U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTERAGENCY AUTISM COORDINATING COMMITTEE

STRATEGIC PLANNING IMPLEMENTATION
WORKGROUP MEETING

FRIDAY, AUGUST 8, 2008

The Workgroup meeting convened at 11:00 a.m. in Bethesda, Maryland, Thomas Insel, IACC Chair, presiding.

PARTICIPANTS:

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

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PARTICIPANTS (continued):

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DEBORAH HIRTZ, M.D., National Institute of Neurological Disorders and Stroke

JANE JOHNSON, Autism Research Institute

DENISE JULIANO-BULT, M.S.W., National Institute of Mental Health

ALICE KAU, Ph.D., *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

CINDY LAWLER, Ph.D., National Institute of Environmental Health Sciences

ELIZABETH MUMPER, M.D., Autism Research Institute

CATHY RICE, Ph.D., National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention

ANDY SHIH, Ph.D., Autism Speaks

BONNIE STRICKLAND, Ph.D., Health Resources and Services Administration

PATRICIA TANSKI, Autism Consortium

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STELLA YU, Sc.D., M.P.H., Health Resources and Services Administration

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PROCEEDINGS

11:00 a.m.

Dr. Insel: Good morning everyone. This is Tom Insel, the Director of NIMH and Chair of the Interagency Autism Coordinating Committee.

We have umm, at this point, we have almost everybody here in the room in Bethesda for the first of these implementationworkgroup meetings.

The meeting is open to the public, both on a webinar, which is just about to go live, it looks like. It is actually coming up, as we speak. Those who are on the phone should already be connected, and we also have some people from the workgroup who are not here in Bethesda, but will join us by phone.

I'm going to hold off just a minute, until we make sure that the webinar is accessible and then we'll be getting started.

Okay, let's get going here. We'll start, first of all, I wanted to thank all of you for joining us short notice and this entire process has been speeded up, so that we

can get to the finish line, which is November 21st, when we want to have a completed strategic plan, to be able to send to the Secretary.

So, we've been moving this at a break-neck speed and I know this is difficult for some people that have to change plans and to get on board so quickly. But we think it's important enough to move quickly and be able to provide a plan that we'll all be able to be proud of.

I'd like to start by just going around the room and having a chance for everybody to introduce themselves, so we know who is here. We'll also ask those people from the workgroup who are on the phone to join in as well. But Tish, maybe you can start. Just say who you are and what organization you're from.

Ms. Tanski: I'm Tish Tanski. I'm with the Autism Consortium.

Dr. Mumper: I'm Elizabeth Mumper. I'm with the Autism Research Institute.

Ms. Johnson: Jane Johnson, also

with Autism Research Institute.

Dr. Kau: Alice Kau, I'm with Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Mr. Dunaway: Wolf Dunaway - I'm a person with autism and I do motivational speeches and help people with autism.

Dr. Anderson: Kai Anderson, Centers for Medicare/Medicaid Services.

Ms. Fallas: Jennifer Fallas from the Department of Defense, Congressional Directing Medical Research Program, Autism Research Program.

Dr. Hirtz: I'm Deborah Hirtz. I'm from the National Institute of Neurological Disorders and Stroke at NIH.

Dr. Gilotty: Lisa Gilotty. I'm with NIMH.

Dr. Wagner: Ann Wagner, I'm with NIMH.

Ms. Yu: Stella Yu, I'm with the Maternal and Child Health Bureau of HRSA.

Dr. Hann: I'm Della Hann. I serve as a Designated Federal Official for the

Committee, as well as the Executive Secretary for the IACC and I'm also a member of the NIMH staff.

Dr. Insel: And can we hear from those on the phone?

Dr. Yeargin-Allsopp: Good morning, this is Marshalyn Yeargin-Allsopp. I'm from the Centers for Disease Control and Prevention.

Dr. Lawler: This is Cindy Lawler. I'm from the National Institute of Environmental Health Sciences at NIH.

Dr. Rice: This Cathy Rice, also from the Centers for Disease Control and Prevention.

Ms. Wojcik: Joanne Wojcik with the Centers for Disease Control and Prevention.

Dr. Insel: Good. Well, welcome to everybody and thanks for helping us with this project. Let me just lay out where we are in this and what we need you to help us with this morning.

The IACC asked us to get together as a group of funders, to look at the question

of how to put budget requirements on the various objectives. I think there are 35 objectives that are in the draft version of the plan. You should have received the draft version. This is now a draft version that the IACC has approved for public posting.

So, what we need to do, in looking at this at this point, is to provide, for each of the objectives, a number, which will be an approximation of what we think it would cost to be able to meet this objective.

I have a set of questions that I wrote down, that I thought would be worth putting on the table before we start, so that we're all on the same page.

The first question is whether this is a chance to re-write the initiatives or the objectives and it's not, and what we're going to do is, we're going to work with what the IACC has given us. You may not like all of the objectives or you may have objectives that aren't in here, that you'd like to see.

But what we're going to do today is to take the ones that we've been given and

we'll come up with numbers for them, and it's also important to remember, this isn't the final plan, that something can still change between now and November 21st and even after November 21st, beginning on November 22nd, we start on the next version of the plan.

So, this is a living document. What we're really trying to do is to get to the strategic plan 1.0, so, we'll have something to work with going forward.

Can we count activities that are currently going on or should those just be forgotten about?

We shouldn't because it's currently being done doesn't mean that it's not going to be in the plan. The plan is an attempt to get an understanding of what's the universe of possibilities and what's the most important things to get done for the mission and the vision that we've laid out for by IACC.

So, the fact that the plan has an objective that somebody is already working on, shouldn't give you a great deal of heartburn.

It should help you, perhaps, to even be able to provide some numbers for the budget estimates, understanding that some part of the budget estimate might already have been covered by a current commitment.

I don't see that as a problem. What we really need is your best estimate of what it would cost.

Do the numbers need to add up to 890,000,000 or one billion or 127,000,000? No, there is no reason to limit this process, to what we're currently spending, what has been authorizing by the Combating Autism Act or by anything else.

The numbers ought to be generated by your best estimate of what it costs to do what is in the objectives, and I don't think you need to worry very much about what the total looks like. That's going to be a problem much further down the line, for congressional appropriators and not for us. So, I would not be limited in the way that you cost these things out.

Often when we're in these

discussions about anything, whether it's for a strategic plan or for any kind of an RFA that we're developing, it's never easy to get a sense of exactly what the costs will be and I'm hoping that part of what the conversation today will be, is around trying to figure out what the best number will be.

It may be useful for us, we'll have to see how we entered into this, but it may be useful for us to talk in terms of ranges. You know, it may be the something with be eight million on the short side and 15 million on the long side and we just won't know.

I think you can give the IACC that kind of information and let them worry about that, if that's what it comes to. If you think that it will be best to frame this, in terms of a range of costs, that's better than having nothing at all.

So, I wouldn't be too worried about coming up with a very precise, single number in this effort.

A final question is, are the

numbers that we come up with today final, and no, they're not.

What we're coming up with today is what we can provide to the IACC. It's their job to come up with - the final plan, not yours, and so, what we're really hoping you will do is provide them with the information, whether it's a range or a single number or even places where you feel like it can't be done, that will help them to be able to wrestle with this. They need the input.

So, your job is really to provide the expertise, in terms of costing out the science.

We are not going to be talking about specific RFAs. We're not at that point. It's more a question of what's the kind of science and what's the cost of the science that would be necessary? We're not going to be talking about who will paying for it or how it will be paid for. None of that is on the table here. This is just a very simply costing exercise. It's what program officers do all the time for a living, and that's the

kind of information we're going to need.

Any questions, based on that?

(No audible response)

Dr. Insel: Okay, if that's the case, we're going to try to march through this in a very structured way, just starting with the first objective and walking through it one by one.

What we'll do in terms of process is, we'll just open it up to those of you who have already come up with numbers. I hope we'll have some conversation about each one.

I am going to be a strict task master about the time, because I don't want to have this meeting go beyond the time allotted. So, if we're taking too much time on any one of these, we'll just keep pushing and we'll have to come back to it or we'll just leave it as unresolved.

Unless there's anything else, I'd say let's go ahead and get started on the very first item, which is under objective one, when should I be concerned, and the first one is a short-term objective: develop with existing

tools at least one efficient diagnostic instrument that is valid in diverse populations for use in large-scale studies by 2011.

So, this could be a like an auction. Can I get a sense of what you think about that?

Dr. Mumper: Actually, I had a question before we start. What is the earliest start date that any of these studies would feasibly commence?

Dr. Insel: Well, some of them may already be started. That's a real possibility.

Dr. Mumper: Okay, so 2008 is an okay start date or would you rather…

Dr. Insel: If it's something that we're not currently doing, it's not effectively going to get going and there's no way it can get going before 2009, because this plan won't even be implemented until then.

There is it's not as if none of this is happening. So, there are a lot of things. There are things in here that are

rolling out, even in the next month.

So, but for something that is not in the pipeline, I think you have to assume that if it's going to become an RFA, the RFA to be released in 2009, it would not actually get into the funding stream until 2010. Fair enough? Anything else?

(No audible response)

Dr. Insel: Okay. So, on this first objective, I just want to get some sense from the group about how many years would be needed to get this done and what the total cost would look like and when it should be started?

Dr. Wagner: I can tell you what NIH/ACC came up with. We thought we actually thought this one could be done relatively efficiently, because it could be a supplement to an ongoing funded grant, and that it could be done in three years at about $400,000 total cost per year. That would be about $1.2 million, and that could start if it were a supplement, it could start could maybe start in 2009 or 2010.

Dr. Mumper: Out of the private sector, I would agree with those numbers.

Dr. Dawson: Ann, this is Geri Dawson. So, I'm wondering, when we think about this, are we thinking about through the life span and what diverse populations are we talking about, actually recruiting minority populations and - you know, which may not be in existing studies.

So, I think that's kind of two questions, because you know, I think I like your idea of using it as a supplement, and that will be a great way, I think, to begin the process.

But to actually reach this goal, you probably have to do some specific recruiting and also, I doubt if the ages are very, you know, well covered. Maybe they would be. But it would be questionable.

Dr. Wagner: Right. Yes, I think you're right, that there might be supplemental recruitment that has to happen. So, I guess I'm not sure what the question is. Are you suggesting it might be more - that might be an

under estimate?

Dr. Dawson: Well, I think if one were just to say, okay, let's take all the say, ACE networks, or whatever you wanted to use as your platform and let's have them, you know, try to use a shortened ADI, you know, what I think maybe it could be done for that but if you were to see whether this works in a Hispanic population in the same way, right, and or different populations, I think it would be more labor intensive to recruit enough, say, African Americans, you know, that takes a pretty extensive recruitment effort, community relations, et cetera. So, that's all.

Dr. Dawson: Okay.

Dr. Rice: This Cathy Rice, CDC. Another point is, I know we are focused primarily on U.S. activities, but if the goal is to look at diverse populations and non-U.S. activities or situations in developing countries, that may be an additional, certainly cost and infrastructure building that would be needed to be built in.

Dr. Wagner: So, this one might be a

range, depending on whether you're thinking with one is thinking that it's more limited or we're looking for one instrument that could be used across all of those things, which may be hard. But does somebody have another one?

Dr. Yeargin-Allsopp: Yes, this is Marshalyn from CDC, and we don't have any existing studies that we can build on. So, this would be a new research opportunity for us.

We estimated five years and a total project cost of $28.7 million, beginning in 2009, and we were thinking of three grantees at approximately $1.5 million per grantee and then allowing for CDC to have installation. We come out with an estimate, as I said, of $28.7 million.

Dr. Insel: That's quite a range. We're between 1.2 and 28.7.

Dr. Yeargin-Allsopp: Right.

Mr. Dunaway: This is Wolf Dunaway. I was wondering, are we also including people that are adults, who are just - because in my generation, it took there are a lot of people

out there that have autism or on are on the spectrum that don't, you know, or that didn't get diagnosed or didn't know that they had autism until later on, and I'm wondering, are we factoring in adults and again, adults in the different racial and you know, all the different diversities that we have there?

I just want to make sure in doing this, that we don't just limit our focus on the traditional children and I want to make sure that we also get adults. So, is that factored into the equation?

Dr. Wagner: I think that is one of populations that was considered, diverse populations of all ages.

Mr. Dunaway: Okay.

Dr. Insel: And to clarify, part of the difference between the 1.5 and the 28.7 I'm sorry, 1.2 and 28.7 was that you were thinking that we already have current projects that, I guess, are NIH funded, that could be supplemented, that could be done.

So, you wouldn't have to build a full infrastructure the way that Marshalyn is

talking about.

But does the info - does what you're talking about, in terms of the ongoing projects, include adults and diverse adult populations or are we talking about only adding onto?

Dr. Wagner: Well, I don't think we had any that cover all of the populations and all of the ages, and so, we were not thinking of this as doing one instrument that would cover all of that. So, the goal is at least one efficient instrument.

So, we were thinking we would find something that looks like it's close to getting us there, as one of the options and would be part of a tool. I think that's different from starting a study that would come up with one instrument that would be validated in all of those populations.

So, I think that's where the discrepancy is.

Dr. Dawson: This is Geri again. I think it also makes a huge difference, whether you're talking about - like, there's a lot of

interest, for example, in using a shortened version of the ADI and in fact, Cathy Lord and I have been talking about doing that in the context in some of Autism Speaks projects, where, you know, currently, it's a two and a half hour interview, but you only use a sub-set of items for the diagnosis.

