR, we allow the investigators to help build NDAR by developing these standards that are community based, and again that invests the community in those standards and into NDAR.

Once the researchers are invested in NDAR, they can, of course, use NDAR as a common platform and, because NDAR is situated in a rich programmatic and scientific context at NIH, we also allow the NDAR users to grow because of the leverages that we can have with these kinds of activities, both in ASD and in

informatics research areas.

So how does NDAR add value to ASD research? Well, we provide new tools and resources to researchers. We allow them to share and compare their data from multiple sites, allowing for things like secondary analysis and meta-analysis, for example.

We facilitate collaboration and collaboratories, doing things like allowing subjects to be pooled, doing things like allowing cross-validation of results and instruments and so forth.

We also have the ability to link with other ASD research resources. I think this is really key, because anytime you link two resources deeply, that adds value to each of those resources, and you go from the autism research enterprise from being a community of isolated nodes to a networked community where they are all working together.

For the investigator, this provides one-stop shopping for autism data,

tools and information.

So if you cast this in another way -- How does NDAR add value? -- if you cast it in the light of the IACC's strategic plan, I think NDAR essentially is the instantiation of this core value, that values cross-disciplinary approaches, data sharing, teamwork and partnerships, and it is described well by these two cross-cutting themes, data sharing and resources.

Finally, I won't go into any detail at all, but if you simply look at the objectives of the IACC strategic plan, I think you can see pretty clearly that NDAR, either directly or indirectly, addresses at least eight of those.

With that, I will thank you for your time, and be happy to answer questions, I guess, with the rest of the panel.

Dr. Insel: Well, thanks very much to both of you. We are staying exactly on schedule. Let's open this up to questions

from the committee. Alison.

Ms. Singer: I have two questions. I will ask the short one first.

Are there any sort of supplemental funding mechanisms that can be given to some of the private funders so that their grantees can be encouraged financially to include their findings and data in NDAR?

Dr. Huerta: Well, that actually is one of the thing is that we try to do with the ARRA funds, and we did that in a couple of ways. We actually solicited whole grant applications, and several of the foundations that support large data resources expressed interested in that.

We also made it available as supplements to existing grants. So that if you have NIH funding, we had the ability to make supplements not only for the linkage but also -- this is an important point -- for those who have RO1, let's say, projects going on who were not required to submit their data

to NDAR, who got funded two or three years ago before NDAR was really accepting data but who, nevertheless, would like to submit their data to NDAR.

There is a small cost to that. It is probably $5,000-$6,000 a year, something like that, to really submit a lot of data to NDAR. We allowed those types of folks to also request supplements.

All of that is in process right now, but I think -- As a matter of fact, before the ARRA funds became available, we had something similar that we supported, and NIMH has supported grants like this, not specifically to connect up with NDAR but to connect up with other major data resources like NDAR. That program announcement, actually, would have been useful in this context as well.

So we did it even before ARRA. It just might not have been as clear.

Ms. Singer: And my other question

is really with regard to the ACE centers overall, but to Dr. Cook's site specifically, which is how you take the results of the studies that come out of the ACE centers and disseminate them and communicate them more effectively with parents.

I'm thinking specifically of the Citalopram studies that came out where there were two different studies that came out of two different ACE centers within the course of about two to three weeks.

One came from Bryan King's center where his study showed with citalopram lack of efficacy, looking specifically at repetitive behaviors generally, versus the study of Escitalopram that came out of Chicago that looked more specifically at -- you looked at insistence on sameness.

That was very challenging to communicate to parents. You know, what was the difference between repetitive behaviors generally versus insistence on sameness

specifically? What is the difference between Citalopram and escitalopram? What does it mean that the electrons spin in a different way?

You know, we have families whose kids are on Citalopram. We have families who are making the decision every day about whether or not to put their children on Citalopram or take them off Citalopram.

This was not helpful in terms of what we can tell those families. So what can the ACE centers do? Is there a mechanism within the ACE center protocol to work on dissemination and communication of the results?

Dr. Cook: So let me clarify. We didn't publish a paper on escitalopram around the same time. This is about a Citalopram study. In fact, I may have alluded to sometimes we have things planned out. We go A,B,C,D, and that is essentially how our escitalopram pharmacogenetic study was

designed as an open trial, because there were A,B,C,D positive controlled trials of this general class of medications.

Now, and as Bryan King and his esteemed collaborators -- this is an outstanding STAART study. Anything I say is to say what does that study tell us in the context of the others, not to say anything wasn't done as it should have been done. This is an outstanding study. But for example, the SAFARI website already has an outstanding discussion that I would, frankly, refer parents to, but again how do we get that sort of word out to those who may be interested, in a sense, in a way to engage.

There's actually some really good questions for Bryan King and Fred Volkmar who wrote some fairly strong statements in the paper sort of clarifying a lot of the questions that parents might have.

In other words, in no way did that study look at, if your child has an anxiety

disorder or a depression and autism, does that mean that it doesn't work; because that wasn't the study.

I think the thing that I am interested in trying to clarify about that study -- help me if I mess up here, Tom -- is that any study has limitations of what it does and doesn't say.

That study actually told me something that, as a practicing clinician, is helpful. So I am going to sort of slip into what is anecdote? It is open. It's 20 years of using this, but it has to do with what did that study tell me, and what did that study not tell me that the next study may tell. Okay?

This is the sort of discussion that we need to get out there, and again in the SAFARI website we had a good science reporter actually sort of think this through. The issue is that I have had patients come in. They are very anxious. The anxiety is

leading to aggression. It is a serious problem.

Some of the time it helps. You saw there, we had irritability go 50 percent in an individual case. it is not a study. It is not controlled, but that is what you see.

Now what will often happen is, okay, the child is no longer seriously distressed by their repetitive behaviors. They are no longer hurting others.

It's a good response, but then there is what I would say -- this child wants to do certain things in a certain way, and maybe those things are counterproductive. They are doing repetitive things, getting in the way of learning, getting in the way of function, but the child doesn't have any problem with it. Everybody else sees that the child should have a problem with it for their full development or even safety.

I would often tell the parents, well, we got a good response; I don't know

that I would push for this, I don't think this additional piece is going to be treated, in a sense -- and that would be a classical clinical discussion of risks and benefits.

We can try to go a little higher. If we push to the point of side effects, we will back off and keep what we have. But maybe we should just leave well enough alone and take a partial response. Then I'll go to the lab and try to work on something better, the rest of the field.

So in a sense, that study tells me I don't think I need to even have that discussion. I think I can now with that study say I don't, with my best inference, see the child or the adult distressed by this. I don't think this is going to work.

The key distinction in that study that I think leads us to think about what would the next one be to refine, how do we look at our previously positive controlled trials and this trial, because I don't think

it is about Citalopram versus Escitalopram. it is not about which way the molecule looks in a mirror.

For those that don't know, Escitalopram is a stereo isomer, and Citalopram is racemic. I don't think that is the issue. I think the issue is, if you look at the Citalopram excellent STAART study, the average -- First of all, there was a significant reduction in aberrant behavior checklist irritability, and that is actually our primary indication in previous studies of what we are trying to treat, not that it's the best measure, but it is what we have.

That was significantly better on drug than placebo, but it is lost in our dissemination, and that needs to be clarified.

So for the people where I think it has been most helpful, it is not just a measure of irritability, but anxiety. If it is working, this is not something to stop. But then that would also suggest what the next

study should target.

The other thing is the average ABC irritability level for that study was what the rest of us consider the baseline. So my view is that what was being treated is something different, something that is not causing distress for the individual.

All that means is one study that tells us something as big as I think we learn from it, that's great, but it doesn't tell the whole story.

Now how do we disseminate how complex science is without just making it sound like it is so complex we don't know anything? That is a challenge I think we all face. Sorry for the long answer.

Ms. Singer: I think we have to separate the two issues, though. One is the validity and the quality of the science, and the second is really the communication of the science to the parents.

I think, if you read the studies,

you can see where they are different, but the fact that they came out so close in time to each other really raised confusion. My question is really: Is there some mechanism at the ACE centers to try to dissemination information in a way that is more coordinated and more focused on value for families that are looking at these science, bit studies, for decision making purposes in consultation with their doctors?

Dr. Kau: First of all, that study did not come out of ACE program. It came out of the STAART program that I mentioned.

Ms. Singer: But the STAART is ACE now. So --

Dr. Kau: Well, right, in a way it is the same core, but programmatically it I snot.

So it is a difficult question. Now when the paper came out, NIH issued a press release and clarified that, and then everything beyond that would need further -- I

think that would go beyond the ACE program. It is a more overall research finding communication with parents.

At NIH, each Institute has a branch or a person doing it.

Dr. Lawler: I think this is just an excellent point that Alison raised, and I think as the ACE program is currently constituted, there is not sort of across the board really a way to make sure that there is some dissemination efforts, some really proactive dissemination efforts going on across the different centers, but there are some ways that we could build that in to say, if there was going to be a future iteration of ACEs or some other kinds of programs -- because it is not only the dissemination of specific clinical research findings from an individual study, but there is more sort of risk communication strategies that we talked about a little this morning in the context of in a baby sib scenario, you've got -- you

know, that is sort of another kind of communication to not only affected -- the study participants, but to the broader science and public communities as well.

So I think the ACEs don't right now have a component built in that would facilitate n a uniform manner that sort of very important activity, and it would be something that we should probably consider in future programs.

Dr. Insel: Lee?

Mr. Grossman: I have a series of NDAR questions, but I will ask one and then, if questions circle back and there are no other questions, I will continue.

The question I have is: Do you want data to be submitted by researchers who are outside of NIH funded projects and, if so, what will you tell these researchers to encourage them to provide that data?

Dr. Huerta: The answer is yes, and in March we issued an NIH Guide Notice

that explicitly said that, if you are collecting human ASD research, any or all of those classes of data, we would like to have it submitted ultimately for sharing with the rest of the research community, and we gave links and everything.

We've got all of this on the website as to how one submits data and so forth.

Dr. Landis: And what was the response?

Dr. Huerta: Well, we didn't ask for any responses.

Dr. Landis: But have you gotten data from non-NIH funded sources?

Dr. Huerta: No, no. We have not yet, no.

Dr. Landis: So that suggests it has not been an effective mechanism.

Dr. Huerta: Well, that was just like four months ago. So I am not too surprised.

Dr. Landis: But are you disappointed?

Dr. Huerta: No, I'm disappointed -- Well, we've gotten responses in terms of people expressing interest. So it's not like we didn't get a response.

The other thing is -- and I mentioned it before -- it's not free to submit data. I mean, it's not a huge undertaking, but if you've got 100 subjects and you want to submit your data, you know, it takes some time and effort to do that, and the folks that are out there right now being funded by grants that didn't have to submit their data don't have that built in the budget.

So one of the things we were trying to do with that was get people aware of NDAR and the opportunity and our interest in having them share the data with us, but also the notion is that folks will start building that into their budget, and we have had people who are out there right now contact us and

say, well, what do you think it would cost; if this is the kind of study we are going to do, what do you think it would really cost us to submit our data.

Now I'm presuming they are doing that to build their budget information for the next grant applications.

Ms. Singer: But I don't know if it makes sense to ask them to build it into their budget. I think that is why there needs to be a supplementing granting mechanism from the NIH to supplement the five or six thousand dollars that it takes for them to input that data --

Dr. Huerta: Right.

Ms. Singer: -- since the data is valuable to the NDAR, not necessarily to the individual researcher.

Dr. Huerta: No, no, I agree, and that is why we had that as one of the ARRA mechanisms.

Dr. Landis: So how much -- I

should know this. My apologies. How much have we invested in NDAR to date in building it?

Dr. Huerta: I don't know what the whole history is, but I know that our current budget is $1.96 million, I think, for this fiscal year.

Dr. Insel: When you add it together over the three years, it is closer to -- I think we've put in about $3 million per year for two years, and now it's down below two.

Dr. Landis: So 3 million for three years --

Dr. Insel: For two, I think.

Dr. Landis: So we are talking maybe $10 million.

Dr. Insel: Not that much yet. It is going to approach that by the end of 2010.

Dr. Landis: So if I am looking -- Just to follow up one more thing, if I am looking at five or six thousand dollars to get

in 100 extra subjects, you could argue that --

Dr. Insel: Yes. Mike, you didn't talk about the scope or how many --

Dr. Huerta: Okay. So, yes. So when I -- I became Director in November, I think it was, and I think then we had 29 GUIDs. GUIDs are global unique identifiers. So that each research subject would have that identifier, the person. So they would represent research subjects.

Last I checked, I think we have about 1200, and I think by the end of the year we actually will have about 10,000 subjects' data in there. Much of that 10,000 will be data that is coming from DM staff, which is the repository for the STAART and the CPEA centers. So Alice actually, who has been instrumental in helping us get that data into NDAR --

Dr. Insel: Lyn.

Ms. Redwood: I actually have three questions, but I will do like Lee did

and start with the one that is most important and, if we have time, then I will move on to the other two.

In looking at the data that you are collecting right now with genomic and neuroimaging and phenotypes, I am wondering if we could expand this to also look at treatment data to obtain historical data as well, because I think there may be some information in there that would be really useful, especially with the questions like you were asking, Alison, with regard to what is most effective, what are parents utilizing now.

I just would really love to see that database expanded to where clinicians and practitioners and families themselves could input that data into the system. Then I think you might see more people wanting to participate, because what you have right now that you are looking, in my mind as a parent, is very limited.

Dr. Huerta: Right. So that is

exactly right. So the answer is yes. The NDAR can accommodate anything and everything, but I think it might be better to have a circumscribed focus purpose for, let's say, NDAR and, instead of just expanding one database, connecting up with other existing databases.

That really is a feature of NDAR that, I think, is really important and shouldn't be lost sight of. I don't want to mention the databases which have submitted grant applications, because all of that is still under discussion, and this is a public meeting. But there are major data resources that ultimately could be, through that mechanism or some other mechanism, connectedly directly up with NDAR.

Ms. Redwood: Could you actually take the kids that are already in the ACEs centers and collect this additional data?

Dr. Insel: Right. So the citalopram data isn't -- Does that get loaded

in?

Dr. Huerta: Yes. Yes, right.

Dr. Insel: Okay. So the treatment data for the ACE centers. What about other studies?

Ms. Redwood: Like historical data, too, medical histories? But I'm wanting a Federal database to do it, too.

Dr. Huerta: Well, so that is the question, as to whether we confederate in with NDAR and agree, and the ATP and NIMH genetic repository, which is all possible, and we have had those conversations, or whether NDAR simply duplicates them all.

I would argue that it is probably better not to duplicate things, but --

Dr. Insel: I still want you to -- I'm not sure I understand the answer to Lyn's question. For the information that is being loaded up now, if someone has received treatment, is there a box within NDAR, within the database that is being collected where

that gets loaded up so that somebody could go back and, if there are 10,000 GUIDs, they could find the 50 that had received Escitalopram?

Dr. Huerta: Yes. So the data are in there, and then it gets to the question of whether -- That is why the information associated with the data is important. So presumably, when the data are submitted, you have submitted with that the methods that were used to generate the data.

Dr. Insel: What about if somebody wasn't in a study but had simply, as part of their clinical history, they had received secretin or had some -- Would that be known as well?

Dr. Huerta: That could be pulled out. If it was submitted, it can be queried.

Ms. Singer: And also I think the other issue is that you can only be submitted in NDAR if you are participating in a clinical trial versus the IAN database where it is a

parent experiential database where you can go in and say these are all the treatments that my child has tried, benefitted from, not benefitted from.

Dr. Huerta: Right. So that is why I think it is -- That is why I am so happy with the ability of NDAR to connect up with those other data resources.

Are you suggesting that we literally duplicate the IAN database?

Ms. Redwood: No. I'm suggesting that you collect additional data on the children from the ACE centers and these different centers that is more robust than genomic and neuroimaging. That is what I am suggesting.

Dr. Huerta: Okay. So we have medical history records. We have -- I mean, that is all part of the data that have to be submitted.

Ms. Redwood: Oh, I see, not part of the data.

Dr. Huerta: Well, the data aren't made available yet, because we have -- So the answer is no, because nobody is analyzing the data yet, because we are just getting it in. So could they analyze it? The answer is absolutely yes. Yes.

Dr. Insel: So maybe what would be helpful is to unpack this line that says phenotypic data and what that really means for NDAR. How comprehensive is it?

Dr. Huerta: Well, for the ACEs it includes the common measures that I think Ed had listed, or maybe it was Alice. We have 29 different clinical assessments. I don't have them memorized, but actually probably Dan and Gretchen do.

We have the charge medical history form and two other medical history forms. We have -- I didn't bring the list of all of those. But the other thing is it can be --

Dr. Insel: That just wasn't clear to us.

Dr. Huerta: I'm sorry. It could be expanded further.

Dr. Insel: Okay. All right, good. Thank you. Lee?

Mr. Grossman: Lyn took one of my questions, which was a good thing, but I still have a follow-up. So question 1(a) -- and then I will go to question 2, because I want to clear this up, because this is still a little murky for me on this first question.

So what you are saying, if a nonfunded -- excuse me -- a non-NIH funded researcher wants to submit their information to NDAR, they have to pay to submit it.

Dr. Huerta: No, no, no. No, I didn't mean to imply that. No, no. When you do anything -- right? If you hire a post-doc and they spend 10 hours in a month doing something, that is what I'm talking about. You know, for hundreds of subjects it will cost some money.

It doesn't cost anybody any money

to submit data to NDAR. I'm sorry if I gave that impression.

Mr. Grossman: I understood it. I wasn't sure if everybody understood it. So I wanted to clear that up.

Then my question number 2 -- and I guess it is probably going to be perhaps a long answer. I'm curious about your cloud technology, because it seems like right now NDAR is more of a repository of data, and I would assume with cloud technology that you will have the capabilities to have the database itself self-analyze the data to come out with perhaps some filtering and --

Dr. Huerta: No. What I was talking about there was the notion of --

Mr. Grossman: Just explain what the cloud technology is.

Dr. Huerta: Yes. The cloud computing is related to web services. It is related to grid technology. The notion is that a lot of -- Let me back up.

So rather than having everybody with a computer on his or her desk with the programs that they stick in the side, you know, on a CD-ROM, and download the program, the notion of cloud computing is that you have computing cycles available via the Internet so that the software is somewhere else, and you are doing your word processing, but the program is not loaded on your computer.

It might be out there distributed on 10,000 computers, and you are using multiplex cycling units for computation power. That requires that platforms like NDAR are organized in a certain way.

My point there wasn't that we are doing cloud computing. The point is the way we've got NDAR developing will avail itself to that future.

Dr. Insel: Alison?

Ms. Singer: I just have a general sense of this. You talked about in your presentation about the cross-cutting themes

relative to NDAR, data sharing and resources. But the number one cross-cutting theme in the strategic plan is urgency.

There just seems to me to be somewhat of a need to focus more on urgency with regard to NDAR. We have been talking about NDAR since the previous version of this committee.