If you were to do something like that, I would think that's pretty straight forward. But if you're going to say, well, we're going to have a diagnostic instrument, because you can't make a diagnosis with only an ADI. You have to have the ADOS and so forth, and start from scratch, then that's a huge that's a much bigger project.

So, one thing, you have to have a gold standard clinician as your reference point, to whether it's valid and so you'd have to have that clinical diagnosis, right, to reference to if it's a new instrument, and that would mean hiring some expert to do that.

So, it's a little bit complicated, but I think, you know, if you were going to just take an existing instrument and try to

see if you could shorten it, that's already been validated, you know, that would be more straight forward.

Dr. Insel: And Geri, just to clarify, I think the screening instrument that you're talking about is the second item. It's the next objective.

Dr. Dawson: Well, I'm thinking of diagnostics. So, it would be ADI and ADOS.

Dr. Insel: Right, so, this one, the one the first one that we're on, truly is the diagnostic instrument and when the original workgroup talked about this, they wanted to make it very clear that there were two different efforts here, that a screening instrument would be for community use and could be perhaps, not entirely specific, but fairly sensitive.

This is the one where they really wanted to see a faster, cheaper, better diagnostic tool.

Dr. Dawson: Right.

Dr. Insel: So, that's where the focus has to be for this investment, and I'm

still stuck on trying to understand the question of what it would cost if want to develop such an efficient diagnostic instrument for diverse populations, including adults.

Dr. Yeargin-Allsopp: Okay, can someone tell me what our current state of knowledge is about our existing diagnostics instruments, in terms of use in adults? This talks about more efficient, but for example, have the ADI and the ADOS been validated in adults?

Dr. Wagner: Yes, yes, there are adult models for the ADI and ADOS, yes. I mean, I guess the question is whether it's realistic to think that one is going to have one instrument that's going to cover all of that and I would be inclined to say no, but I don't know. I mean, I don't know.

Certainly, it would be a big effort to try to develop that. We don't have that at this point.

Dr. Lawler: And not only the age issue, but the severity and sub-typing issue

as well. I'm assuming we're expecting it to cover that also.

Dr. Insel: So, given this, so, we started off at the 1.2 figure. Ann, what's your sense? Should we be revising this upward, maybe short of 28.7 million, but you know, even - I like the idea of knowing that there's an infrastructure that you can build on, and I'm just trying to get a sense of whether that infrastructure is sufficient for this task, and if so, then maybe simply expanding it out, as you're suggesting, will do it.

But you guys are the ones who are going to do know that. What's your sense?

Dr. Lawler: This is Cindy Lawler. I think that it sounds like that uncertainty for that really centers around how we're going to define diverse populations and how we're going to capture that, if we're going to want to make sure we can capture young and adult or if it's the more international or ethnic diversity, but that's what's really driving the uncertainty.

Dr. Kau: But then it also depends on what are we going to use existing measures like Geri said or are we going to use a new measure?

Participant: Yes, I think that's what Marshalyn was thinking about.

Dr. Dawson: Yes, I think finding a new measure is kind of a life time of work, whereas, if you wanted to take the existing measures and then use them as they are, you know, or a shortened version of them, which is already under discussion and the different populations and different ages, that's more doable.

Starting from scratch, that's a pretty big task.

Dr. Insel: So, just again, the objective as stated from the IACC as to develop with existing tools, at least one efficient diagnostic instrument.

Dr. Yeargin-Allsopp: But I think the 1.2 or 1.5, I think that sounds very low to me, even given the infrastructure that's there. I think it should be revised upward.

It doesn't have to be 28.7, but I think it should be somewhere in between.

Dr. Insel: And the other point is that they want it completed by 2011.

Participant: Yes.

Dr. Insel: So, it shouldn't be a five year effort, at most. I would assume it would be a two year or three year effort, right?

Dr. Wagner: Well, so, if you doubled, that would be one instrument tested would be 2.4 million and then you could say you're going to have to test more than one, to get maybe one that works, so that you could say five million. What do people think?

Dr. Rice: Well, I think - this is Cathy, Cindy's point about the base population is an important one for the cost because there may be the infrastructure there, but will the existing projects need to cover a much wider base, sample a whole lot more and do a lot more than we're putting the typical clinical samples in.

So, that could certainly double

the cost of what's needed to do this

Dr. Insel: Can we get clarification on that? Do we have clinical populations now that are diverse?

Dr. Dawson: Well, I know that the agreed group is - has been funded to supplement with some diverse, you know, populations. So, there may be specific projects that could be really looked at for that specific region.

I think if you were just to take, say, the ACE network, you would find that it hasn't built in that kind of diversity, probably well, there might be a few, like some of the (inaudible) studies might, say, (inaudible) who is doing more of an epidemiological approach.

Dr. Rice: I think the CHARGE study has a pretty significant Hispanic component. So, there is some diversity in that, a vague population, that could be used to address some diversity questions. So, that's at least one.

AGRE, I don't think will be up and running in time to…

Participant: Oh, that's right.

Dr. Rice: to do this.

Participant: And none of those studies include adults.

Dr. Rice: Correct.

Dr. Insel: So, I'm going to make a recommendation, because I want to move on here. I would assume that we would have to expand this further than what we originally talked about because this was not including for instance the AGRE population and some of the other studies. But I'm wondering if, since it's only at most, a two year or two and a half year project, if we doubled the commitment here, whether that would allow us to cover enough additional studies and enough additional populations, remembering that this is only for clinical samples.

So, the next one is the community sample, but here, we're talking about people who are already in a clinic and already diagnosed and we're listening for a way to do it best, better, faster, cheaper. Does that get us about where we want to be?

Participant: When you say double, are you talking 2.5?

Dr. Insel: Two point five, yes. Does that seem realistic for the program folks? I see heads shaking. Okay. If we have problems, we can come back to some of these, but that's at least a ball park to work with.

I want to move on to the community sample, it's the next one, validate and improve sensitivity and specificity of existing screening tools. So, here, we're into screening, not diagnosis, for detecting ASD through studies of the following community populations that are diverse, in terms of age, SES, race, ethnicity and level of functioning by 2012, school aged children, general population versus a clinical population.

Now, this will be at 2012. So, it's a short-term objective and your sense here of what this would cost.

Dr. Wagner: Okay, I'll start again. We're probably going to have the same conversation, because we were again thinking that this could be supplements and that - to

currently funded grants, and we proposed two supplements, for a total of 2.4. We were using the same kind of costing as before.

Dr. Insel: Other ideas here?

Dr. Dawson: Well, I mean, I think this one, we actually, you know, have a pretty good tool that could be used for this age. The focal communication questionnaire, you know, you could start with that, and then I think that the tricky thing would be just getting enough to - people at different ages, SES, race, ethnicity and level of functioning.

So, yes, it's probably on the same scale, in terms of cost, as the first one.

Dr. Rice: I would just add that although the focus is on the screening, the validation will also include the diagnostic component. So, that will be an additional expense.

So, we may want to make sure that that is included in the budget as well.

Dr. Dawson: When we do a population, that might be a little more you know, take a little more effort, because I

suppose you'd have to go out and think about, are you just going to go out in an epidemiological way and sample the general population and how big would that need to be and how many places you'd have to do it.

That would be harder, in terms of maybe as a supplement, depending on how it was designed.

Dr. Yeargin-Allsopp: This is Marshalyn. We don't have any existing studies, so we're not thinking supplement. We're thinking new studies. We don't have any we can build upon easily. So, we're thinking of new studies. Our estimate is much higher. It's 25 million for over four years, and a lot of that, as you alluded to, was starting a new effort in the general population.

Dr. Insel: Is that feasible to do by 2012, Marshalyn?

Dr. Yeargin-Allsopp: I think it would be very difficult to do. I won't say impossible, but it would be extremely difficult, because the methods would have to be developed or at least, we would have some

starting place from what we've currently done.

But I think it would be a challenge. I don't think it could be done by 2012 – in the general population.

Dr. Insel: Unless there were current projects that this could be built upon. And just to clarify, I want to make sure we all understand what the group is saying - There are, indeed, community based studies that this could be added to, is that right?

Dr. Wagner: We do have them. They don't cover the whole age range, at this point. But we do have them, prospective studies that are looking at the diagnosis.

Dr. Shih: This is Andy from Autism Speaks, and I just want to add that I think that some of this work that could be done internationally, we might be able to get other funders involved. But I think timing might be an issue and resources might not be as an important factor.

Dr. Wagner: So, you think doubling this estimate, similar to what we did on the one before, do people think that's a

reasonable estimate?

Dr. Dawson: Well, it could definitely get you started.

Dr. Shih: Yes.

Dr. Insel: So, Ann, give us a sense of what you think would be reasonable then here. Again, we're talking about getting this done in three years. It looks as what you're thinking about are two supplements to currently funded efforts, is that right?

Dr. Wagner: Right, so…

Dr. Insel: But the efforts also, if I understand you right, would need to be expanded somewhat, so that they have a broader community base?

Dr. Wagner: Correct, so, five million would double that.

Dr. Insel: Okay, any additional thoughts about this, or should we move on?

(No audible response)

Dr. Insel: Okay, let's go to the long-term objectives. So, this is where we get a little more ambitious. Validate a panel of bio-markers that separately or in

combination with behavioral measures, accurately identified before age two, one or more sub-types of child at risk for developing ASD, and this would be by 2014.

Dr. Mumper: This is Elizabeth Mumper at the Autism Research Institute.

We feel very strongly that this needs to have a very big focus for attention. We think that a database is crucial. I've got a couple of different estimates.

One would be that we could figure out what could be measured across sites now, with standard procedures. My estimate from some folks at Harvard for that is $15 million over five years.

We also have a more of a sub-category, looking at a specific area of bio-markers for glutathione and methylation status, which our work has suggested, is absolutely crucial and looking at it in this age group, the estimate for that is two million over five years.

Dr. Insel: Deb?

Dr. Hirtz: So, I'm wondering in

your estimates, what is the population that we use to get the bio-markers? Is that part of the major issue is because children are generally not identified, that yes, we need cohorts that have biological sampling in infancy or before they're identified.

So, do you have something in mind, in terms of what the populations are, or are you talking about developing prospective samples?

Dr. Mumper: In collaboration with several other organizations, we are looking at a collaboration. Martha Herbert at Harvard is actually the one that's heading up this initiative, and it was her estimate, based on some of the ground work that she has done with her database.

I can be glad to provide more information about what that entails. But I found out about this meeting a week ago. So, it's hard for me to give you specifics on any of the specific studies, at this point, but we can do that.

Dr. Insel: I think what I've

heard is the idea of using a baby sibs effort. So, that already exists in many different forms. So, there you have a high-risk cohort and then the question is, what we would need to invest in collecting bio-samples and having them analyzed for the baby sibs.

A lot of this is going on, of course, not the analysis, so much, and the other possibility, which you're involved with, Deb, would be the one of the large birth cohort studies, where you have again, a bio- sample repository that could be mined to develop bio-markers.

Dr. Hirtz: Yes, well, that was what the NIH project program offices had discussed, in terms of what have we got now and what would we need, and we have two existing cohorts and possibly more.

One of them is a study that NIH is funding in Norway, where there are in fact, biologic samples already in the repository. So, you have the opportunity to do a case control study of children who do and do not have autism and what kind of bio-markers they

had birth, or in pregnancy.

The other is the Newschaffer study, which is starting with the baby sibs and then there may be others, as well, that either are starting or could be started.

Probably, the furthest ahead, in terms of actually having samples, as well as children who are in the process of being identified early is the Norway study. But all of these studies, as large as they are, even with 100,000 pregnant women, we come out with maybe 500 children identified with autism.

So, I think we clearly need to combine different studies and do this both with what we have now and then also, set it up prospectively.

Dr. Yeargin-Allsopp: And building on that, of course, we have several opportunities through CDC. We have the Denmark study, where we have biologic samples already collected and then we have the new SEED study, funded under CADDRE, and as Deborah mentioned, we have a population of children with autism and a population of

children identified without autism.

Dr. Wagner: So, Marshalyn, did you have an estimate of what it would cost to supplement both studies?

Dr. Yeargin-Allsopp: We do and I guess our estimates seem to be high, compared to NIH's, but we thought for five years that we would probably need about $30 million and that would be supplementing Denmark and supplementing our new grantees.

Dr. Insel: So, just an editorial comment here, since I work on bio-markers for the Foundation for NIH, and we see a lot of projects come through.

We are spending about $60 million for bio-markers for Alzheimer's, $25 million for a single project through breast cancer. Bio-markers are really tough and proteomics is really expensive. I don’t know how much people have drilled into this. People have talked about glutathione and redox studies which are not very expensive but a lot of the discovery projects really will be, particularly if you want to collect multiple samples. We have not begun to

look at stuff like induced pluripotent stem cells but that's obviously a place where we will want to go in autism, just the way we are right now for ALS, and we ought to have some pretty good numbers about what that would cost to be able to develop stem cell lines in 1,000 kids at risk for autism.

Dr. Yeargin-Allsopp: Well, I would second that. We did quite a bit on our work in Denmark and this has been the method of development for individual bio-markers and it is quite extensive.

Dr. Mumper: Could we go on record at the Autism Research Institute as saying that we have scientists in place and clinicians in place that are using methylation bio-markers. Anecdotally, we think that as many as 80 percent of children with autism have problems in that area.

So, it seems to be an area where there's a relatively quick connect between the basic science and the clinical application, largely in the fact that it involves nutritional supplements, as opposed to the

development of new medications.

So, I would like to propose that as one of our biggest of low-hanging fruit and a sense of urgency directed toward that. We've already got the clinicians in place. We've already got the scientists who can measure it.

If we could have access to the samples like from Norway, we could move that forward pretty quickly.

Dr. Insel: It's a great area of discussion. Again, just an editorial comment, because the tools are changing very quickly. It's only been in the last six weeks that we can do whole genome-chromatin remodeling studies, just out in cells. It's only been done so far in T-cells.

So, that's going to be very different over the next six months. There will be the tools to be able to do this for the first time and a lot of people are running forward with this in inflammation and in cancer, and clearly, this is the opportunity for autism.

But I must say, I don't think we actually have the tools yet developed to do this. But we're not far off. I would think that if the plan is going to happen by the end of November, we'll know much more then than we do now and certainly, by the time all of this could be funded a year from now, there should be much, much better resources for doing whole genome-epigenomics, which is what this is.

The advantage of that is it gives you a discovery tool, not just candidate gene search or a candidate epigenome search for methylation. It's difficult to put numbers on this, but it's clearly a great opportunity.

Dr. Dawson: Tom, this is Geri. I just wanted to mention a project that Autism Speaks has been putting together, which I think you're aware of.

But what we've done is to develop a collaboration between Craig Newschaffer's ACE network and Joe Piven's ACE network, and then between both two networks, there's a total of 1,500 network infants and we're

providing supplemental funding to each of those projects, to allow them to both collect DNA, as well as on the whole family, as well as to collect a wide range of environmental exposure data, and we've already committed five million to that project, Autism Speaks has.

Then what we still though haven't completely been able to pay for all of the, well, the genotyping or anything such as what you're talking about. But it is, I think, an opportunity to take advantage of following a real sample like that.

Ms. Tanski: This is Tish Tanski from the Autism Consortium. We too have been looking at bio-markers, based on white blood cells actually, and our cost estimate is for 1,000 kids or people, it wouldn't have to be kids, somewhere between 10 and 16 million, depending on how much new recruitment you would have to do.

Dr. Insel: So, one of the questions here will be whether we're talking about a predictive bio-marker, that is

something that would be done before age two or even before age one, or something that's used more as a diagnostic bio-marker.

I think that for the discussion that the workgroup had when they were developing this objective, they were focused more on the prediction. They were trying to identify a high, high risk child or baby, so they'd know who they might be able to intervene with and what I think they'll need to do, given that we've got these cohorts already, is to get a sense of what the cost would be, to really make all of the kinds of measures that it says here, it's a panel validating a panel of bio-markers.

So, that will require both a discovery phase and then a development phase, and actual prospective study, once you have a panel that you think works.

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So, that is expensive. That's going to be a huge undertaking to be able to validate it, as well as to just discover it. I think you're talking about getting this done in five years.

I mean, I can tell you that for Alzheimer's and cancer, we don't think we can

do it in five years. But for autism, maybe either because it's a rapid onset, maybe we can do better.

What do you think? We have numbers that range from 15 million to 10 million and then there was one that I think was 30 million, is that right?

Dr. Yeargin-Allsopp: Yes, and I still stand by the 30 million.

Dr. Insel: You know, what I'm going to suggest here, and I don't want to be heavy handed, but because I think the concern here is that there is so much happening in this area and this is obviously going to be a huge growth area for this plan and for autism research area, that we shoot high and not low.

And so, you know, to use the CDC number, it seems to me as a way of capturing everything that's likely to happened and this even 30 million, I can tell you, is not where we are for Alzheimer's.

But at least as a starting point, maybe that would make sense for this. Is that okay with everybody?

Dr. Mumper: That's one of our highest priorities. So, thank you very much.

Dr. Insel: We're not actually giving anybody money. We're just trying to figure out what this is going to cost for someone, some day.

Moving on, develop measure of behavioral and/or biological heterogeneity in children or adults with ASD, beyond variation and intellectual disability that clearly relates to etiology and risk treatment response and/or outcome by 2015.

So, thoughts here about what this would cost.

Mr. Dunaway: This is Wolf Dunaway again. I think that this one is probably going to be on the expensive side. I really don't want to give a number because I think a lot of people in this room are better suited for that.

But I think it will involve lots of community outreach. It will involve schools, going into work and helping trying to help people on the disabled roles, in prisons,

different hospitals, mining information from the family.

I mean, this is going to be something that if we do it right, and we're talking about getting etiological data, you know, that goes back and it's really worth it and it can be validated.

It's probably going to be expensive. I mean, I just wanted to put that in.

Dr. Insel: Yes, I would think so too. So, what for those of you who cost these things out, how do you read this? What would you say?

Participant: I have an estimate of 2,000 per subject for 100,000 children, which is $200 million, as long as we're shooting high.

Mr. Dunaway: I hope there would be some more than these children. I mean, I've just got to put that in there. Adults as well.

Dr. Hirtz: So, there are lots of different ways to approach. It's not one

study, but it could be many studies and some of the studies that we have now, that are just beginning, are impressive, address this question, but only one part of it.

An example is, we're just starting a clinical trial in one of the ACE centers in Detroit and several ACE Centers at that treatment trial, but they're looking at PET scanning in the children before they start treatment, as a bio-marker to predict how they'll respond to treatment, and then once the trial is over, they can see if the bio-marker in fact, did work and did predict.

So, that's not something that's useful for everybody all the time, but it's just one of the several instruments. So, I think we have to look at this as not one study or two studies, but a whole range of studies, some of which we can tag on to existing studies to check specific bio-markers.

So, that kind of thing is already in practice and not too expensive.

Dr. Dawson: Yes, the other idea, kind of along a similar line is, you know, to

think of this also as a supplement to ongoing treatment studies that are funded, you know, through different mechanisms.

So, for example, there is an ACE network that is a randomized multi-site, randomized controlled trial of early intensive intervention, that involves three sites and they're actually are a lot of, you know, moderators and predictors of response to treatment that they're looking at.

But if, for example, they collected DNA on all those kids, which they're not, which I thought, you know, it would be an opportunity to really look at what is the difference between the kids who do so well in these treatments and the kids are just so severely affected, or other bio-markers?

Dr. Wagner: So, NIH may approach this the way Deborah was describing. We were thinking about we looked in some studies that are doing this now, to some extent. So, nobody is looking at everything, but they are looking across the board and another she already gave some examples.

But another one is, Deborah Fein is looking at what she calls optimal outcomes and how are those kids different that really respond well to treatment and do well.

And using it's sort of looking at what we're funding now and the cost of those studies, we came up with an estimate of 20 million and funds to fund five studies.

Dr. Insel: Ann, was the sense from the NIH people that that was that that would do it? Would that $20 million investment, we could, in 2015, have this done?

Dr. Wagner: We could have five million and I think we could have five measures.

Dr. Insel: So, you really thought that for that investment, you could deliver?

Participant: Because we already have several ongoing studies.

Dr. Insel: Okay. Tish?

Ms. Tanski: Tish Tanski from the Autism Consortium. We've actually been looking at a five-year project and it's we've costed it out at 20,000 kids, samples, people,

and our number is that to do the recruiting and genotyping and chips would be somewhere north of $40 million over five years and that would help you get to the, the purpose of that would be to try to get to the heterogeneity question.

Dr. Insel: I know that Simon's foundation has just done a very big phenotyping effort. Is anybody on the call from Simon's? Okay.

Participant: We're at the Autism Consortium are in the midst of a phenotyping effort as well.

Participant: But you know, I think the tricky part of this goal is the treatment response, right, because I think there's a big difference between a big phenotyping effort, where you look for sub-types that are related to say, severity of the symptoms and a sense of and treatment response.

Because you can only really answer that if you're looking at a clinical trial, otherwise you get such confounding between variables, it's hard to you know, parse it

apart. They may be related, but different projects, if you're just confining this to treatment response. So, I would agree that they may need to be separated.

Dr. Insel: And to clarify, and the NIH, the 20 million figure for the existing five studies, are those all treatment studies? So, you would because this Geri raises an important point, that it's part of the point of this was to provide the prediction of treatment response.

This is to go into the personalized care effort ultimately.

Dr. Wagner: It says treatment response and/or outcome. So, I didn't really read it that way. But I think Geri is right, is that one can take ongoing trials and add in the measures that are not already there.

Dr. Insel: Geri, what do you think this would cost if we were to do it in the best possible way, to get this done by 2015?

Dr. Dawson: Well, I mean, I do think the idea of looking at the existing

studies and then, you know, I think DNA should be put on pretty much every trial, because the you know, the cost of doing those studies is so high to begin with and they're so hard to do.

Yes, I don't know. I'd have to look at all the different you know, there are a lot of different treatments out there and whether you're talking about a pharmacological treatment versus an behavioral, it's hard to say.

But I think your 20 million is probably reasonable. But again, I think it's not a one-time thing. It's a whole process of different kinds of studies and some of them supplement, some of them large phenotyping efforts. It's really hard to say.

Ms. Tanski: Geri, this is Tish Tanski. Just for clarification, would you 20 million have included DNA collection and analysis?

Dr. Dawson: Well, the genotyping, right, is very costly, and again, it just depends on what you know, how many kids you're

looking at and what studies you're doing. It's all you know, we can figure out pretty much a fixed cost for collecting blood and genotyping the analysis.

I think the issue is, what's the sample size? How many people are you going to do this on?

Ms. Tanski: Absolutely, that's right.

Dr. Insel: So, help us there. What kind of numbers of people do we need to do this up? What do you think is going to be sufficient or optimal to get five measures?

Dr. Dawson: Well, the problem is that when you think about treatment response, that's just so broad. If you're talking about response to intensive behavioral intervention, then you know, it's possible that by supplementing that ACE network, that that would be one way to go.

But there's a lot of different treatments. Treatment responses to what, might be more pharmacological or biomedical. So, yes, I'm having a hard time with this one.

Dr. Insel: So, let me encourage the group. Well, two things. One is especially for those people on the phone, but even those here in the room. It's good to identify who you are, before you speak, so everybody knows who is talking.

But for the entire group, I think there's a danger here of being limited by what we're currently doing and the whole point of the strategic plan is to think boldly and be ambitious about things that we haven't done.

I don't think we should discount something because we've already done it. But I also don't want us to ignore the fact that there are lots of needs that aren't being addressed.

So, on something like this, which we keep coming back to, this is kind of the phenotyping issue, right, and I've been hearing about this for five years, that it's the most important piece that needs to get done.

There isn't really anything right now that has totally finished off the question

of providing the sub-groups or sub-types that have any real clinical application or practical validity.

So, I'm not again, I'm not convinced that what we're doing now, if we just keep doing it, will necessarily get us where we want to be. I'm just wondering, what we're not doing, whether it's more individuals, more tests, more - a different approach, what is it going to take to be able to get this done by 2015?

Ms. Tanski: From the Autism Consortium point of view, we would like to see 10,000 reasonably well-characterized samples.

Dr. Dawson: You know, I can say that having been involved in the autism phenome project for a while now and having watched them sort of struggle with the design of it, I think they pretty much landed on, it has to be a longitudinal study, to really parse apart some of the phenotypes.

So, it's going to be hard to do a snapshot approach, where you have people at varying ages, for lots of different reasons,

that I won't go into now. But methologically, it gets very complex.

I think, you know, it will have to be a longitudinal study.

Dr. Insel: So, would Tish's estimate of $40 million buy that? Would that be able - would that make this doable?

Participant: I think so. I mean, that's a lot of money. Yes, 500, I would hope we could do five for $40 million.

Dr. Insel: Can the $20 million now, Ann, that's being spent, is that longitudinal or is that mostly cross-sectional? You have to use your mike.

Dr. Wagner: Combination of treatment studies and longitudinal studies.

Participant: In terms of looking at the treatment responses from a new paradigm, we feel very strongly that we need to move in the biomedical area, into single subject designs with multiple baselines.

Because of the issue of heterogeneity and individuality of response, that complicates the study design. But we

feel that some effective interventions for sub-groups are lost when the results are averaged. That makes more complexity and therefore more (inaudible).

Dr. Insel: Yes, we're going to come back to that under the treatment part. That's a really key point. Don't lose that. We'll need to raise that in about another hour.

Dr. Wagner: I guess the other question with regard to the $40 million is whether that longitudinal study can be done by 2015?

Ms. Tanski: Yes, my board would say it should be done in three years.

Ms. Tanski: Tish Tanski of the Autism Consortium. Can we assemble 10,000 well-characterized samples in over five years? We think so.

Dr. Insel: Okay, want to go with the Consortium's estimate here? What's the sense? Heads are shaking. We can't see them shaking on the phone. So, tell me whether you think that's way off.

Again, this may be a place where there's a range. We've gone from 20 million to 200 million in the range. But 40 does sound like it. It gives the wiggle room to expand, if we need to do much, much than what we're currently doing.

Dr. Yeargin-Allsopp: I agree with 40. This is Marshalyn.

Dr. Insel: Okay. I want to move on, because we're already way behind time. Identifying developed measures to assess at least three continuous dimensions of ASD, symptoms and severity. That can be used to assess responses to intervention for individuals with ASD across the life span by 2016. Estimates?

Those of you on the phone, people in the room are throwing their hands towards the sky.

Dr. Yeargin-Allsopp: We did not come up with an estimate. We don't have any we don't have much expertise in this area.