I remember very clearly Jon Shestack sitting at the table talking about NDAR and the number of data points in the NDAR, and we are still now three years later into this project and, honestly, it didn't sound like a robust number of data points in the NDAR yet, and it is still not at the point where it is accessible to researchers for use.

So it seems to me that we need to do everything we possibly can to encourage the private funders or the non-NIH funded study project lead investigators to input their data and really figure out a mechanism to get that done so that we can reach a point in this NDAR

project where it is actually useful.

Dr. Huerta: Well, I think the point is well taken. You know, I can only speak to the last nine months of this, and I honestly don't -- You know, I know we've had development time, but I was not involved with NDAR at all up until November.

I think in the last nine months we have made incredible progress. I have overseen projects like this as a program officer since 1991, and I would say that we are not in second place to anything that I have seen over that time in terms of the progress we've made in that time.

You know, the previous two and a half years or whatever, I really can't speak to that, but I think we are on a good path right now. The urgency I agree with entirely, and our team certainly agrees with that.

Dr. Insel: Maybe in response, Mike, it would be good to talk about the timelines going forward and what you foresee.

You said 10,000 GUIDs by the end of the year.

Dr. Huerta: I think probably somewhere in there. I mean, 10,000 is not -- you know, it's not a guaranty. I think probably in the next 10 months we will probably have the 10,000 GUIDs in. Then it is really -- But the life blood of this thing is data -- or are data, and those --

Dr. Insel: So that Alison was saying, you know, at what point does it become useful? When do people start to jump on here and drive?

Dr. Huerta: Well, that is a good question, and that is the question whenever you have a platform like this. I know that, if you look at ADNI, which is the Alzheimer's Disease Neuroimaging Initiative, they have some 800 subjects in that database. People are starting to publish papers based on the data in the database.

You know, it has taken a few years for that to get going. The ability for

something like NDAR to have kind of the seeders, the ACEs in this case and now the ARRA funded awards is really important, because until you've got something in there, nobody is interested in looking, and nobody is interested in sending their data in there. Right?

So this is not an exact science, if you will. Right? So with the ACE data coming in, with our ability to continue to encourage folks, and with our ability to continue to make NDAR attractive because of the features and capabilities we have, that will increase the likelihood that people will want to put their data in there.

I should say that, when people submit their data to NDAR -- and I would like to change this, and we are actually looking at these things. There are policy implications. There are practicality implications, and the technical implications are really the least among all of these.

You know, ideally I would like to have the timeline from the time the data are generated to the time the data are available for sharing much reduced from what it is right now. Again, I was not involved in writing the language that dictates that. If I am involved in writing language in the future, I am going to try to shorten that.

The shorter that time is, the more attractive it is to the field, because the data are fresher, and it gets out faster. Right now we have for the common measures nine months from the time it is submitted until the time it is ready to be shared with the public. The idea is that will allow the investigator to doublecheck it and the NDAR staff to doublecheck it and all of that, but I would like to see that shortened considerably.

Ms. Singer: I think we have to turn this into an action item at this point. I think we should think about -- maybe this is for the Strategic Planning Subcommittee --

looking at how many studies there are that would be valuable to put into NDAR and give them each $5,000 to upload their data so that we get to the point in the database where it is actually useful, and see how much that would cost to do and whether or not we want to included that as an item in the next iteration of the strategic plan.

Dr. Insel: My understanding was that is what the ARRA funds were going to be used for. Is that right, Mike?

Dr. Huerta: Right.

Dr. Insel: So when will we know the results of that?

Dr. Huerta: Well, those -- Well, ultimately, we will know -- I think, probably by the end of next week, those reviews will all be finished, but it as just a one-time opportunity.

On the other hand, if there is an investigator who is interested in submitting his or her data to NDAR and that investigator

contacts Lisa Gilotty or Alice Kau or any program officers that's in charge of that grant and says, you know, I would like to submit this data, I think there would probably be some interest and enthusiasm in entertaining those kinds of supplement requests.

Dr. Landis: So I think it might be good to think about, if there are private funders, that the private funders understand what the available mechanisms would be to get funding to put their data in.

I mean, we may -- NIH funded people may know you go to Lisa Gilotty or whomever, but I don't know that your people know or Autism Speaks people know or SafeMinds people know that that is a pathway.

So having a clear plan for communicating that and also maybe a report on the grants from the ARRA money that are going to be -- I mean, I'm just picking up on your urgency, and there is another meeting coming

up, and maybe a plan to get more data in could be presented.

Dr. Huerta: That would be great.

Dr. Landis: Having had this wonderful overview that talked about --

Dr. Huerta: I'd love it, believe me.

Dr. Landis: -- talks about the resource, now we could talk about a plan to actually double that to 20,000 GUIs.

Dr. Huerta: GUIDs. GUID from NDAR. It sounds like a science fiction movie, doesn't it?

Dr. Insel: Lyn.

Ms. Redwood; I just have a really quick question, not being a researcher. Does a GUID account for one person or is it multiple data?

Dr. Huerta: An individual de-identified subject.

Dr. Insel: Does that answer the question that Ed was asking in his

presentation about somebody who six years from now wants to go back and get his data? Can that be done?

Dr. Huerta: In terms of policy, I would not answer that question. Della doesn't look like she is encouraging me to say yes, but technically, yes. Technically, absolutely yes.

Dr. Hann: It does involve some interesting policy discussions as well as legal questions with regard to who owns data, who doesn't own data, and who has access to the privacy of things.

I want to just sort of to say at this moment, too, because you were talking about the length of time it's taken to get NDAR up and going: I will say, at least from my experience, and Mike has far more than I do with the various databases, etcetera, and registries that have been created at least through NIH funds, the NDAR database is incredibly unique.

It was the first one to have negotiated successfully the policy barriers to be able to do exactly what we were just talking about. So that, if Ed has a person in his study and Joe Piven has the exact same person in their study, that data is melded together in the database. So it is one person with all of these data points hanging off of them.

Other data registries that have been created do not do that. It's Joe's data. It's Ed's data. It's Ann's data. it is all separate, and you have no idea if you've got similarities of individuals across that, which can be incredibly difficult if you are doing some analysis and you have overlap of subjects.

So this has been -- This has truly been a very landmark database in terms of the technology that has been created as well as the policy accomplishments that have happened in order to create NDAR. And you are right.

It's a wonderful platform, and now we have to figure out how to populate it.

Dr. Insel: Ed.

Dr. Trevathan: So that raises just another question in my mind. So if -- take Dr. Cook's Chicagoland area. Let's suppose a child is in an ACE funded study and is in the NDAR database through that, and yet that very same child is in another study somewhere else in Chicago that is not an NIH funded study. Those data are then submitted to NDAR.

Are you able to exclude duplicates or to merge those data, or not?

Dr. Huerta: Yes. It's the unique capability that Della -- In fact, I had it in my talk originally a discussion of GUIDs, but I thought it might get a little less -- but it's an important point.

Dr. Insel: But the flip side of that is you don't know who that child is.

Dr. Huerta: Right.

Dr. Insel: The only person who would know would be Ed.

Dr. Huerta: The PI, yes.

Dr. Trevathan: You are not counting the same child twice in the total dataset. So for example, some of the issues that Lyn has raised, that would be really critically important that you don't count the same child twice in the entire dataset.

Dr. Huerta: Right. And obversely, I guess, it allows individuals' data to accumulate over time and over studies. So as -- I think, as we all know, with the relative scarcity of autism subjects for research, very often they are enrolled in multiple studies, and this really allows n individual's data to accumulate, and then you have that data as well as if they have neuroimaging, if they have the genotypes done. And so all of that accumulates over time and can be very powerful.

Dr. Houle: I have one question.

So who has access to using the data in the database? The general public, researchers, or how do they go through and get access to the functional uses of the data?

Dr. Huerta: Right. Researchers who are at NIH recognized research institutions.

Dr. Houle: So it would be research institutions. It wouldn't be to the point of -- Well, an individual researcher could go through their research institution.

Dr. Huerta: Yes, right.

Dr. Houle: To get access, if they wanted to see what was in the database vis-a-vis their individual research project?

Dr. Huerta: Right. In addition o the data itself, of course, researchers can look into NDAR once we have it populated a lot and find out the kinds of studies that have been done as well.

Even if you don't want to get down to the level of individual subjects, it can be

very useful, I think, for researchers.

Dr. Insel: Okay. Well, I think what we are hearing here is the appreciation for this being, as you said, Mike, an opportunity for data sharing and for developing a resource.

The other cross-cutting theme that we had in the plan was the urgency piece, and I think there is a very evident concern here that we need to move this along quickly. It has been in discussion for years, and there has been a lot of money already invested.

In terms of the action item that you bring up, Alison, I am just a little concerned about our moving ahead with anything now when there is, I know, a lot going on that we can't talk about based on the ARRA funds. We hope we will be able to make that public very soon, but the reviews aren't actually going to happen until next week.

We know that there has been real interest in adding onto NDAR and interacting

with it, and there will be real money for that purpose through the stimulus package. So if these do well in review, we will have a very different conversation about this the next time we meet.

So why don't we plan to do that, is to come back to this in the next meeting, which I think is in end of September, October, at which point we will have all that information. Then we can decide whether there is something more that we need to do to push this forward, especially with respect to some of these non-governmental sources. Okay?

Anything else before we break for lunch? Okay. We will reconvene here at one o'clock.

(Whereupon, the foregoing matter went off the record at 11:53 a.m. and resumed at 1:03 p.m.)

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AFTERNOON SESSION

Time: 1:03 p.m.

Dr. Insel: Let's come back and start the afternoon session, which involves a series of updates about recent progress.