Dr. Wagner: We came up with $1.5 million, because again, we were thinking that

these could be supplements to ongoing grants and/or a component of new intervention initiative. So, what is the challenge -

Dr. Insel: This is Ann Wagnerfrom NIH.

Dr. Wagner: Sorry. What are the challenges of doing this? Sometimes you can combine the efforts that go into different objectives, into one thing. So, we were thinking this would be combined with something else. But that the component would be 1.5 million.

Dr. Dawson: Yes, this is Geri. I guess the lifespan part makes it a little more ambitious, you know, because we'd have to sort of standardize them, right, developmentally, whatever this measure is. If it's quantitative, you'd have to have some sort of normative or some way of you know - anyway.

So, it's really measurement development over five year. So, you know, I would estimate it a little higher, maybe more like you know, a couple million a year. So,

10 million, just because if you're really talking about young kids, elementary school kids, adolescents, adults and capturing these and you'd have to develop the measure. Then you'd have to pilot it and have to get everyone trained in reliability across all those sites, and then refine it again. That's it's a lot to develop a measure.

Dr. Insel: And Geri, are there no measures like this at any of those age points right now?

Dr. Dawson: Well, I know Cathy Lord has been working on one, which she's been mentioning that she's been working on one. I don't know whether it's across the age groups. Does anybody know?

Dr. Shih: This is Andy Shih. I know that she's working very hard and it's actually being applied to the CDC study already.

Dr. Dawson: Okay. So, that would make has she done it across the lifespan, Andy?

Dr. Shih: I don't think so.

Dr. Insel: Andy, do you have any idea what that costs for her to develop this?

Dr. Shih: I don't, sorry.

Dr. Wagner: Well, there are other measures out there that measure - continuously measure ASD symptoms, but they haven't been shown to respond to treatment.

So, one of the questions was whether one can do the work, to see if they can be truthful or actually responsive to treatment. So, I guess I'm not sure if one has to start from scratch.

Dr. Insel: So, here, we've got a span from 1.5 million roughly to 10, is that right? My sense here, I don't think we know enough to know what the number ought to be.

Would the group be comfortable with leaving that as the range and we will have to drill down and find out what the real whether we can get information from Cathy about what it costs? I would think that if she's done it and we have a number that of what it costs at what age range, we could at least have a better estimate.

Dr. Dawson: Yes, I think.

Dr. Insel: Okay, moving on. The last one in this first panel, effectively disseminate at least one valid and efficient diagnostic instrument that's briefer and less time intensive in general, clinical practice by 2016.

Dr. Wagner: This is one where we thought was actually an extension of a prior one and the prior objective was developing this instrument. So, what then needs to happen is, that has to be validated in a general, clinical study.

So, we were estimating a validation study of about two-and-a-quarter million dollars for that study. But that doesn't include developing the measure because that was done with another objective, if that makes sense.

Dr. Insel: Other estimates or other thoughts?

Dr. Dawson: This is Geri again. I was reading this as the challenge was the effective dissemination, and so, it was more

around training of physicians and maybe even having to understand and study the barriers or what is the best method for having physician's learn to use this – is it the nurse that does it – you know, really kind of working more on the process of dissemination as being the more labor-intensive part.

Dr. Yeargin-Allsopp: This is Marshalyn. We have a little bit of experience with background – Learn the Signs, Act Early campaign, but we're partnering with the AAP. So, I think our estimate would be very low for our contribution.

So, I don't really have an estimate. But there is some mechanism in place, some early work that we could build upon to do this.

Dr. Strickland: This is Bonnie Strickland, and we also work with the American Academy of Pediatrics. We have a rather large national center with them and I think we could certainly contribute there.

I think the question for us, in terms of an estimate, would be to what extent

do we want to go beyond dissemination and look at implementation and impact?

Dr. Insel: Bonnie is from HRSA. She wasn't here at the beginning of the meeting, just so people know. Any sense of what that could cost?

Dr. Strickland: If it's only dissemination, I would say a million dollars. But if we want to look beyond that in an ongoing evaluation of uptake and utilization, I would say it's more of about five to ten million, depending on the complexity of whether we wanted to go beyond the community of pediatricians to other primary care providers, and depending on whether it's lifespan or just pediatrics.

Dr. Insel: Again, in the spirit of wanting to have the greatest impact with this plan, I don't know why we would want to limit ourselves just to pediatricians. So, we want to push this out and the way I read this, effectively disseminate, at least one instrument, so that it's in general, clinical practice means really broad.

And so, if that is the sense of what HRSA thinks it would cost, I think we ought to be in that range, if that makes if that works. So that's, you said, five to ten million dollars.

Dr. Mumper: I'd like to suggest that from our perspective, the time line of 2016 does not really conform with the sort of urgency that we all feel for this.

This is crucial to implement as quickly as possible. I think it needs to be disseminated to pediatricians and family physicians and case neurologists.

If we could build on existing coalitions with the AAP and get this done earlier, I would strongly endorse that.

Dr. Yeargin-Allsopp: I agree.

Dr. Insel: Well, again, remember, we're not going to be able to change what the the IACC had recommended. But we can always make comments back to them, that will be considered in time, I'm sure.

Can I before we move on, I just want to make sure how you all read this,

because some people would say that we currently have a diagnostic instrument and it's just a matter now of getting it used more widely.

Others would read this and say, "Well, this is going to be dependent on developing all the instruments that we just talked about, in the previous objectives." What was the interpretation here that the group made?

Ms. Fallas: I think having the briefer and less time

Dr. Insel: This is Jennifer.

Ms. Fallas: I'm sorry, Jennifer from the DoD, briefer and less time intensive. In parenthesis there, we'd indicate you're looking for something new, rather than existing.

Dr. Rice: This is Cathy from CDC. Actually, this one is dependent on the first short-term objective, developing with the existing tools, to be briefer and less time intensive and then, it can be disseminated.

And another comment, I think we

would should go on the broader end of the HRSA estimate, given that if we're talking about diagnostic tools, we're probably not talking about primarily pediatricians, as we would if we were talking screening tools.

Here, we're talking about specialists, for the most part and so that's more diverse multiple communities to reach out to.

Dr. Insel: And expensive. We do this for many other disorders – dissemination is incredibly expensive – this kind of research. There's no way to do it well on the cheap.

Dr. Rice: And if it's an instrument currently owned by a publishing company that can add a great deal of cost.

Ms. Tanski: This is Tish Tanski. I know I may be in the minority here, but as I read that, I did read dissemination of existing instruments, but I'm hopeful that we're not just thinking of behavioral characterization and we might also consider in this and I don't have a cost figure, but dissemination of new tests or other biologic

based, things that might help in diagnosis and treatment.

Dr. Insel: I think that's why this ended up at the end, with the hope that this would build on what came in the short- term. So, the short-term gets us some of those bio-markers and other things, and then we have something to disseminate.

If we're all on board

Participant: We might have something.

Dr. Insel: Let's move onto the second panel, how can I understand what is happening, and the first item there is establish an international network of brain and other tissue, such as skin fibroblasts, acquisition sites with standardized protocols for phenotyping, collection and distribution of tissue by 2010.

So, this again, is short-term. We're talking this is very short-term. So, we this would basically be over a two year period. What are your thoughts?

Dr. Kau: Well, the minimum

estimate is two million a year and…

Dr. Insel: This is Alice Kau.

Dr. Kau: Alice Kau from NICHD and five years is 10 million. So, that's minimum, because international, I mean, two countries international, I don't know how broad we want to do it.

So, obviously, the cost, if we increase it, the scope increases.

Dr. Wagner: These are estimates based on the ongoing discussions about utilizing the current brain bank and the standing brain bank and what people are thinking it would cost.

Dr. Kau: Right.

Dr. Insel: Alice, would the brain bank be expanded to do other tissues, skin fiber blast, CSF?

Dr. Kau: Yes, actually, the current bank is just tissue bank. We already collect anything beyond brain tissues, so, we can make it to be, you know, anything we want it to be.

Dr. Insel: Tell me – let me ask

about it though, because it is, since it's based on a brain bank, it is all post-mortem. Is there a sense from the group that that is sufficient or is there a need for repository of hair follicles, fibroblasts, plasma samples, other kinds of tissues that could be used for children at risk, that could be used longitudinally, those kinds of things?

Dr. Kau: Yes, that goes beyond the scope of the current bank. The current bank actually is only post-mortem tissues and also, they're only brain tissues. We would be collecting other organ tissues.

But we are going to, I mean, that would be a great increase. But I would think conservatively, two million a year is still doable, but if you want to be more in an aspirational, it would be three to four million a year.

Dr. Lawler: Does that include two international sites, did you mention?

Dr. Kau: Two million could two million is based on two sites. So, up to, but no more than two.

Dr. Rice: Two international ones or one U.S. and one -

Dr. Kau: One U.S. and one international.

Dr. Dawson: This is Geri Dawson. Hi, Alice.

Dr. Kau: Hi.

Dr. Dawson: So, just thinking about this, now, when you're talking about the two million, so, currently, you're putting in, I think 1.5 million into the NICHD bank, is that right?

Dr. Kau: Right.

Dr. Dawson: So, are you thinking than that - but that is for a lot of different purposes, not just autism, right?

So, are you thinking when you say two million, that it's only specific to autism or are you talking that 1.5 to support the whole bank with lots of different disorders, and then add $500,000 to it?

Dr. Kau: It's maintaining the current bank, the scope of the current bank, and adding an international component to it.

Dr. Dawson: Yes, I guess because when we had been talking about this, it seemed like that we just with adding a more intensive recruiting and phenotyping effort, what we were already at, I think, 2.3, but that didn't really count on international sites and it also didn't count, you know, if we wanted to do any more phenotyping or really any more elaborate processing of the brain tissue even that would allow researchers to have ready access to data. So I think that might just be too conservative.

Dr. Kau: (inaudible)

Dr. Dawson: you know,

Dr Kau: Yes the extent of the protocol would increase the cost. So conservatively, I feel two million can do the basic work and then if we increase the scope the funding would need to increase.

Ms. Tanski: This is Tish Tanski again from the Autism Consortium. We've costed out DNA plasma and cell lines and for those 20,000 individuals we talked about earlier, that would be about $6 million. That

does not include hair follicles or other materials, which we think should be included.

Dr. Insel: It doesn't include brains?

Ms. Tanski: No, it's just –

Dr. Insel: In the - again, going back to the workgroup that talked about this, the big push was to have high quality brain material. That's what we heard from several people, the frustration that after so many years of discussing it, we still don't have the quality of tissue that is needed to do quantitative neuroanatomic studies.

So, the two million, Alice, what you're telling us is that the two million is for building the brain bank, basically, or for supporting the brain bank.

Dr. Kau: Right, you have to have a yes.

Dr. Hirtz: This is Deborah Hirtz from NINDS. I think we're probably being a little unrealistic in our estimates and in this in particular because even if we only consider brain samples, there’s so much labor

involved, there is so many materials, transportation costs, it's probably costs that I think are going to go up in the next few years, just because of the cost of labor and transportation and if we particularly is we include international samples, we probably should at least double this, even just as a baseline for a brain bank.

Dr. Insel: Yes, Deborah, this is Tom. I agree, what we heard was that this is what we're doing and it's not working. We have 97 samples after five years and they… only a handful of them have the quality that we need.

So, we can't just keep doing what we've been doing. We've got to figure out how to bump this up to a different level. So, I don't know whether doubling is the answer or...

Dr. Hirtz: That would be brain tissue alone, and then the question is, do we want to include other kinds of samples, like skin fiber blast, and I think if we do, we should add a few more million.

Dr. Dawson: Yes, and I think the other thing that we would want to make sure to cost out would be the recruitment network, you know, putting a little more effort into the actual recruiting and getting a lot of sites onboard and then if you talk about having at least one international site, I think we're really talking about quite a bit more money too. So we said double which might be five million a year, I think that might be minimal to get started and we might very quickly wish we had more.

Mr. Shih: This is Andy Shih. I would agree with that too, because when we set up the ACPUP network - there's three specific costs that goes into it. One is to maintain the basic infrastructure with one coordinating site, and their recruiting cost, which obviously, will be significant.

Then the third, the approximate cost, which would depend on how we could depend on how successful the recruitment effort is going to be. So, I think five million is probably the minimum that's needed to get

going.

Dr. Insel: And so, it's five million per year. Now, this was to be set up by 2010, but the I assume the group feels that this is not a one or two year project. This is ongoing.

So, it would be five million every year thereafter, is that right?

Dr. Dawson: Yes.

Dr. Yeargin-Allsopp: This is Marshalyn.

Does that include the cost of recruiting brains and other tissues from typically developing individuals, because I understand that that is a tremendous problem as well?

Dr. Insel: Alice?

Dr. Kau: Yes, the current bank, with the 1.5 million, that does include normal controls for recruitment.

Obviously, we want to increase the scope you know, increase, so, I think if we increase the total budge to five million, that will definitely cover the (inaudible).

Dr. Insel: Okay, we're moving on, support at least four research projects to identify mechanisms of metabolic and/or immune system interactions within the central nervous system that may underline the development of ASD during prenatal or post-natal life by 2010.

Ms. Fallas: This is Jennifer from the DoD. We estimated three to four years, at a range of three to four million.

Dr. Insel: Three to four million per year?

Ms. Fallas: Total.

Dr. Insel: Total, okay.

Ms. Mumper: This is Liz Mumper from ARI. We would suggest four metabolism toxicology based studies, 1 to 1.5 million spent over four years, for a total of about six million.