Before we do that, let's take a moment to go back over the minutes that are in your notebooks, and look for any need for edits or comments, changes in the minutes. This is for the May 4th meeting.

Ms. Redwood: Tom, in the future could we include the actual votes, like the numbers, when we have votes?

Dr. Insel: Do we have the votes? Do we actually keep track of the votes? I guess we can.

I had one comment on the minutes, as I was looking at them, and I am trying to find this now, which was -- There was a comment attributed to me about the Journal of Molecular Psychiatry saying that it was not a rigorous -- oh, "a less rigorous journal," it

says. It is in the bottom of page 5. I would hope that we could make that less pejorative.

So maybe it could say, "The study has been published in a journal with a lower citation impact score" or something like that. Do you think we can make that change? I just wouldn't want that part of it, particularly since I know the editor of that journal quite well, and I would like us to remain friends. I don't think that is the right language.

Any other comments for changes? Can I have a motion to accept the minutes with that change and with the suggestion from Lyn Redwood as well?

Dr. Cooper: So moved?

Dr. Insel: Second?

Dr. Lawler: Second.

Dr. Insel: In favor? Okay, we are moving on to talk about the updates. The first one is from the Services Subcommittee, and Lee Grossman will take us through that, with Ellen Blackwell providing back-up by

phone.

Mr. Grossman: Ellen, are you there?

Ms. Blackwell: Yes. I'm here, and thanks, Lee.

Mr. Grossman: Excellent. I know that there is a slide. Is it just -- Okay. There is just one slide.

Anyway, the first slide that -- and the only slide that is going to be up there is the announcement for the Services Subcommittee Town Hall meeting which would be held next week.

The purposes of this update is going to be fairly brief. I doubt if we use the entire 15 or 20 minutes that's allotted to us, but we are just going to walk you through some of the discussions that have occurred recently, and some of the future activities that are planned for the Services Subcommittee. Ah, there's the slide.

On the PowerPoint is the really

wonderful graphic. I truly like the design that the IACC team put together for this announcement of the Town Hall meeting.

Next week at the Autism Society's National Conference on Friday, the Services Subcommittee is sponsoring a Town Hall meeting. I must say that the IACC team has just been wonderful for my staff to work with, and we have been able to put together, together, a very good program.

The venue is going to be a theater, which is a Broadway quality theater -- so the seats will be comfortable, and the sound will be good, etcetera -- and it is separate but not too far removed from the rest of the conference, so that people can enter from its own entrance, or those people that are attendees of the conference can easily get to that area of the resort.

We have posted four people to comment, write suggestions, and to bring their questions in. The Town Hall Meeting will be

live webcast. So we expect that questions will be coming in from beyond the venue itself during the day.

The format of it is that there will be about 30 minutes where each agency and subcommittee member will have the opportunity to make a presentation on their activities, and then we pretty much open it up for those people in attendance to ask questions or make comments on the Services Subcommittee's activities, the services in the United States as well as the strategic plan for the IACC.

As we have all noted, when you have a town hall meeting, it is very hard to direct and truly not the purpose to monitor what people say. So anything is open, and I am sure we will be receiving comments and questions and opinions from the full gamut of autism.

The theater that we are in seats 350 people. There are no guaranties on how many people will be there. We are expecting

about 1800 people at the conference, and during the time of the Town Hall Meeting there really is -- We have put the Town Hall Meeting during a time where there really is no other competition.

So I don't believe 1800 people will stone the gates to speak. With town hall meetings, you are either interested or you are not, and if the queue is very long for people to eventually speak, you will lose a lot.

So there are no guaranties if we are going to get 50 people, 100 people or fill the room, but I think it is a great opportunity for the IACC to solicit and receive comment, and we are expecting it to be a very, very good, productive day as being part of our conference.

Again, I want to emphasize the fact that the IACC team has been just absolutely phenomenal with their help, and has relieved my staff, who I said we are going to do this, Autism Society staff, and everyone

are like, oh, that plus hosting 1800 of our closest friends. It's not an easy task, but the IACC staff has taken this on and has taken it on as their project.

Ellen, do you have anything else to add to that?

Ms. Blackwell: I would just add that, in addition to the great support from the NIMH autism team, we have also had really excellent participation from our IACC members. In addition to Lee and me, CMS and ASA we will have representatives there from HRSA, the CDC. Alison Singer will be there, Steven Shore, our Department of Education colleague, Gail Houle, and also, I believe, Jennifer Johnson from ACF.

So this is a very rare opportunity for folks to participate on a real time basis with the IACC, and we certainly hope that people will take advantage of it.

Mr. Grossman: Okay. And moving on, I'll talk a little bit about our last

Services Subcommittee which was held a few weeks ago.

We are making an effort at each one of these Services Subcommittees to have agencies present on activities that they are involved with relative to autism, and we had an extraordinary presentation at the last meeting by both CDC and HRSA that were talking about learn the Science Act early as well as their activities related to the Combating Autism Act.

It was, from my standpoint, wonderful to see these two agencies working so collaboratively together, and to see how robust their programs are in terms of addressing autism and autism services.

There was a -- To me, the highlight of the meeting was the conversation that the committee got involved with in terms of discussing the various teams that are working throughout the country on autism, and from us and -- This is part of the power of

convening at these type of committee meetings. You get to learn so much about what others are doing.

What we found out, that the Department of Education, the Association of University Centers for Disabilities, HRSA, Easter Seals, and then individual state legislative mandated autism teams, the Autism Society as well, have these various teams working at state levels coordinating activities.

I made a comment that there are so many teams out there, we can form our own league. So it was obvious that there is a lot of repetition. There is a lot of cross-pollenization among these teams of members, and it seemed as though we needed to pull that back and to become much more organized and, in that, put together a much more comprehensive plan in terms of how we would move forward, bringing these people of like mind together so that we can actually move forward in a common

purpose.

I believe that, as we move forward with future meetings and future activities, much of our energies will be devoted toward exactly doing that.

The next Services Subcommittee meeting, which I think has not been scheduled at this point, it being late August, we are going to have a presentation by the Department of Education at that one.

Again, that is our goal, is to have this type of information shared amongst the committee members so we have a greater understanding of what is happening at an agency level.

In October at the IACC meeting, there will be, I believe, half a day dedicated to service related issues, and we will have speakers there on behavior analysis as well as early intervention.

I can't go without saying that one of the speakers that was there who is

considered the father of positive behavior supports, Dr. Ted Carr, about three weeks ago, unfortunately, was killed by a drunk driver, and it is a terrible loss for not only the Autism Society but the entire field of behavioral -- positive behavior supports and the entire autism community.

We are now in the process of searching for a replacement for that October talk, and certainly those are some hard shoes to fill, but Ted would want the show to go on.

That's the end of my presentation. I'm sure Ellen probably has things to add.

Ms. Blackwell: No, actually, thank you, Lee for doing such a great job. The only thing I would add is that the Services Subcommittee meetings are also open to the public, and I think that they have a lot to offer folks in terms of learning more about the services arena.

So I hope that people listening to today's meeting will also think about

participating in our Services Subcommittee meetings as well.

Dr. Insel: Thank you. Comments for Lee, Ellen and the team? Questions? Okay. Why don't we move on.

The next part of the agenda is about the Subcommittee for Planning the Annual Strategic Plan Update. That sounds a little redundant, but the point is that we are going to be updating the autism research plan every year. So this means that by January we have to have whatever revisions, if any, that we want to put into this plan.

We talked to you last time about how we were thinking about doing that. You will remember that there are sort of three topics that we went over. They are shown here.

One was the importance of doing a portfolio analysis, and we wanted to take you through those results today. They are in the slide sets in your notebooks. There's lots of

interesting data included.

Also we talked to you then about should we do a town hall meeting? Should we have an RFI? Should we do workshops? The sense of the group in our last meeting was probably don't need to do town hall meetings at this point. Maybe next year at IMFAR we could do something, but we should think about an RFI that could go out in July so we would have responses back in August or September, and we should do a scientific workshop.

The plan was to try to schedule that at the end of September, and a little bit about the ideas we have had as a work group were part of what we wanted to share with you today and get some feedback.

So those are kind of the three topics that I want to cover very quickly, and other members of the Planning Subcommittee are around the table, and I'm sure they will want to add in some thoughts as well.

Let's talk about the portfolio

analysis. This was -- We did this a in sort of less intensive way about a year ago when we were trying to put together the original strategic plan, and remember, we put that in the terms of doing a gap analysis to find out what was already being done.

When we came back to it this time, I think we were a little more prepared. Remember, we asked you for who should be in this portfolio. Who should we be asking? We ended up with 19 Federal and private funders, and what we asked each of them for was what did you spend, what did you spend it on, and how does that match up with the strategic plan objectives.

We got quite a bit of data back, and I will take you through that very quickly. These were the ones that we asked, and this was a list, actually, that was informed by all of you, and these are the results.

Now it may be hard for those of you around the table to see them on the

screen. So you can look in your notebooks and follow through some of the numbers, but we thought it was important for you to actually see what is being spent.

The most obvious thing to notice here is that this is an arena with very active private funding. So Simons Foundation and Autism Speaks are both spending over $30 million a year on research, which puts them into a category that looks a little bit like an NIH institute in terms of total amounts.

The total figure, as you can see at the bottom, is around $222 million. That is a figure which -- A little more than half of that is coming from NIH, but there are lots of other sources that are in the mix.

It also might be worth looking at the differences in the average funding per project, because you can see that Simons is invested in some very large projects, and CDC tends to do even bigger ones but maybe not as many. So we can get some idea of the

character of the kinds of science that are funded.