Ms. Fallas: I'd be willing to up our amount.

Dr. Insel: Can we get other estimates in here? Deb?

Dr. Hirtz: This is Deborah Hirtz.

I just want to add, not particularly from a financial point of view, but we have discussed this extensively at NINDS and feel that we would benefit a lot from looking not just at autism, but at other related diseases and disorders that might have some common mechanisms, so that we should broaden this particular initiative, to look at some common mechanisms that might help us elucidate pathways in autism.

For instance, include tuberosclerosis or Fragile X or Rett syndrome or other diseases that might help us understand autism.

Dr. Insel: Ann, you were going to make a comment.

Dr. Wagner: I was just - we were coming in at about the same. Our estimate was 4.3 million.

Dr. Insel: So, we're between four and six as a range. Shall we say six million is a place to go? Okay, launch three studies that specifically focus on the neuro-development of females with ASD by 2011.

Dr. Yeargin-Allsopp: This is Marshalyn from CDC and we feel that our some of our existing projects can contribute to population level phenotyping, so we can build upon our ADDM network, with a research component, our early ASD surveillance, our SEED study, our Denmark studies, and the cost of building on these studies every year would be $560,000. So, not terribly expensive.

It would be about $50 million, I mean, $50,000 for each grantee per year, over three years.

Dr. Insel: Other estimates or suggestions?

Dr. Wagner: We were thinking of it as a new project, as a program project or central grant kind of project, where there might be more than one related project. So, human and animals maybe together. We were so, we estimated seven and a half million.

Dr. Insel: This is interesting. This is so useful to have everybody involved in the conversation, as their this is just the flip-side of what we dealt with in the

screening tools.

So, here, CDC has a study ongoing that can be supplemented and it makes a lot of sense, I think, to build on the infrastructure you've got, rather than rebuilding it in a separate effort.

So, Marshalyn, again, the final figure for you was $560,000, something like that?

Dr. Yeargin-Allsopp: Correct, that's what we came up with, yes.

Dr. Insel: And that’s

Dr. Yeargin-Allsopp: That would be three grantees and we would be supplementing some of our existing research studies.

Dr. Lawler: This is Cindy Lawler. I like the idea of including in this estimate, some basic science, because we really don't have that in other places in this plan, that would kind of provide the substrate for how you may see these differences in males versus females, in terms of the etiology or the expression.

So, I think that at NIH, we talked about a program project that would address this in a more interdisciplinary fashion. And a subsequently higher budget of 7.5 million.

Dr. Yeargin-Allsopp: And so, Cindy, you would be able to do that, you think, in three years, right? Short time line here.

Dr. Lawler: Well, we have five years.

Dr. Yeargin-Allsopp: Oh, it's at well, 2011.

Dr. Insel: No, it's to launch the studies by that time.

Dr. Lawler: Right, launch.

Dr. Yeargin-Allsopp: Okay, I see, okay, just launch them, all right.

Dr. Lawler: I think if we're going to really get a handle on this male versus female, then it needs to be more than just kind of a descriptive level of phenotyping and some basic mechanism work would seem in order.

Dr. Yeargin-Allsopp: I would certainly support that, and that's you know,

we're not able to do that. So, we can expand and we can go to the limits of our capability with our existing studies and describing the population, but I certainly agree with getting to some more basic science, mechanism work.

Dr. Lawler: Yes, I mean, I really think we need both.

Dr. Insel: Okay, that sounds like 7.5 million plus $560,000. So, should we say eight million?

Dr. Yeargin-Allsopp: Sounds good.

Dr. Insel: Okay, onward, long-term objectives, complete a large scale, multi-disciplinary collaborative projects that longitudinally and comprehensively examine how the biological clinical and developmental profiles of children, youth and adults with ASD change over time, as compared to typically developing individuals by 2020. So, this is one of the ambitious ones.

Mr. Dunaway: This is Wolf Dunaway. Okay, on this one, I really feel rather strongly. It says I think that people here kind of use the standard they have a standard

metric way that they normally do things and I don't really think that when you're dealing with autism, that that standard metric always serves you well.

Because it's kind of like, when you have autism, it's sort of like trying to typify the pattern, the motion pattern, the jell-o, when you put it on a shaker table.

I think if you know, I think because autism is so unique and it affects each individual in such a unique way, that you really should and especially in this case, what you're thinking of, because the truth is, if you're going to get a really good sense of what multidisciplinary effort on everybody's part to actually make this one come true and I guess I just want to let you know that it's going to be a harder job than you think.

Dr. Yeargin-Allsopp: Wolf, I agree with that. This is Marshalyn. We have a big number here. We have 138 million. So, we appreciate the fact that this is, as it says, comprehensive, so this is and it's over 11 years.

Mr. Dunaway: You have me with you.

Dr. Yeargin-Allsopp: Okay. So, we did think that we could supplement some of our existing studies. But again, it would require a big effort.

We said five grantees, supplementing our intramural efforts, supplementing our SEED grantees and then building on this, to create a longitudinal component, which we currently don't have.

Dr. Lawler: This is Cindy. What about the national children's study, Marshalyn? Do you think there is opportunity to…

Dr. Yeargin-Allsopp: I think there is. There's also been discussion about the sample size with that, but I think that there is and Geri is on the phone, there's already discussion underway about doing what we can do with the national children's study.

Of course, there is the ability there to add on, to have adjunct studies, which we may want to consider, to make it a larger sample.

Then when we talk about adults, the longitudinal aspects of this, right now, it's only funded to age 21. So, it wouldn't give us information about what's happening during adulthood. So, we would have to supplement that or advocate for expending the National Children's Study.

Dr. Insel: But that will come up after 2020.

Dr. Yeargin-Allsopp: Right. Dr. Insel: At this point, we really only need to worry about the first five years. That's the part of the funding that we'll be responsible for. What would it cost to do an add-on to the National Children's Study that would enrich for autism?

Dr. Yeargin-Allsopp: I don't have that. Do you have any ideas, Geri? I don't.

Dr. Dawson: No, that's a hard one, because I think it also depends on what we mean by multi-disciplinary, right?

Dr. Yeargin-Allsopp: Right.

Dr. Dawson: Whether this was perceived as a study that has, say, brain

imaging and more in depth measures that really would I don't know about tacking those on to the national children's study because I think they're very concerned about burden.

And so, I think that's one decision, is whether the more focused genotyping projects versus yes.

Dr. Yeargin-Allsopp: Exactly. It's like taking the national children's study and marrying it to the female projects.

Dr. Dawson: Yes, I don't think I have a feeling they might, given these burdens, I'm not sure, but given the burden, it's a question of whether they would let that level of additional measures be done.

Dr. Yeargin-Allsopp: Well, not within the core, but I think that you could use that as a mechanism for recruiting families and then with, of course, the consent of the families that are willing to do it, then be able to have another component.

Dr. Dawson: Yes, it's possible, and it definitely would be worth floating the idea.

Dr. Yeargin-Allsopp: Yes.

Dr. Insel: So, the numbers we have here, we're at 139 million, which is a little bit this sounds a little bit like a Framingham study for autism, and so, that's about what you would spend.

Dr. Wagner: There might be a different design way to go about it then following children or people from infancy all the way to adulthood. So, you can do sort of a cross-sectional longitudinal design where you and then you can you don't have to take 30 years to get the study done.

Dr. Yeargin-Allsopp: Right.

Dr. Wagner: And so, that would be less expensive.

Dr. Dawson: Yes, I agree. I was thinking the same think, that if you wanted to do this sufficiently, you'd use that cross-lab

Dr. Wagner: Right, exactly. Dr. Dawson: And I think with a cross-lab design, you could and the other thing that would be efficacious about that would be the National Children's Study, is

that this isn't asking to look at kids at risk after diagnosis, So, you know, as I said, it's a little different focus.

Dr. Yeargin-Allsopp: Yes.

Dr. Insel: So, using that approach, what kind of costs would you estimate?

Participant: Well, not $140 million because it's way too high. I don't know. Ann, what do you think? If you use the cross-lab design and you had large samples it's probably, I guess I would say $25 million or $20 million.

Dr. Wagner: You know, I was thinking that pediatric MRI study, which uses that design, has - you know, starts at birth and it doesn't go all the way to adulthood. But that, so far, has cost about $25 million or it cost about $25 million to get the data.

Dr. Yeargin-Allsopp: Over what period of time?

Dr. Wagner: I don't know. It's probably been going it's probably about five years, yes.

Dr. Insel: It's about five years. Now, that's one we're usually, for these kinds of broad, longitudinal descriptive efforts, we're in the 25 to 30 or 35 range, for most of the things we do.

Now, that one, it's a lot of imaging. So, that's part of what drives the cost there. This one could be maybe broader, but not quite so deep.

Mr. Dunaway: This is Wolf again. I think the problem with not so deep is the fact that again, you're not getting all of the you know, you're not getting all the variations of how people that are adults live on the spectrum and I think that if we're going to help people, we're going to need to get as much information and we're going to need to be as aggressive as possible.

Now, I know that probably costs more money, but I think that that's what we really need to do, if we're going to serve the people that are adults that are trying to struggle with living with autism. I know, because it's been difficult for me, but I know

other people that are on the spectrum and I've talked to people in, I believe it's WrongPlanet and a lot of different other places, and I sit out there and I see so many adults struggling that are living on the spectrum, and I don't see a whole lot being done to help these people.

I guess I feel like I have to advocate for them. So, I think that this is a lot too low. I really do.

Dr. Yeargin-Allsopp: Well let me just add to that it seems to me, it says comprehensively examine this and I know this is probably how that do this for labs but when I read it I was thinking it was big and broad and it is sort of the Framingham study for autism, or maybe I'm misreading it. But that's the way I thought of it. I know that there are ways that we can do cross-sectional samples at different ages and that can give you a snapshot, but that wasn't the way I interpreted this.

Dr. Dawson: The cross-lab design is not really a cross-sectional design because

you have a longitudinal component where you overlap the ages and the nice thing is that then you don't have a confounding between age and time. So anyway I think it would probably be the most efficient way to do it.

Dr. Yeargin-Allsopp: So, the design sounds good there, but the estimate sounds a little low.

Dr. Rice: This is Cathy, and also that you're not just talking about the autism spectrum, but typically developing children as well. You're talking about new recruitment here so that could get very expensive.

Dr. Insel: Someone may be able to correct me. I think when this came up in the workgroup, the idea of using the National Children's Study and making sure that that Would answer questions for autism, but I may not be remembering that correctly. Was anybody there for this discussion? Tish?

Ms. Tanski: Yes, you're remembering correctly from the workshop.

Dr. Insel: The National Children's Study is a billion dollar effort and I'm not

sure that it's realistic to put in another billion dollar effort you know, another National Children's Study, because that's never gotten off the ground after eight years of discussion and we don't want to have the same problem here.

So, I think we have to there has to be some way of leveraging that effort, since that is now finally in `08, collecting samples for the first time, if this was meant to be built up upon that, and I think that's where the 2020 came from, because that was the time when it was originally 2030, but that was when we thought we would have enough from the national children's study to have 100,000 children that had been surveyed and that we'd be able to get enough people with autism that could be followed.

It doesn't get to what Wolf was talking about, which is the adults, and that may call for a different kind of project.

Ms. Tanski: Yes, this is Tish Tanski from the Autism Consortium. If you think about the 20,000 sample collection,

which we've thought about it as a separate project and it truly is, because it focuses on well-phenotyped affected individuals, there maybe some way of - and that was $40 million.

That did not include a lot of medical, didn't include any imaging. It didn't include any real medical assessments.

You might be able to think about the 20,000 sample and adding on some things that might help you combine with the child health adjunct that Marshalyn is talking about. So, you may actually be talking about something like two $40 million initiatives.

Dr. Insel: We really have numbers of 139, 80 and 25 or 30 and there's also a five million dollar number that was floating around at one point.

So, this sounds like a place where we need a range on struck by the again, the vagueness of what we're talking about, how much of it would be leveraged, how much of it would have to be built anew.

Clearly, the adult piece that Wolf is bringing, it doesn't exist from anything

I've heard about. So, if were to put a range of 50 to 100, is that going to be able to capture what we need here? This is, so far, the big project for this plan.

Dr. Yeargin-Allsopp: I think that's reasonable. This is Marshalyn.

Mr. Dunaway: Yes.

Dr. Insel: Okay, that will be the range. Again, we may have to refine that for the IACC, but that will also give us a chance to collect some information. Fifty to 100 is what we're where the discussion went, and we'll have to do a little bit of homework, to find out whether that's realistic or whether it needs to be bigger or less.

We are close to when we were going to do a lunch break. We have we're only a third of the way through, where we wanted to through the whole list and we're one panel behind. I'm recommending we take a break, but not 30 minutes for lunch. Let's do this, if the people here in the room can grab food and come back and we can work through.

So, if we take 15 minutes now and

reconvene at just before one o'clock, we'll start right on time and we'll march through the rest of this. By the way, is there is anybody who is on the phone who from the implementation group, who has joined us, who didn't have a chance to introduce themselves? This is a good time to do it.

Dr. Dawson: This is Geri Dawson and I'm chief science officer at Autism Speaks.

Dr. Insel: Right, and Andy, you're on as well?

Dr. Shih: That's correct, Andy Shih for the Autism Speaks.

Dr. Insel: Anybody else with us on the phone, who wasn't here at the beginning? Okay.