This is the breakdown, so about two-thirds Federal, one-third private at this point in time out of the total of $222 million. And this is what it looks like when you map this onto the strategic plan.

So we've got our six questions, and perhaps no surprise, because we had heard this in discussions we've had previously, that questions 5 and 6 are pretty small pieces of the pie.

As you had said, and we knew this from the original analysis, 3 and 4 are quite large, and the concern that you raised last year was that 4 should be, if anything, larger. There was a surprise that we weren't doing more in the way of interventions.

If you break it down into really mapping these onto the objectives -- so that last pie graph sort of says how does the money array across the six questions, but it doesn't

talk about how it addresses the specific objectives. This gives you a picture of that.

You have to remember that we weren't -- none of these agencies were funding by the IACC research strategic plan, because it wasn't available until January.

So this isn't a measure of how well they match with that. This is a measure of how the funding that was already out there would map onto the things that we said were important for us to consider, knowing that some of the things that we listed were identified as gaps. So it shouldn't be too surprising that there are places where there we can do a lot better.

This is then looking at the funding that is specific to an objective, and that is -- which would be in red, the part -- I mean that is not specific to an objective in red, and the part that is specific in blue, and again makes the point that much of what is being done on those large questions is not

completely aligned with the objectives we have.

What the team has done here is they have really unpacked it, because they thought it might be useful for you to actually see for every objective what does it look like in terms of current funding. So there is no point in trying to do all of this in great detail from the screen.

I think you can look through your own notes here and see what we've got, but this gives you a pretty good sense that there are some objectives for which there doesn't seem to be any investment at this point in time and others that are actually fairly well supported already.

You can look at this one, number 38, genetic risk factors, and at least 50 percent. Well, we got almost $37 million being invested and about another 6 million in the general area of risk factors that don't seem to map onto any of the current

initiatives.

Then just to take you through all of them, number 5 is the one where we have said there is actually not very much currently invested, and you can see there are at least two items with nothing behind them, and 6 as well where there is real opportunities for new investment.

So we can come back to these for discussion. There may be more information here than you wanted, but we thought it would be useful for you to have a chance to really dig into this so you can see what the current portfolio looks like with respect to the current strategic plan and where we need to be thinking about going forward in terms of the next gap analysis. This will inform how we do any particular revisions to the plan.

The RFI was the other -- the second item that we wanted to put in front of you, and you will recall that we talked about doing this at the last meeting, and you gave

us approval to move ahead with this.

What we decided when we met in June as a subcommittee was to do an RFI that was fairly targeted. We would ask for what is missing or underrepresented, what are new opportunities that may have arisen since January or December that we need to know about, and while that sounds like a ridiculous idea, in fact there are many.

This is such an active research field. The whole idea here is that we are always updating based on the most recent science that is coming out. So the RFI will ask for that, and then any suggestions about how we prioritize the current objectives.

We thought it would be useful to do this, now that we had the portfolio analysis to also get a sense of where we are currently funding. So this will help us to kind of gauge what we might want to do going forward.

So we are about ready to go with

this, and the idea is to put it out for 30 days. It will be posted, as you can see on the slide, in many different places, including we will be able to get tweets. So we now have a Twitter account, which we will have to see what that does to both the quantity and quality of ideas that come in.

Anyway, that is about to go forward. So we wanted to update you about that. The point of doing this is to be able to have this also as data that can feed into the Scientific Workshops, which will be at the end of September or very beginning of October. I think we've got the 29th and 30th of September set aside for this.

Now we did a little bit of talking about this at the last subcommittee meeting, because we were trying to think about what kind of workshops we want to do and how to make these most useful, and who should be at the table.

We thought we would just share

with you the conclusion of that discussion and get your feedback about whether this makes sense and whether this is the right to do it.

So remember, the goal here is to do just what we are doing with the RFI. What is missing, what is important, how to prioritize, right? And what is the opportunity that we didn't know about before? And if the group says, hey, there is really nothing new on question 4 or whatever it happens to be and you've got the right priorities, then that's fine. But we need to on an annual basis get that kind of input.

We thought we would take two days. Last time, you remember, we talked a bit about should we do just one question a year or should we do all the questions, and this discussion was to cover the whole six questions but to do each of them in a structured way.

So we will do that. We will focus on the six chapters. We want to have

presentations that would be from many perspectives. So we have decided to bring together clinicians, researchers, and family or personal experts, and we are going to do this in a kind of -- at least what we thought about was we would do this in a very interesting, kind of interactive way.

So we would invite people to start working on this well ahead of the workshops, and then the workshop would be a time for a group to collaboratively present their best ideas about where the opportunities or the new priorities ought to be.

So the groups that we are thinking about -- remember, we will have six different questions that we want to address, and so for each of the six we will invite three people within one of these three categories, a provider, a researcher, family or personal experience person with ASD.

We've got some ideas of the people who might do this. We want to be able to cast

a pretty broad net and maybe bring in some people who we haven't heard from in the past, because if we are going to get new ideas, they are likely to come from new people, that would be really a helpful way to think about this.

We will have someone from the committee who will serve as an ambassador, liaison, somebody who will help to pull this thing together and provide some coherence.

So this is what it should -- could look like. On the 30th we would -- You will see the structure here where for each of the questions we will take about an hour and a half. Maybe that is not enough for some of them, but we think we can make this work, if we are really careful about it, and if we do a lot of preparation.

So there will be this presentation from those three -- the three groups; that is, the three categories of people, who will work ahead of time to create a collaborative presentation. There will be a discussion then

from a group of panelists who will be invited, who can be again a fairly broad representation, and then a public discussion thereafter.

In each case, remember, this is not to rewrite the strategic plan. This is to say, look, this is the plan; this is what is being funded. And by then we will have the ARRA funding to add into it. So you will be able to have a pretty good picture of what is out there. How are we doing, and where do we need to think about tweaking the plan that we have, so that we take advantage of the most recent breakthrough or the most recent new insight.

This will go on through each of the questions, and then we will have a summary by the IACC groups; that is, by each of you, by our ambassadors, at the end, and adjourn by the second day around middle of the afternoon.

This is what we will have as the source of information. So again, you have

seen the portfolio analysis that would be provided. The new funding initiatives, both ARRA and non-ARRA, whatever comes in, in the RFI, that will all be available to the participants.

Anything from the services town hall meeting that is germane to research we will bring into this as well, and then we will bring forward -- There were a series of about nine or ten items that we did not deal with in the previous plan, the original plan, because we said either we needed more information or we needed more time or we needed to really think through the details, and we want to make sure those are on the agenda to be discussed by the workshop participants.

Then, of course, the plan and the summary of events will be made available. So there may be other things that you would want to make sure they would have, and we would be interested in getting your ideas about that.

So this is really what I wanted to

bring forward for your feedback. Does this format look like it makes sense? Can you give us some ideas of who should participate? Can we get people who will volunteer to serve as one of the liaisons for the workshop, and in this case we would like it not to just be the planning subcommittee but the whole group? And we would also like to be charged by you to go back and do the final selection of who is going to participate and, as it says here, to use the workshop proceedings for updating the strategic plan. That would be a great thing if you could tell us if that was good to do.

So that is a real quick run-through of where the subcommittee is. As I hope you can see, there has been actually a lot of progress. I will open this up for comments about either the portfolio analysis or the RFI or these specific items that we need your feedback on for the workshop.

Dr. Lawler: Tom, I just have a quick question. Could you clarify for each of

these sessions, there's three people that are going to be leading the discussion, and then the fourth would be IACC, or is that workshop panelist discussion -- that's a panel of scientists that will be there?

Dr. Hann: Let me jump in there. As I recall the discussion from the Planning Subcommittee, it was that you would have -- Each panel, for which there are five because we combined 5 and 6 together, there will be a researcher, a family and/or person with autism, and a clinician. So that is 15 people across the five panels.

That then becomes the workshop participants. That group of 15 becomes the workshop participants. So the idea was that you would hear this collaborative presentation from the three involved with that particular panel, and then it would be opened up for discussion amongst the panelists -- that is, the 15 -- first, and then it would be opened up broader for whoever was attending the

meeting in terms of people who were attending the meeting. So that was the idea.

Dr. Lawler: It does raise issues for me about whether that is going to give you sufficient breadth to really cover all these sessions, and just as one example, in the session 3 with the risk factors. It is hard to imagine that you are going to get a real expert that has the requisite background to really make an informed presentation regarding genetic risk factors versus environmental risk factors. You usually don't have those two rolled up together in one person.

Probably the same kind of criticism might apply to these others. It seems like you are putting -- potentially putting a lot of power into the hands of very few individuals, which is the opposite of last year. We had very broad workshops of 15 or more scientists coming together, and now we -- you know, it's much smaller.

Dr. Insel: Judith.

Dr. Cooper: I support what Cindy is saying. When we were talking about this at the Autism Coordinating Committee, I was concerned about the potential for a small number of people who might bring either their expertise, lack of expertise, bias, lack of bias, and the power, as Cindy says, to have such a small number of people dealing with what is called a scientific workshop.

I just worry that maybe -- I know what we did in January was one end of the spectrum. This seems to be the other end of the spectrum, and I would hope we could sort of get somewhere in the middle where that we would have more science representation than just six individuals. That is a burden for one person, and then the potential conflicts that I do worry about.

Dr. Insel: Lee?

Mr. Grossman: Yes. The discussions that we had at the Planning

Committee was how to speed this along, and that was-- This suggestion was the best that we came up with.

Everything and anything that is discussed or concluded at the workshop was then going to come back to the full IACC for their consideration and further discussion. The workshop was designed to get a broad look at and have very, very laser focused detail by these three people on the portfolio and that question, and then raise it to a larger audience.

It was primarily done, since I think we are looking at December that we have to have the next iteration of this concluded, and we really couldn't figure out a better, more expedient way of accomplishing that.

Dr. Insel: Anyone else from the Subcommittee want to comment on this question about the numbers?

Dr. Lawler: Well, I think the notion was we have a plan. We are not

creating a new plan from whole cloth. We are going to be looking at the plan, what is actually funded, what new things have happened that would either ask you to cross of something that was on the plan, or to add something new to the plan.

So the hope was that, if you had the right three people plus other people in the audience who can, if they feel someone is showing extraordinary bias or inappropriate focus, would be able to bring the group back on.

I kind of like the idea of three people with very different points of view discussing. I mean, nothing like people who have children or relatives with autism constantly reminding us about the issue of urgency, and a basic scientist -- a scientist and a clinician to try to get the balance for each of those questions between, okay, do we need to do more animal studies or do we need to do patient intervention.

Ms. Blackwell: Tom, this is Ellen. You alluded to this earlier. It might also be helpful if we had more than one IACC member leading the smaller group. So that would at least enlarge those groups by one, and also increase the regular committee participation.

Dr. Insel: Right. So I think that is a good way to think about it. So the hope would be that these groups would be formed fairly soon. It's too soon now, but once the information from the RFI comes back, so sometime, let's say, early September, and that they would be working together as a group to do some of their homework.

This actually in some ways is sort of reporting out what their findings would be. So one of the ways to think about this is that t hey could be charged, for instance, to get more input from colleagues or from other sources. But if the committee feels like, particularly for maybe questions 3 and 4,

there need to be more heads put together on this because they are so broad, I don't think there is any rule against adding additional people and saying, well, maybe for those rather than having three we should have six or should have a different kind of representation. Lyn?

Ms. Redwood: I agree, Tom, and I think Cindy's point is really valid. So maybe when we pull together the people that have been suggested so far for nominees, we can look at fleshing out those areas, especially question 2 and 3 where I think we are going to need a little bit more technical expertise, especially with environmental factors.

Dr. Lawler: And I think the last IACC meeting we mentioned thinking about a way to involve the workshop chairs from the first iteration of this plan. Is that something that we could consider? That would be sort of an easy add to each one of them to at least -- because those did represent a pretty broad

spectrum of opinions and have good familiarity with the plan.

Dr. Insel: I think we talked about that at one point, and I can't remember where that ended up. Anyone else from the Planning Subcommittee? There were four people that we had.

Dr. Lawler: Right.

Dr. Insel: Some of them are in a different place than they were when they came a year ago, but -- I don't know. That is maybe better than focusing on those individuals. If you are comfortable with it, I think the Subcommittee would be happy to put their heads together to come up with a list of additional people to add in.

At one point I sort of recall in our discussions this also came up in the Subcommittee, and the people thought that maybe for some of these issues we needed more than just three people. So if we have your encouragement, we can go back to the drawing

board and supplement. Particularly, I would think, questions 3 and 4 are the ones that are going to require the most attention. Chris?

Ms. McKee: I think it might apply to 5 and 6 as well. As I have gone back and looked at the strategic plan and read through the summary of advances, I was reminded of Ellen. "Across the life span" kept getting added in.

One thing that is not added into the plan is across the spectrum. I think that we are hitting some populations really well and not others. I think that is especially true in services when it comes to education and options for adults.

So I think that you might also find narrow expertise in 5 and 6.

Ms. Blackwell: This is Ellen. I think Christine has a point, since we have condensed questions 5 and 6 together, that leaves us with only three people to address those very broad questions.

Dr. Insel: Am I hearing a suggestion that we just double up through this whole -- that better than having 15, we have 30 people involved? I'm sure it won't be hard to find, or is there a sense that maybe what we need to double up on is the scientific membership, the research personnel? What is your sense of the group? Do we want to -- Should we add more researchers or add more of everything? Everything? Heads nodding. Okay.

Dr. Hann: I can say that was a unanimous suggestion.

Dr. Insel: Okay. Alison?

Ms. Singer: The clinicians -- I don't know if we need to have more clinicians, I guess? It wouldn't hurt to have more clinicians.

Dr. Landis: You are saying a clinician who just treats patients, kids with autism or are you -- I think we were thinking clinical investigators, and that thinking

about how you get science, basic science, moving toward the clinic faster. I don't think you would want to have just one of those.

Dr. Insel: Yes, I think we kind of left that open, but when we were talking about it as a subcommittee -- but I think the sense of the group is always that you want to pick people who are expert in some fashion. So if these are clinical experts, it is quite likely that they could also be clinical investigators. We certainly wouldn't refrain from using a clinical investigator. Lyn?

Ms. Redwood: If we are adding two more, if we are going to have two in each of those categories, maybe for the clinician we could have one that is actually a clinician in the trenches that is seeing children with autism and treating them, and then another who is a clinical type researcher. Would that work, Story?

Dr. Landis: That would be fine.

I mean, I think we are all going to work very hard to come up with the right names for people who will actually take this seriously, do the homework between now and then, have a broad view, and be willing to take off their normal hat and think across the whole set of questions.

Dr. Insel: So that is a really good point, Story. One of the things that we worry about at NIH when we do these kinds of things is that people come in with their agenda for their -- they want more of what they do funded, and that is probably not what we are going to need here. We need to have someone who can wear the big hat and think beyond their narrow piece of this.

So what we would like as a subcommittee is, if it is okay with the full committee for us to race forward with this, we will come up with the nominees. We have some already that we have been gathering, but I think the subcommittee can work this out

probably electronically and fairly quickly, because this is already mid-July. We are going to have to start inviting people now. Della?

Dr. Hann: I was just going to suggest, though, if you all wanted, if other members who aren't part of the Planning Committee have suggestions, that we might be able to take those, too, and fold them into the mix.

Dr. Insel: And if there are people who are not part of the Subcommittee who want to volunteer, that's even better.

Dr. Hann: Liaison.

Dr. Insel: We can use your help in both ways. So if you have suggestions for who you would like to have serve, Della, what is the best way for them to nominate these?

Dr. Hann: I will send a reminder out probably like tomorrow or at best Friday and ask you for your suggestions and give you a due date, probably sometime next week, to

come in with your suggestions.

Dr. Insel: What about the overall format? Does this work for you? People okay with what the Subcommittee came up with? Okay. Heads are shaking, and I guess people on the phone are okay with this? Good. Virtual head shake.

This is the time course we are talking about. So this is pretty -- You know, there is a lot to do very quickly. We can't really put most of this off, if we are going to try to get everything done by December/late November to have the updates ready to go, and so we can deliver them in January.

So we are going to be off and running, and the only other thing I wanted to hear from you is whether you had comments or thoughts about the portfolio analysis. There is a lot of information here. In your notebooks, we have listed every grant.

So that is what most of that paper is in a later tab, if you want to really drill

down and see how this has been done. But we wanted you to see the sort of summary graph so you can get a sense of how the data will be presented to this work group that we will be putting together.

Dr. Lawler: Tom, will the portfolio analysis be available publicly for people that are going to be responding to the RFI?

Dr. Insel: You got it. So you are seeing it here, because this is a public meeting, and it will be public, and I should say the organizations were told that as well.

Dr. Hann: Yes, it will be a public document. Because of 508 compliance issues, it will not be posted, however, on the web. It will be something people will have to request.

Dr. Insel: You know what 508 compliant means. So it is the Americans With Disability Act requirement that you can't put anything on a website. It has to be -- Della

can explain this better than I can. It has to be accessible to the broadest range of individuals.

So there is a whole series of guidelines that we have to follow, and that actually becomes very complicated for a big table like this. it becomes actually unmanageable. So we can provide it by request, but we can't post it unless it is made 508 compliant.

Dr. Landis: So I guess it is worth -- I think the committee reviewed this as an experiment in a different to have a workshop, to collect input, and that an important piece of that process would be at the end to critique it. How well did this work? If we were to do it again this way, what would we change or was it a dismal failure? Was it less than optimal, and that we should come up with a very different strategy for the succeeding year?

Dr. Insel: Exactly. That was

very much the spirit of what we talked about as we were trying to put this together, and we will know. I mean, we will be able to say, hopefully, by October/November whether we got what we wanted.

It's a little tough to do, and I think we all realized that this was going to be -- this first year you don't really want to make a lot of changes in a document that hasn't yet even been implemented, but this is a good year to try this out and to see if it is working or not. Then we can -- As Story says, we can tweak it as needed.

The other thing I wanted to say is I have never seen a portfolio analysis like this. It's the first time since I have been working in the autism world that I have seen all the public and private funding in one place at one time. I think it is quite an achievement, actually, to be able to see this.

I don't know that we have this for most other areas of biomedical research, but

it is going to be very important to, I think, continue this process of having the transparency across public and private players and to get a sense of who is paying for what and to make sure that we are not always paying for exactly the same thing.

So until we had these data, there was no way to begin to do that. So it is quite an accomplishment already to be able to have this kind of a document.

Any other comments or questions?

Dr. Lawler: This is, I guess, a related question. I think part of the rationale for having this strategic plan like this is to be able to guide research. So is this plan for updating the strategic plan -- had there been discussions in that work group about how we are going to go about seeing how we measure up, because, I mean, putting new goals, deleting goals -- you know, none of that makes a lot of sense unless it really does drive the science and we can see that,

yes, we have now funded more research in this area. So how do we go about doing that?