Dr. Hann: Wait one second. For those of you who are on the phone

Dr. Insel: This is Della.

Dr. Hann: Yes, this is Della. If you would please send me your conflict of interest forms, so that I have them. They need to be signed, as well as on the front

page, there's an options area that needs to be checked and I really do need to have them today. Thank you.

Dr. Insel: We will begin again in 15 minutes.

(Whereupon, the above-entitled matter went off the record at approximately 12:45 p.m. and resumed at approximately 1:00 p.m.)

Dr. Insel: Okay, in the interest of getting back on schedule, we're going to re-begin. I was in such a hurry, I skipped over some of the slides at the beginning and I thought we'd take a couple of minutes now, just to make sure you know which groups are involved, especially for people who are joining us from the public.

You can see here, there's a list of the organizations and individuals who were invited to be on the implementation group. This was the recommendation of the IACC. The next slide is people who are on the phone call today.

So, for those of you who have been

getting just first names, you can see. I think there are a couple of people who, for one reason or another, have not been able to make it. Melissa Foresythe is not able to join us and I believe that Doreen, apparently, had some travel problems, but she is joining us by phone.

Ms. Granpeesheh: I am on the phone.

Dr. Insel: Great, okay, terrific. Welcome, thanks for joining us.

Ms. Granpeesheh: Thank you.

Dr. Insel: There are also members of the IACC who are maybe not in the room, but are on the call. So, if there's anyone from the IACC, we're doing all this for you. So, it might be useful to take a minute at this point, if you have any advice, for whether this is granularity that you need or there's more information that you'd like, whether this is going to be helpful or not. If you could let us know at this point, that would be helpful.

Ms. Redwood: Hi Tom. This Lyn

Redwood (inaudible) and yes, this is very helpful. I wish we had more time to hear more details regarding some of these initiatives.

I just would like to also point out that I think there's a little bit of danger in doing supplements. If you build on existing research,you may not get the new research and diversity that you need. Thank you.

Dr. Insel: Thank you. I see a lot of heads nodding in the room here. Anyone else from the IACC on the phone who wants to chime in?

(No audible response)

Dr. Insel: Okay, well, ready to go back to work? Let's this is the – why don't you go back to the slide, just so we can remember how we started here, back one more. Back to the summary slide at the beginning, the one before that.

Develop cost estimates for conducting the research estimated range, the total cost, number of years, study start year, not to revise or edit the plan.

Okay, let's go back now. We're

ready for panel three. What caused this to happen and can this be prevented, and we're going to be looking at short-term objective, initiate studies on at least five environmental factors identified in the recommendations from the IOM report, as potential causes of ASD by 2010.

So, let us know, what do you think, in terms of number of years and total costs.

Dr. Lawler: This is Cindy Lawler from NIEHS. I came up with a total cost of about 7.5 million and this was with the understanding that if you look over those recommendations, there is a large number of environmental factors that are cited in that report and the other assumption that I made in costing this out is that a single study will probably look at more than one environmental factor and the kinds of data that could be collected or looked at would include retrospective data that could collected through medical records, if you're looking at infectious agents, you have access to occupational

histories, so, it appears that would be another retrospective assessment to help get at a potential occupational related exposure. So, with that in mind, I thought that the combination of leveraging existing studies, there could be add-ons of new ones or environmental factors that could be addressed in CHARGE or any of the CDC studies for environmental factors that were not anticipated - that that would be a way to get a fairly quick answer, given that this is a short-term objective and also I think there could be a role here for two or three small clinical studies using clinic-based populations and comparing environmental factors of interest against a relevant control population, so that was my thinking and I came up with about two to three total studies 1.5 million a year for five – 7.5 million.

Dr. Yeargin-Allsopp: This is Marshalyn from CDC and as Cindy pointed out, we do have some existing studies. We have actually, five grantees and CDC as well. The focus of our SEED project is not focused

primarily on looking at environmental exposure as narrowly defined, but we could extend that, and if we did that, we could add about one million a year for funds,

and if we did that two year because this talks about initiating this for two years would be really, a pretty short time span if you don't have an existing study, the total would be about 14 million, so for two years the total would be 14 million and it would be five or six sites.

Dr. Mumper: This Liz Mumper from ARI. I have recommendations for two studies looking particularly at thimerosol exposure and a typical(inaudible) pattern and genomics. One would look at two hospital based pediatric populations and do retrospective exposure histories with polymorphisms at three million and the other would be two million for looking at A-typical porfernces with cypoxin injury.

So, I think that the 14 million would be the figure I would rather go for, as opposed to the seven million or perhaps, even higher.

Dr. Insel: Other comments?

Dr. Yeargin-Allsopp: The only other comment that I would make - this is Marshalyn, is being a part of the ICC for the National Children's Study, looking at a lot of environmental exposures, I've come to appreciate how expensive it is to study these individual environmental exposures.

So, this is a depending upon how we define environmental exposures, this can be quite costly.

Dr. Lawler: This is Cindy from NIEHS. I agree that my estimate was probably on the modest side. So, doubling that to around 14 million is - I would be comfortable with that.

Dr. Insel: Okay, let's go on. Thank you. Coordinate and implement the inclusion of approximately 20,000 subjects for genome-wide association studies, as well as sample of 1,200 for sequencing studies to examine more than 50 candidate teams by 2011. Ann?

Dr. Wagner: This is Ann. We

consulted with our genetics folks here. There was a little - we do come up with a big range, because you can interpret it a couple of different ways.

So, one estimate was that if you're talking about 20,000 subjects, adding them to the repository now, it would take about four years of funding and be $34 million.

But if you're talking about 20,000 ASD cases, it's a lot more and it would be probably an additional $30 million. So, the estimate goes from $34 million to $64 million that would be the range.

Participant: I would just say thatthis is where we costed out our 20,000 and we came in more than 40. So, it's consistently a range. We did not include the re- sequencing, however or sequencing. So, I'll have to spend a few minutes costing that out.

Dr. Insel: Yes, I think the - I don't have anyone here. I think it's about $2,000 per case for the re-sequencing effort,

something like that. We're doing we'll have to do the math. It may be more than that.

For a re-sequencing effort, it says a sample of 1,200 for sequencing studies to examine more than 50 candidate genes.

Dr. Shih: The cost for this is about two million dollars. That's added in the overall estimate.

Dr. Insel: Okay. So, two million and it's part of the $34 million?

Dr. Shih: Yes.

Dr. Insel: Anybody have information other information to put in here? So, we're Tish, you're saying it's about I'm sorry, the number you had was 40?

Ms. Tanski: More than 40.

Dr. Insel: More than 40 and the number we started with was around 34 or somewhere in that range.

Participant: The original number was 34 to 64.

Dr. Insel: Okay. This is one of those places where it's such a moving target. The power of the tools is going up every six

months and the cost is going down every six months.

So, especially if it's going to be launched in 2010 or 2011, one can only assume that it will be much less expensive. So, why don't we start at why don't we put 40 down as a working number and knowing that that is is very much an estimate, because it's going to changing, certainly by the time this gets done.

Within the highest priority categories for exposures for ASD, validate and standardize at least three measures for identifying markers of environmental exposure in bio-specimens by 2011.

So, this would link some of the bio specimen collections and others other items that were already discussed.

Dr. Lawler: This is Cindy Lawler from NIEHS. Again, I think the best way to address this would be through supplements to existing studies, you know, would include organizing protocol development, some round-

robin studies of splitting samples. It may involve travel between laboratories to help standardize analysis. The costs of course are going to be very dependent on the analyte of interest.

I ended up with a total of 600,000 and it could be much more than that and the real cost will be once you have a harmonized protocol in harmonizing it and being able to validate it, not only the different kinds of populations, but also with an independent measure of that exposure.

So, Marshalyn, I'm interested to hear from CDC, about what your impression might be of the cost of this. I know you guys have a lot of experience doing that in the labs down there.

Dr. Yeargin-Allsopp: Our experience has been primarily with our Denmark study and I know that a lot of effort has gone into just looking at individual analytes. The cost has been roughly about a million dollars a year. So, over three years, it would be about three million, and that may be on the low side.

Again, this is you say at least three measures and I'm talking about the effort that has gone into looking at one over several years.

We've come to appreciate how long it takes and how complicated this science is, in terms of looking at these individuals analytes.

So, I guess if we then if we did by three, then it would be more like nine million, right. So, maybe nine million.

Dr Lawler: So, Marshalyn, is that including assay development because I was assuming that there was a fairly well developed assay that would be available and this would be more just harmonizing on site.

Dr. Yeargin-Allsopp: Well the progress has been very slow to be honest. I feel like we should appreciate how complicated and how long it takes to develop the methods and the methods are different for each one of the analytes. My understanding is that sometimes it’s not that helpful if you begin to look at a different analyte. It’s been very

slow and requires a high level of technical expertise to do this.

Dr. Mumper: We feel very strongly that this is an area that needs further work and I'm struck by the discrepancy between the 40 million for the genome and the three to nine million for the environmental component.

We're very concerned about genomic pre-dispositions and environmental impact. So, we'd like to see this area heavily funded.

Dr. Lawler: This is Cindy Lawler, again. I think it depends if this objective is going to capture development of measurement of exposures that we don't already have a good handle on now, that could involve or need a much larger budget. But as I read this it was not the development aspect more just the working out so that the different academic laboratories that arrive at the same quantitative measurement given the same measure and there was consistency in how the samples were collected and stored and so on.

Dr. Insel: Cindy, you were part of the

discussion and maybe you can help me clarify this. I read this as something completely different. I thought this was developing the tools, like epigenomics or methylation tags or ways of monitoring and then standardizing those to look at environmental exposure, often maybe years after the fact.

Is that not what the group was talking about, because that's very different than measuring 500 analytes in a plasma sample that's been stored away.

Dr. Lawler: Well, I think both things were talked about. Certainly, we there was some discussion about - making sure that some of the tools that are under development now would be available to be applied to the autism arena.

As one example, I think that CDC has been working on ways to miniaturize and get more information out of blood spots as one example, and I think that's still under development. So, that would be a place where you may need some more development work and then it would need to be applied. And then

there are other cases where we do have to good methods but there's still a lot of variability across labs. So, my sense was that there discussions at both levels and what I read here was more of the standardization, but I agree that if we’re meant to include a development aspect than the cost is exponentially greater.

Dr. Insel: So, I think we're talking about two very different things too, because the - if it's development, this isn't going to be done by anybody who is in the autism community currently, and we're talking about work that's probably going to happen through a biotech, space or some place, where people are doing this kind of work on a very high level and it's not likely that it's going to be limited to autism. It's going to be something that could be used in a very broad way.

So, I'm not I think it's really helpful or would be very important to know what it was that the workgroup was recommending for this objective, especially because it's a

short-term one and there seems to be some ambiguity about what they really expected to come out of it.

Ms. Mumper: Liz Mumper from ARI again. I appreciate Dr. Insel's insight into looking at mechanisms of injury or markers of injury. I think we're barking up the wrong tree if we continue to try to look at individual analytes.

So, I would be more interested in looking at synergy of exposure. Maybe one way to move this forward would be to add some of the environmental candidate genes to the genomics exposure, so that we're specifically looking at some of the genes of interest and handling detox pathways.

Dr. Lawler: That's a great idea. I think that is captured in another objective, the in the I think the last objective, trying to understand gene environment interplay.

Dr. Yeargin-Allsopp: Well, I'm struck by the comment that Tom just made, that this is short-term and this is to happen by 2011. So, some assumptions must be there about

what we already know, since this is just to validate and standardize. So, I am a little confused also, by what exactly what this is.

Dr. Insel: So, we have to move on. But what I'm hearing in the discussion is that if what we're really talking about is just harmonizing those tools that we currently have and the techniques that are in use, then Cindy thinks this can be done for about $600,000.

If what we're talking about is developing new procedures that will have a greater impact, it's going to be considerably more and the - again, the figure was what? Marshalyn, what was the number?

Dr. Yeargin-Allsopp: Well, based on the numbers here, if you talk about at least three measures, then my estimate is about nine million.

Dr. Insel: Yes, so, between $600,000 and nine million, and one option here again, would be to provide a range for the IACC. Let them sort out what it is that they really meant by this. It sounds to me like

we're not clear on what they wanted.

Dr. Wagner: Can you clarify, Marshalyn, how long it take if you were doing a development too? You said two or three years wouldn't work.

Dr. Yeargin-Allsopp: Well, I would, well, maybe we could do it in two or three years. So, I would have to get more information.

Dr. Insel: Yes, I have the plan in front of me and I can't even tell from that, what it is that this exactly supposed to be. So, let's figure out the range and if they want it to be clarified we can do some homework to give them a better sense of what the cost is. Long-term – to determine the effect of at least five environmental factors on the risk for subtypes of ASD in the pre- and early postnatal period of development by 2012.

Dr. Lawler: This is Cindy Lawler again. My contribution to this estimate was my understanding and knowledge of the CHARGE study, which is in a position to address this currently and if we're, it's being funded

now, not only through a project in a PO1, but also through an independent RO1, so if you add that up its about 1.5 million a year to support a single study and you're certainly looking at more than five environmental factors.

That provides you some idea of the range of a single study if you're going to bring that to bear on this question - I've got two million per year for a total of 10 million.

Dr. Insel: Okay, other estimates for what this would cost?

Dr. Yeargin-Allsopp: Well, our estimate from CDC would use our existing infrastructure for SEED, where we have five grantees and CDC and then, we would have to do some supplementing and I think this is related to the first short-term objective, where I talk about the fact that our primary focus is not on environment, as defined narrowly.

So, we would have to sort of re-tool this to a certain extent. So, we would do it over four years and it would be about 30

million. Again the existing infrastructure -

Dr. Dawson: Marshalyn, this is Geri. Is that existing infrastructure, are you following the children from the pre and early postnatal period?

Dr. Yeargin-Allsopp: No, we're not. So, one of the discussions that we've had here is whether we could use the families that we've already identified and make it more of a baby sibs type study by recruiting the younger siblings, by getting the history of the mothers.

The children are enrolled three to five years of age, and so, some of those women may have a second child or they may be pregnant. That's not part of our current study.

Dr. Insel: But is that part of the charge study?

Dr. Lawler: There are children are enrolled at three to five, but there are some clever ways to get at earlier exposure, this would include interpreting the environment risk factors broadly, so there’s abstraction

from the medical record or medical conditions, medications, there's the newborn bloodspot that can be used, there's some exposures that are fairly persistent. A sample taken at three to five years old will provide an indication, there's a pesticide use reporting system that can look at relationships between residents during pregnancy and types of pesticides that were applied around the residence, so there are other ways to try to get at past exposures even though children are not enrolled until they're two to five.

Dr. Yeargin-Allsopp: And similarly, we are getting information from records, so we could extend the questions that we are asking from the records, and we do interview the mothers and ask questions about the pregnancy. Again, we're not collecting an environmental samples, but we do have biologic samples.

You know, we do have blood specimens and we do have hair analysis for mercury levels – so there's some information environmental factors, we speaking about

toxins in particular.

Dr. Insel: So, isn't that the advantage of the CHARGE study, that it really is already in place to do something like this, if it could be expanded?

I'm also mindful of Lyn Redwood's comment, that we don't want to be limited by what we're currently doing, that this is a risk in building on current projects. Part of what we were doing the plan for is to recognize that whatever it is that we have been doing, hasn't gotten us to where we wanted to be. So, we want to be always thinking about how we can move forward in different ways.

Cindy, maybe you can help us whether the CHARGE study could be refashioned in a way. If you're saying it's about $10 million to do this, to actually be able to deliver this by 2012. Does that sound realistic?

Dr. Lawler: I think the investment that we have already will provide some answers to this objective in that time frame, because

this isn't it's in its seventh year.

If you're going to initiate a new study, first of all, you couldn't get the results, if you were going to initiate a birth cohort study or another type of case control study, it's going to be hard to get much within a five year period so I think that in this time frame the best bet is something like CHARGE.

There are other possibilities as well, this within the timeframe, but I don't think can be done is to really initiate an entirely new study at this time and get results within a five year period or by 2012.

Dr. Yeargin-Allsopp: And I just want to briefly add that charge study the charge study started before the CDC SEED study and basically, a lot of the methods are similar, that we have some common PI's, and so, they're meant to complement each other.

So, I just wanted to make that clear, that they're both, you know, epidemiologic studies and they are looking at risk factors and there is they've very

complementary.

Dr. Insel: Again, I want to pull us away from thinking about anything that exists. The value for us to talk about CHARGE and SEED was is you can tell us what it

Dr. Yeargin-Allsopp: Right

costs to set something like that up.

Dr. Insel: But one shouldn't think for a moment that what we're talking about is dollars that will go to either of those studies.

Dr. Yeargin-Allsopp: Right.

Dr. Insel: That's not what the discussion is about. But if we were going to set up something equivalent to what charge is doing, you're saying we could do it for $10 million.

Dr. Yeargin-Allsopp: That's what Cindy said, right Cindy?

Dr. Lawler: Yes, that's what we projected, in CHARGE, yes.

Dr. Insel: So, that's probably what it would cost to do this to accomplish this objective. I think that's what you're

telling us. This could be done for $10 million.

Dr. Lawler: I think so.

Dr. Insel: Okay, onward, conduct a multi-site study of the subsequent pregnancies of 1,000 women with a child with ASD to assess the impact of environmental factors in a Estimates? period most relevant to the progression of ASD by 2014.

Dr. Lawler: So, this is similar to the EARLI Craig Newschaffer study that NIH is supporting now. That will be a 10 year study. They haven't begun enrollment yet.

And so, if we just cost out that study, it's around about three million a year for that and they hope to have end up with 1,000 pregnancies and again, within that timeframe they'll maybe a third of the way through by 2014 so they'll have some questions if there are large main effects or so on.

So, I don't' I can't imagine beginning another large scale study of that type.

Dr. Insel: So, that gives us a

really good estimate, if that's if it's three million to do 1,000 women.

Dr. Lawler: It is three million, although I will say that the analysis, that this it's primarily for the recruitment and diagnostic assessments and bio-specimen collection and storage there.

There really isn't money to do any amount – the three million is for the infrastructure. The assumption is that there will be additional funding made available to look at specific hypotheses so that would add to the three million.

Dr. Insel: And it’s three million per year?

Dr. Lawler: Per year.

Dr. Yeargin-Allsopp: Per year? Dr. Lawler: It's about three million a year.

Dr. Yeargin-Allsopp: Okay.

Dr. Dawson: Cindy, this is Geri. So, in the design of the EARLI study, it - you know, it is, like you say, it's a ten year study, right? So, you'd have to think of it as three million for 10 years.

Dr. Lawler: That's correct.

Dr. Dawson: Right, okay, and the other thing is that it really is pretty significantly under funded. You know, I mean, I do think these really it's challenging to do it for that and also, there's quite a few measures that were not incorporated, that you'd probably want to incorporate.

So, I would want to put a little bit more money in, to make it a little bit more feasible.

Dr. Lawler: So, maybe five million a year? analysis and - -

Dr. Dawson: Yes, I think so. Dr. Lawler: To pay for some

Dr. Dawson: Well, yes, because it doesn't have any processing of the assays or analysis. It's just really banking, and that's it.

Dr. Lawler: Yes.

Dr. Dawson: And so, if you wanted to look at any kind of gene-environment interactions, they weren't able to collect DNA on the whole family, just part of the family

and it's just - it's one of those studies where they did the best they could with the limits that were provided by the RFA.

Dr. Insel: Okay. So, that would be five million per year. How many years do you think this would - I guess, if you look at what we've done so far, we've been pretty much constrained to the five year commitment or less.

In this case, we can provide the figure of five million per year, but can you give the IACC some guidance about how many years to support this or how many years it will take?

Dr. Lawler: It's going to need 10 years, given the number of sites and the projected rate of enrollment. So, the original application came in, you know, explaining that this was meant to be a 10 year study and although the ACES are only funded for five years, there's going to have to be -

Dr. Insel: Yes, so, again, I don't want to be too constrained by what we've been doing. So, if it's going to take 10 years at

$5 million per year, are you saying that maybe we should be spending $10 million per year to get it done in five, is that feasible?

Dr. Lawler: I guess you could add an additional try to add additional sites.

Dr. Dawson: Yes, I think - well, you have the there are four years of development, right, that you're tracking, because you start at conception and you actually enroll the women before they're pregnant, ideally.

Then you have to take them through age three, and so, whether you could just throw more money at it and do it more quickly, I'm not sure. You could probably get it done a little bit, like in seven or eight years. I doubt if you could I don't think you could do it in five years with the existing expertise that's out there, because they're maxing using a lot of the sites to do this kind of work.

Dr. Insel: Okay. That's what I needed to know. So, we'll put in a per-year cost. With Mr. Dunaway here, I'm very

sensitive to wanting to not have initiatives that aren't going to be able to pay out in his life time.

So, to have a 10 year project is not exactly where we want to be. But we'll I can understand this one is constrained.

Mr. Dunaway: I just want to say one thing. I just want to know, will by concentrating it, are we going to lose quality or will you be able to make sure that they continue to have the same high standards that you would have if you had the 10 year?

Dr. Lawler: I think it goes back this is Cindy Lawler, to what Geri indicated. Craig has recruited the obvious players in this field who are able to mount enrollment campaigns, to try to recruit moms that are at risk for a subsequent child with autism.

So, I'm not sure if throwing more I'm not sure how much more capacity is out there right now, so you could think about adding more sites, there would be a ramp-up effort so I don’t think you can double the cost and halve the length. As Geri indicated you may

shave a year or two off by trying to concentrate more sites and part of that, as you bring up is more important to do that in a thoughtful way that doesn't compromise the quality of the data collected.

Mr. Dunaway: I just want to make sure that the data collected, the quality is still there. It's important that we don't lose anything in quality.

Dr. Lawler: That's an excellent point.

Dr. Insel: Okay, moving on, identify genetic risk factors in at least 50 percent of children with ASD by 2014. This is… Ann, you get a chance to swing at this.

Dr. Wagner: Well, we had to get some consultation on this one – according to our genetics experts, this will take about 50,000 subjects, assuming that 1,000 controls can be provided by the genome project and again there's going to be a huge range dependent on the kids on analyses your doing, so the estimate is that using exonic sequencing it would be about $30 million.

Using whole genome sequencing it would be $150 million.

Dr. Insel: Andy?

Dr. Shih: What is the relationship the short-term two and this particular long-term objective? I mean, is there any way we can take advantage of the work that's going to be done in the short-term objectives too?

Ms. Tanski: Yes, this is Tish Tanski from the Autism Consortium and I would say yes, that there that one is a building block for the analysis for the other, and another way, one can't be done without the other.

Dr. Insel: So, what I'm trying to understand here is that if the short-term objective is completed and 20,000 subjects are entered into a genotyping and 1,200 into a sequencing study, is that likely to actually deliver the 50 percent of children with ASD, identifying genetic?

Ms. Tanski: You'd have to add in some analysis cost, which I think was done in our original estimate. So, what, that might

be $500,000 a year, starting in maybe 2013 or 2014, something like that, 2012.

Ms. Granpeesheh: This is Doreen Granpeesheh with ARI and I have a question: It seems to me that it’s difficult to answer this question with any type of study at this point given the environmental exposures as well. What type of studies are you guys thinking about that would warrant that amount of funding?

Ms. Tanski: Are you asking about the 20,000 sample study?

Ms. Granpeesheh: I'm just wondering how we can look at purely genetic factors without considering the environmental and I looked at the question for a long time and I thought “great, if we can figure out these genetic risk factor, we would have the problem more or less solved.

Ms. Tanski: I am not a scientist myself, but I'll give you the layperson's version and maybe one of my scientific colleagues can jump in and help me out.

The goal is to try - the goal of

that project would be to try to identify those genes that are involved and behaviors or characteristics that those genes map to, or that the other way to say it would be the behaviors or characteristics mapped to those genes.

Ideally, we'd be able to find genes you could then look at in fact, we know we'll be able to find genes. You can then look at which of those genes may or may not be involved in what we know about environmental or other possible environmental factors like in utero environment and begin to get at the gene-environment interaction. It’s not the only place you can start from but it’s a place –

Ms. Granpeesheh: So some of this funding would look at the interaction with environmental.

Ms. Tanski: It will provide the information that those who who have the capability of looking at environmental interaction could use and those are in different boxes that we talked about.

Dr. Shih: This is Andy – I would agree with Tish's assessment - I think that the gene-environment studies will help us with information about CNVs so I think that will help us move the identification of risk factors forward that way, and in terms of the related foundation for looking at gene-environment interaction, you can identify environmental risk factors potentially without the (lost audio).

Dr. Insel: Again, we don't really have to worry about the value of any of these, just the costs. So, if it's up to the IACC to decide whether this is worth doing, and I think they've already told us from what they've sent us, that they want to they want this on the list.

Now, the question is what it would cost us to do this. Thomas Lainer is here, who is our genomics consultant and he's clarified that unlike the short-term objective, which has 20,000 subjects, those - that's actually only about 7,000 cases.

So, the difference here is that

the long-term objective is to move to 15,000 cases, 10,000 for a discovery sample and about 5,000 for replication, with another 1,000 control, which we could borrow from projects that are already ongoing.

So, I think that the sense is that this builds on the short-term objective by growing the samples significantly, so that you can identify even lower penetrants or smaller effect-size risk factors.

So, at 7,000, you may be able to pick up an odds ratio of 1.3. This would allow you to go down to 1.2 or 1.15 and at least in the case of Type II diabetes, that's when everything broke open, was when they went from 7,000 in that case, to 30,000.

That also happened, of course, for prostate cancer and for cardiovascular disease. So, we've got some pretty good example of where this has worked really well. It looks like it's working very well in asthma, which is also another disorder where there's always been a long debate about environmental versus genetic interactions.

But I hope that's somewhat helpful. That's the rationale for having this in here, in addition to the short-term objective. So, this basically doubles what was done in the short-term objective and it takes a different approach.

Dr. Yeargin-Allsopp: Yes, that's very helpful, Tom.

Dr. Insel: Okay. So, Ann, what was our estimate of cost?

Dr. Wagner: Well, it was depending on type of sequencing – 150 if you're talking about whole genome sequencing.

Dr. Insel: Yes, and I think that since we're talking about 2014, the cost of whole genome sequencing will be it will be very different in 2010, than it is now. So, it's impossible to estimate. Thomas, do you want to -

Dr. Lainer: I asked our colleagues from the Genome Institute that are involved in sequencing, development, to estimate what it would cost to do sequencing with sufficient coverage by 2010 (lost audio).

The number I was given was about $10,000 per project. That's projecting a couple of years out.