It's difficult for this year, because we are only six months into it, but to me that is the bigger question, and whether in future years we could get feedback from the workshop participants about how -- you know, what some of the obstacles to implementing other -- Of course, money is one obstacle, but is it that we are not training our young scientists in the right ways to be able to tackle some of the questions that the community thinks is really important?

I would hate to lose out on getting that kind of feedback that could help us refine how we think about using and implementing the strategic plan.

Dr. Insel: Presumably, the sorts of graphs that we had up here we will have every year, and we will be able to track, and it will be really interesting to see how they change.

I think, from our perspective, everything that we are looking at now is essentially baseline, and one hopes that we will be able to see the impact of having a plan going forward.

We will certainly be able to see, I think, some bump in the amount of NIH money because of the stimulus package providing -- definitely providing a bump-up in 2009-2010, but the question will be whether that additional funding actually helps us to jumpstart the plan or not and how -- in that diagram where you map it against all the different objectives, whether we are at the same place or whether we are actually seeing that some of the gaps are being closed.

I think you are right, Cindy. I mean, we are not really going to be able to see anything like that in September, but a year from September we ought to have some information. That and also the summary of advances, which will be the other piece that

we can look at.

Lyn always mentions that when we do the summary of advances, we ought to track that back, too, to the source of the funding, which will be really interesting to do, now that we have all of that information.

So maybe someday all this will end up in NDAR, for all I know, but it is a great resource for us to begin to look at, how this field is moving.

Now we are scheduled to take a break after this presentation, but we've got time here. Unless people want to break now, what about going ahead and hearing about the update on the status of the summary of advances? Can we go ahead and do that, if we've got -- see if the slides are up here? They are, and Dr. Hann, you want to take us through this?

Dr. Hann: Sure.

Dr. Insel: Thank you.

Dr. Hann: Okay, So this is the

other topic that Tom just alluded to, which is the annual summary of advances, and you will recall from our last meeting we had brought to you a long list of articles, and we also discussed the methodology by which we selected those articles. So this is just a little reminder, this slide, in terms of the methodology that was used.

I think foremost you all encouraged that we use peer reviewed papers that were published, physically published, not just e-published but also published in 2008. We looked at a variety of databases. We had great help, actually, from the Library at NIH in helping us do this search, essentially to prepare all of this.

So we took all that information, and we took the recommendations that you all provided us at the last meeting, and originally we had 257 articles that we brought forward to you. They were roughly divided into the six areas that basically map onto the

six primary areas in the strategic plan.

At your last meeting, you asked us to focus in on 37 of those articles, that those would be the articles to really provide the gist, if you will, for the Summary of Advances. Then you charged my office with writing and drafting this report for your consideration.

Also during the discussions last time, though, everyone was quite, I think, happy with and really appreciated that there had been 257 articles that had been identified for this area of research, and so you asked us also to prepare an appendix that would include all 257.

We are working on the appendix. It is not included in your materials, because we are preparing it strictly for the web. So it is an interactive took that people can click on the article and then go have it retrieved essentially through PubMed and so forth. But that is in the works.

Last week, I think it was, or week before last -- I think it was last week -- I mailed to all of you electronically the summary. It is also in your booklet here. I believe it is Tab 12 -- yes -- which is the Summary of Advances.

We were very grateful for one of our staff members, Erin Bryant. She did most of the heavy lifting in terms of reading through the articles and preparing the information, what we hope anyway is a more easy, friendly way to describe sometimes very intricate science so that folks would understand.

You will see that essentially the document now goes on for about 20 pages. It is about a 20 page document. The last section is the bibliography, if you will, for the articles that were selected for the 37.

You also see for those 37 articles we did pull out, if the paper included information on funding, that that was

included, as well as, if the journal had an impact factor, we also included that, and we are working on similar kinds of information with regard to the listed 257. That will be in web format.

So with that, I turn it over to you all for comments and discussion.

Dr. Insel: Lyn.

Ms. Redwood: You know, at the last meeting when we voted on this and we had option, I think option 2 and option 3. The vote was sort of confusing, and I know several of the members didn't vote, because they were confused by the vote.

In reading through these, I just don't really feel as though it captures all of the advances. I think there's significant research that was in the 127 that didn't appear in the 37 now.

So I would really encourage us to go back and look through those again. I know, just for example, the work of Wietzman that

talks about mitochondrial disorders in autism, which I think is a really promising area of investigation, was not included.

The work of Jill James with oxidated stress and increasing glutathione levels using methylcobalamin and phthalic acid, that wasn't included. That was a big treatment study.

There's several others here that were in the 127 that don't appear in this work, and I think that it just doesn't capture the breadth of what was published or what was -- yes, published since last year.

There is also -- When you looked at the 127 that were option 2, and then you looked at what was selected out of those, it's not balanced, like there were only four out of 24 that fell under the category of treatment that made it over into option 3, which we have in front of us, where there were 22 out of 36 in the risk factors category, which then made the risk factors look so much bigger than the

treatment categories.

I think that is sort of -- I just don't think it really captures everything that was important last year. And there's also some studies in there that aren't specific to autism. There is a study about cord clamping that looked at total health outcomes, and didn't look at autism. That's in there.

There is also just an editorial that was in there that just reviews science that wasn't any new science. So I think we need to look at it again.

Dr. Insel: Other comments or thoughts? What was here was what the office -- the OARC thought was the sense of the group, because we had talked through what you wanted, and you voted on going in this direction, and the articles that were here were ones that everybody voted on.

So none of these -- The list itself came not from OARC but from you, from all of you, suggesting papers that we should

include. There may have been differences in how people thought -- what people thought was important to include, but the sense that we had from the last meeting was that you wanted a shorter, more high impact list, and we talked a little bit about using citation index as a way of doing this and realized we probably weren't ready to do that.

We also talked about trying to come up with a consistent way so that next year we would have something to compare to, where the articles had been selected in the same way. But it may be that the -- and I don't remember the articles that you mentioned, but those just may be ones that there wasn't enough support for from the group.

Ms. Redwood: I know, Tom, personally I didn't vote. Cindy, I don't think you voted.

Dr. Lawler: No, I voted.

Ms. Redwood: You voted?

Christine, I don't -- I was waiting for another option for voting on. If you read through the minutes, you see where several of the committee members also said that they thought that option 2 was the better option. So I just wanted to bring that back up to the IACC again to say is this really what we think is the --

Dr. Insel: Well, we can vote again, if that is what -- What we did was based on the vote that people took at the last meeting.

Ms. Redwood: I know. I understand, and I just -- Personally, when I read through this, I was disappointed, because I think there is a lot more. So I just was wondering if any of the other committee members, when they looked through it, felt like there were gaps in this.

Dr. Insel: Any response? I guess I do feel that there is still a gap in the methodology. I still think we need something

that we can all agree on as a way of doing this every year that is consistent.

We have talked about a couple of options. I am not sure we have yet come up with the right way to do it, and maybe we are not going to solve that today. But we would like to be able to use this summary of advances as one of the ways of monitoring progress in the field, and if we change the way you collect the advances every year, it becomes a little difficult to do, or if you leave it up to just whatever people on the committee seem to like in terms of science, then the list of articles changes entirely based on who is sitting on the committee.

So it is not ideal. Alison?

Ms. Singer: I felt that the summary was a good summary. I felt that what was missing was some sort of impact statement somehow relating the advances of the year to what resulted in an improved quality of life, so some way to, maybe not this year, look at

the studies that really changed and improved outcomes for people. You know, why was this study important, not so much because it was published as being the metric by which we judge value, but really looking at impact on quality of life.

Dr. Insel: And maybe that will be especially important to do when -- Again, if we treat this as the baseline year, because in a sense it is, if we can link to the strategic plan, link to a new investment and then talk about what the results are, in just those terms, in public health impact.

So that is a good note to take for next year as we think about how this should look. As Story said before, in a way we are kind of feeling our way here and trying everything out in an experimental way, and we will tweak as we go along. Chris?

Ms. McKee: I echo what Lyn said. It's kind of an odd process with the number of people who weighed in. We had three public

and three government members weigh in and vote, and it is not an exciting read. My favorite advance didn't make it in either, which was related to services.

The other thing that I think is lacking is on page 2 where it talks about the topic areas contain noticeably more articles than others, and this reflects the category breakdown of the articles selected by the committee.

I guess what I think is lacking there is our whole discussion about that what is really reflected here is the disparity that mirrors the reality of what has been funded, and how we have so many subject areas that are not funded, and it's not just that we liked these certain categories more than others. So I think that that needs to be reworked and tweaked a little bit.

Dr. Landis: So you could imagine that next year it could be coupled to the funding diagram.

Dr. Insel: Right, and I think the assumption is that all this will eventually form one large document that will link to funding, public and private, and link to new initiatives and link to the plan. Right.

We don't want to do that now, because none of this is linked, because it hasn't -- I mean the plan hasn't really been implemented, and the funding hasn't changed, but hopefully, by next summer, we would be looking at that.

That would be, I think, really powerful, if we can add in information about impact, and I think these comments about trying to come up with something that doesn't look like it is just whimsical.

I hadn't read it that way, but the way you read it does sound like this was -- the things here were just whatever we felt good about. So that is, I think, a tweak we can make. Hopefully, we can make that in this document before this gets submitted. Lee?

Mr. Grossman: I, unfortunately, had to leave the last meeting early, so wasn't engaged in the discussion or the vote. When I saw the summary when it was forwarded to us, I was disappointed. It really doesn't address the urgency of the issue.

I would have thought that there must have been much that was left on the cutting room floor in terms of what true advances would be. It doesn't address at all the areas where I see the major advances occurring that are actually affecting people alive today, which is in the applied field, and there is much data and review available there.

This goes back to the first time we discussed this, I guess, which is two meetings ago where I felt that we shouldn't -- because of the nature of the condition, the urgency, the attention given to it, we shouldn't try and limit ourselves.

We should be more expansive, and

this document, although I think it is brilliantly written with the information that was selected and I think the staff did a great job putting it together, it was disappointing, because it just doesn't -- It misses the mark quite a bit.

So what I would suggest is that, as we move forward and move toward next year's update of this, that it does take these factors into consideration, that we do make it something that can really be a shining light of the multiple advances in many different areas of this field, and truly highlight all of them, and not just limit itself to medically peer reviewed journal work and be broader.

I know that it is sometimes hard to validate it, and when it is peer reviewed in a major journal, it has that seal of approval generally put to it. But there is much great information out there that is floating around that is in other areas that

are really what I see, and I think many of our constituents see, as what is driving the field forward and has more immediate payoff.

Dr. Insel: Other thoughts or comments about this? So we hear sort of low enthusiasm for this document in its current form, opportunity to change it for next year. We can do a little tweaking this year.

Since it hasn't gone forward, it is certainly possible to add some sense of impact to this and to try to make it more relevant, but we are eager to get -- With some changes we are eager to get this going.

Della, when is this actually due? Do we have a specific date?

Dr. Hann: Last year's was done in July of 2008.

Dr. Insel: And submitted when?

Dr. Hann: Shortly thereafter. It was at the July meeting that it was voted on with some minor changes, and then it was finalized and sent forward shortly thereafter.

Dr. Insel: What is the sense of the group? What do you want to do? I think the choices are we can tweak this a bit taking your comments into account, and send it forward, if you are willing to vote for that, or if you are not comfortable with it, we can go back to the drawing board and keep working on it until we see you in October. What would you like?

Dr. Cooper: I vote for tweak.

Dr. Insel: Tweak and twitter? Okay. Others? Lyn has made a motion. So vote number one would be tweak and twitter, and number two would be to scrap and redo.

So can I see hands for tweak and twitter?

Dr. Hann: Okay. The vote for tweak, one, two, three, four, five, six, seven, eight, nine.

Dr. Insel: And for scrapping and doing this again?

Dr. Hann: One, two, three.

Dr. Insel: Okay. I think we are going to tweak, but there is an opportunity for making changes for next year, and I still want to go back to this issue of process. I think we do need a process that works better, and we now have a year to think -- well, not a year, but let's say nine months to think about it.

Between now and then, it would be nice to have this automated in a way that doesn't make it so awkward for us to figure out just how we want to do it, and also something that can be very consistent from year to year.

Dr. Landis: One of the things that bookstores often have is books selected by staff. So you could imagine that this represents a consensus that almost everybody would buy into, but that each person sitting around the table would want to think -- I know this is a bit random. I apologize, Tom -- think about what they personally perceive to

be the most important events.

So some people would have the elephant's trunk. Some people would have the elephant's legs, but I think that that could be something we could think about as accurately reflecting the diversity of views about what an advance in autism research means.

I think, if you set that up as a paradigm -- I mean, I don't think we should vote on it. If you set it up as a paradigm, it is something we could think about, and would that be truly reflective? Then maybe you want to have a blackball or people could have three things and -- I mean, but just to have some way to reflect the individuality of the views of the whole committee.

Dr. Insel: Oh, that's great. So I came into this thinking in a different way. I was thinking about science top 10 each year that they do, and so sort of 10 best, and it never occurred to me that we would have more

than 10. So when we got to -- it was 41, and now it's down to 37, I thought, whoa, that seems like a lot. But certainly 250-something seemed excessive.

So I guess we came into this with quite different expectations, but the idea of allowing the committee to also play in this and to suggest their favorite two or three findings could be really useful.

Alison, you had your hand up. No?

Ms. Singer: I was -- Under the headline of tweaking and twittering with it, the one thing that I noticed reading through it was that I think the exercise of having to assign each study to a particular question may not lend itself -- I know we wanted the summary of advances to map onto the strategic plan, but in many cases I felt like there were some studies that really feel both within biology and treatment.

So for example, Mark Bear's work is really only mentioned under biology, when

really it has tremendous implications for treatment.

So that is the kind of thing where, I think, next year we might want to just think about more of a narrative and not necessarily trying to fit each one into the boxes.

Dr. Insel: Just so we are all on the same page, what we have agreed to here, not unanimously but by majority, is that we will tweak this with the comments that you have made, and it could include even the comments that not everybody likes the way this was done this year, and we want to do it a little differently next year, as well as trying to provide some sense of impact and something about that section that makes it look like this was really just personal preference.

We will come back sometime in the next nine months to think with you about a better way to do it for 2010. Okay?

According to my notes, I think that is the end of our scheduled agenda for the Committee, but we do have time for public comment, and again rather than taking a break, it would be better to move forward with public comment. We are more than hour ahead of schedule.

Is there anything else, though, that we need to address before we get to that?

Okay. Let me ask Elizabeth Emkin to come forward, if she can join us. Hopefully, she is here. We will just move forward with that part of the agenda.

That's the problem of being so early. Jim Moody from SafeMinds.

Mr. Moody: Good afternoon, and thank you for the opportunity to make public comment.

I am a Director and legal counsel representing SafeMinds. I thank the Committee for the opportunity to offer public comment on vaccine safety objectives. Our primary focus

today is on the need for IACC's strategic plan to encompass autism specific vaccine safety research.

The question whether vaccines can cause autism has been answered by the Vaccine Injury Compensation Program, basically the vaccine court, in decisions and in concessions by the government on numerous cases going back to 1991 in which they have compensated various biological conditions that have led to a diagnosis -- a behavioral diagnosis of autism.

The questions that remains are how many children are affected, and how can new cases be prevented and/or existing cases be treated? Congress tasked the Committee with finding the cause of and treatments for autism, among other objectives.

Vaccines were the only cause specifically singled out in the legislative history. The unanimous passage by the National Vaccine Advisory Safety Working Group of recommendations from April and June on

CDC's Immunization Safety Office agenda identified crucial gaps in vaccine safety science.

Many of the recommendations implicate IACC's research agenda, where autism is a desired outcome. The continued growth in the body of research indicating that autism is environmentally triggered also supports the investigation of vaccines' role in autism.

The Combating Autism Act's colloquy statements, IACC public comment statements, and in correspondence to the IACC from many individuals in autism organizations eave no room for doubt as to the undeniable Congressional mandate and wishes of the public in this respect.

The IACC must be accountable and responsible for autism specific vaccine research. As such, we ask that any applicable research objectives currently contained in the IACC's strategic plan, particularly with respect to environmental causation, encompass

vaccines as a possible etiological factor worthy of study.

In addition to this request, the removal of previously approved vaccine safety objectives in the strategic plan last September was based on the false premise of NIH's lack of vaccine expertise, and we think there is plenty of expertise at NIH, lack of support from the scientific workshops, and there was plenty of support for those workshops, and the acknowledged conflicts of interest must be righted.

These same objectives were supported now in the NVAC recommendations, and on NIH's expertise and historical involvement in vaccine research are a matter of public record and well known.

The IACC transcripts documented much research was vetted and supported by the science workshops and strategic planning work groups, public comments and process.

An independent panel along the

lines recommended by Dr. Noble during his presentation in the IACC earlier this year could easily convene to acknowledge -- or could easily overcome the acknowledged conflicts of interest existing within HHS in determining the feasibility of some of the vaccine research in question.

In addition, animal projects could be begun immediately, as there are no serious ethical or methodological problems. Other vaccine research identified as necessary could also easily be required to be conducted by independent investigators who have no ties to industry and avoid conflicts of interest that have plagued this field of research previously.

These steps would begin to assure the restoration of public confidence in the government's ability to conduct sound and necessary vaccine safety research.

In short, given the latest recommendations from the NVAC and the false

premise put forward by some of the Federal members at the IACC last January, there is no logical reason or barrier preventing this much needed research to be included in the IACC strategic plan.

Additionally, the scientific community involved in the strategic planning work groups on numerous occasions and in engagement with autism organizations and the majority of the public IACC comments stated the need to autism as a multi-system disorder, as well in the inclusion limitation of studies used in the "What We Know" section of question 3, the addition of research supporting vaccine and environmental concerns.

We request that these items be corrected in the updating process for the strategic plan. The inaccuracies noted by the strategic planning work groups and the autism community regarding vaccine research and the current plan's reference to the 2004 IOM vaccine safety report are a matter of record,

not opinion, and must be corrected to remove the bias contained in the present strategic plan in this regard.

I just want to add one comment with respect to the discussion that occurred this morning. That is that it is not really optional, as we see it, that the vaccine and vaccine type program, both in humans and animals, be conducted.

it is not a question of -- It is not really an optional question. Public confidence needs to be restored by getting accurate baseline research. Until then, doubt and ignorance are no substitute for sound science.

This baseline research is necessary to be done, so we can know what level of adverse events there are, including autism, so that the vaccine schedule can be fixed, so that new cases can be vetted, and existing cases of autism can be more effectively treated. Thanks.

Dr. Insel: Thank you. Elizabeth Emkin? Ari Ne'eman? That is the full list that I have. Let's check. Anyone else?

Okay, if that is the case, unless there are any further issues or comments, we are adjourned, and we will see you again. Next meeting is October 23rd?

Dr. Hann: Yes, I'm pretty sure that is correct. Yes, October 23rd.

Dr. Insel: Okay. October 23rd, and the location will be probably in Bethesda. Thank you very much.

(Whereupon, the foregoing matter was concluded at 2:23 p.m.)