Dr. Insel: Do you want to put in the range or you know, on this one, with all due respect, Thomas, I suspect we're going to be on the lower end of the I mean, the $30 million by itself sounds pretty ambitious. But we'll have a chance to come back to this, based on the short-term data anyway.

So, why don't we stay with a lower range of this, unless, Tish, you have a different feeling of what the Consortium has picked up, because you also are involved in costing out whole genome efforts, aren't you? I mean, the whole genome sequencing?

Ms. Tanski: No, I just want to clarify though, that the number that I had given of 40 upwards of $40 million for the 20,000 subjects did assume a pretty well characterized population and I had not included sequencing. So, I defer to the geno-institute.

Dr. Insel: Thirty million and then

in parenthesis, the upper end will be 150, given that there's a possibility of understanding that sequencing costs will come down. It's actually not even doable today, in the sense that we're talking about or at least not in anybody's budget that we can imagine.

It would be much more expensive. But it will be manageable as time goes on. Thomas?

Dr. Lainer: Exonic sequencing may be sufficient. The direction would be (lost audio) and it would have to go beyond the sequencing. But I'm certain, even if just sequencing would be done in large proportion, maybe even 50 percent of (inaudible).

Dr. Insel: Okay, onward, support ancillary studies within one or more large scale population based epidemiological studies to collect case-control data on environmental factors during pre-conception and during pre-natal and early post-natal development, as well as genetic data that could be pulled as needed, to analyze targets for potential

gene/environment interactions by 2015.

Deborah, this sounds like the kinds of things we talked about for the Norway study, for the Denmark study. So, what are the costs going to be for this?

Dr. Hirtz: Well, this basically is the design. I think the cost would come in adding additional elements and as new technology becomes available.

We had estimated adding an additional $1.5 million per year over five years to come up with $7.5 million, but that would that's in addition to the core protocol, which does address these issues.

Dr. Insel: Have we got other estimates or other suggestions for this?

Dr. Yeargin-Allsopp: This is Marshalyn. We had a higher estimate, based on our Denmark study, and the experience that we have with SEED. So, we came up with approximately one million dollars per site, for six or seven sites, just depending upon how big we want to make this, and we came up with this estimate, since it would be until 2015, of

about $40 million.

Dr. Insel: I'm sorry, how did you get from a million dollars per site to $40 million?

Dr. Yeargin-Allsopp: Well, because we have we were basing it on using seven - using six sites. If we just use site as Denmark, then it would be closer to what Deborah estimated.

But if we wanted to think about a range of different sites, then it could be, I guess, from about seven or eight million to about 40 million, depending on how many sites we wanted to do this in.

Dr. Insel: So could we say about 7.5 million for the first site and then the range would be based on the number of sites. That's 7.5 over five years, right, because it's essentially 1.5 million or one million per year.

Dr. Yeargin-Allsopp: Per year, right.

Dr. Insel: Somewhere in there, okay. So, you agree on whatever cost just to

have the scope and how many sites involved.

Dr. Hirtz: This is Deborah again - yes, but that is predicated on an existing infrastructure. If we were to develop this infrastructure totally new, the cost would be astronomically more.

Dr. Insel: So, I think the - this one, I do remember. The workgroup was specifically saying, let's take those large population-based cohort studies that are around, build the case control efforts into them. What will it cost? In fact, aren't there really only the two, Denmark and Norway? Are there others? I guess there's a Finnish cohort.

Dr. Hirtz: Well, I mean, in fact, the Newschaffer study will provide this kind of nested case control design, when it diagnoses the children at risk, that will be controlled.

Dr. Insel: So, they're asking for within one or more large-scale population base studies. So, if we can give them a cost of about a million dollars a year per study

and we cost it out over five years and we can suggest that it will be between five million then and ten million depending on whether they want to do one or two studies or more, and I think the IACC can work with.

Dr. Lawler: I agree with Deborah. This is Cindy Lawler, because if we're not going to build on the Norway study, then you know, the cost should at least double per site.

Dr. Insel: But I think the workgroup was very clear that this was going to be built on existing we're not talking about building a new Norway study or this isn't to build a population cohort. It's to use the ones that exist and to mind them.

Dr. Dawson: This is Geri. How about the national children's study for this?

Dr. Yeargin-Allsopp: Could be done. I think that that's also a possibility. So, in terms of cost, I have to think about that for just a minute. Obviously, it would be more than a million though, per year.

So, maybe five million, and I'm

just guessing. I'm just totally guessing here, because these are multiple sites and the data are not as easily available, as if you think about Denmark or Norway, where there is more in place already to do this.

So, I mean, although the design is there, I think that the data collection aspect of it probably means it would be more costly than using the existing Denmark or Norway cohort.

Dr. Insel: Yes, so, let me clarify. The workgroup really wanted us to use Norway or Denmark. They said you've got 100,000 children that have been carefully followed in two places. Make use of that, and what will it cost to make use of that over these five year periods?

So, the figure I'm hearing is about a million dollars per year, per site, to really get the best value. It's not even clear if the national children's study would have the same kind of bio-samples that already exist and that somebody just needs to go back to.

So, I think we've got that one finished. Let's move onto the next panel, which is on treatments and interventions, and the first short-term objective is launch four research projects that seek to identify biological signatures that measure significant improvement in ASD core symptoms across the lifespan.

Can we get some ideas of what that would cost?

Participant: Five million, maybe more, but -

Dr. Insel: Could we have any existing projects that would give us a sense of what it costs to do this in one project? Is there anybody who is actually now trying to get the biological signatures for improvement, following treatment, and that may give us a bit a good ball park about it, then we can multiply by four.

Dr. Dawson: Participant: Isn't the Tugany study using the - didn't you say they are using tests as a predicator or also a response to treatment?

Dr. Hirtz: It's actually being used as a predictor for response. So, it's being done initially, but it's not being done at the end of the study. That would require a supplementary fund.

Dr. Dawson: Well, I know that the folks where I used to work, put in grant proposals to study electrophysiological outcomes in response to treatment.

I think if there were an RFA on this, they would just I mean, it's not that hard to design or do, and you would have to use fMRI or something that was of interest, as a biological outcome, but I think there's a lot of groups that could do it.

Ms. Granpeesheh: Hi, this is Doreen again. I just I was wondering, if we do look at something like a biological signature, wouldn't we have to then tie it into the behavioral symptoms for ASD core symptoms and that hasn't been done, as well.

Dr. Dawson: Well, some of them have looked at correlations between some of these biological measures and behavior. So, yes,

actually, some of them at fMRI and ERP have both been correlated with different symptoms.

Ms. Granpeesheh: Right, so, all those aspects would have to kind of be thrown in for all the various symptoms as well.

Dr. Dawson: Yes. There is just a bunch that seek to identify. So, I just think that there would be several groups that would have hypotheses and possible ways of approaching this that could respond to something and get it going right away.

Dr. Insel: So, Geri, your suggestion that we essentially supplement current trials and just build this in, so that you're not paying for the whole treatment effort?

Dr. Dawson: Right, that would be one way, although I think that probably to do this right, you're going to be choosing specific treatments and specific kind of methodologies that have the best chance for working and whether or not that would just automatically work with the ones that are ongoing, I don't know.

I think it would almost be more effective just to put out an RFA and say we'd like to see treatments that

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Dr. Insel: So, Geri, you're suggesting that we essentially supplement current treatment trials and just build this in, so that you're not paying for the whole treatment effort?

Dr. Dawson: Right, that would be one way, although, you know, I think that probably to do this right, you're going to be choosing specific treatments and specific kind of methodologies that have the best chance for working, and whether or not that would just automatically work with the ones that are

ongoing, I don't know.

I think it would almost be more effective just to put out an RFA and say we'd like to see treatment studies that have biological signatures and core symptoms as an outcome and I think you'd end up getting a lot of good projects in.

Dr. Insel: Yes. What would it cost to do a project like that?

Dr. Dawson: Well, I think you're pretty much looking at a randomized clinical trial, not too big at one site, that also has some expertise in something like mirror-imaging.

So, I guess I'd say a million dollars for each study. That would be $300,000 a year. That's probably low, so maybe a million and a half for each study. So, that's why I said five million. That would be for three. So, yes, five to 10 million, five to seven million.

Dr. Insel: Okay.

Dr. Wagner: And I guess again, we were not thinking this was necessarily

treatment studies, or just sort of outcome in general, as to what kinds of kids have better outcome. But I don't disagree with the cost estimates. I think even they would be about the same, regardless.

So, for instance, I mentioned the Deborah Fein study before, which is not a treatment study, and that's $580,000 a year. So, it would be about the same.

Dr. Insel: Okay. So, again, Geri, the figure that you were suggesting, just to make sure we have it?

Dr. Dawson: Yes, I think we came to about if you had four of these and they were $500,000 a year, you know, it's $2 million a year for three or four years.

Dr. Insel: Okay. So, about seven million. All right, moving on, support three randomized control trials that address co-occurring medical conditions associated with ASD by 2010.

Dr. Mumper: Liz Mumper from ARI. I have one project that would cost out at $2 million over five years to study methylation

markers and this might be another point to bring up the issue of the double blind placebo controlled model versus doing single subject design, because I'm concerned that if we only allow for that model, we may miss things.

When we costed out a single subject multiple base line study for only 30 subjects, it was $450,000 over three years with relatively modest interventions being studied.

Dr. Insel: So, it sounds like, as we were just talking about, the figure for again, no matter what kind of trial it's going to be, is around is in the neighborhood of about $500,000 per year, $400,000 to $500,000 per year and then you can just scale up from that.

So, in this case, we're talking about three randomized controlled trials, if we assume it's about $500,000 per year, say, $450,000, that would be -

Dr. Wagner: About seven and a half million.

Dr. Insel: Right, okay. That's

$7 million or $7.5 million, does that sound right to everybody?

Dr. Dawson: Yes.

Dr. Insel: Five randomized controlled trials with early intervention for infants and toddlers by 2011.

Dr. Dawson: Is this multi-site?

Dr. Yeargin-Allsopp: I would think so.

Dr. Dawson: It doesn't have to be. I don't think so.

Participant: There's a later objective. If you flip the - I don't know if you have to flip the page, but it's the last one under short-term objectives. That's the multi-site RCT one. This is not multi-site.

Dr. Yeargin-Allsopp: The last one on the long-term?

Dr. Insel: This is the third short-term objective.

Dr. Yeargin-Allsopp: Oh, the third short-term.

Dr. Insel: So, this is the preemption piece, the early intervention.

Ms. Mumper: I have a - this is

Liz Mumper with ARI. I have a cost analysis of a biomedical intervention for children suspected of ASD between 12 and 24 months, looking at redox and methylation status with targeted nutritional invention, two million over five years.

Dr. Insel: NIH folks, what do you think?

Dr. Wagner: Well, I think we're thinking the same cost range as the other clinical trials. So, we've at five, that would be $12.5 million.

Dr. Yeargin-Allsopp: I know we can't change this, Tom, this is Marshalyn, but it seems like this is really a short period of time to do this. Does this mean complete and conduct these studies by 2011?

Dr. Insel: It means conduct. Dr. Yeargin-Allsopp: Conduct? Dr. Insel: It won't be completed.

Dr. Yeargin-Allsopp: Okay.

Dr. Insel: But we're back to then, the same basic number of about five

so, it's just scaled up. So, what you're saying is, it would be $500,000 times, in this case, five instead of three.

Dr. Dawson: So, yes, I mean, the ace network that I was part of, that was doing this, it was $2.5 million a year for three sites and a data coordinating center and I think the funding was just about right.

So, that's it's more like around 600 a site. They are more labor intensive than other kinds of interventions, because of all the treatment that goes on and training of therapists and so forth.

So, I would up it a little bit, compared to some of the other biologically or treatments.

Dr. Insel: So, let's say three million per year, Geri, that's closer?

Dr. Dawson: Yes, I think that's better.

Dr. Insel: Okay, and then over five years, that would cost out at about $15 million.

Dr. Dawson: Right.

Dr. Insel: Launch three randomized controlled trials of interventions for school-aged and/or adolescents by 2012. Are we talking about the same basic figure, we'll just scale it up?

Dr. Wagner: Yes.

Dr. Yeargin-Allsopp: I would think so.

Dr. Insel: So, let's say in this case, about around $500,000 per site. That's $1.5 million per year and

Dr. Yeargin-Allsopp: Can we say for three million per year, times five?

Participant: It's three on this one.

Dr. Yeargin-Allsopp: Three? Dr.

Dr. Dawson: I think it would be just about the same as the infant/toddler one.

Dr. Hirtz: This is Deborah Hirtz. I'd like to make a comment on these. I'm concerned with assuming that we can manage with single site trials for some of these.

It's very hard to get the sample size that you need to answer the question and

even if the design is fine and it's a randomized controlled trial and I think we're being – I think we're low-balling here because I think even if it's a small trial, you may need three or four sites and $500,000 per site is probably about right. Could be a little bit less per site, but the total might be more like two million
a year.

Ms. Mumper: Liz Mumper from ARI. Deborah, the other point is, is that you're exactly right, if we're going to look at sub-sets and heterogeneous populations, that's very difficult to do at a single site.

Dr. Hirtz: Yes, I guess I was just thinking that there's so few of these, that you'd almost have to do a smaller study to begin, right, but you could, I suppose, go right into a multi-site study.

But there would be a lot of development that would need to go on, in terms of manualizing things and so forth, which Would -

Dr. Insel: And this is a short-

term objective.

Dr. Hirtz: Yes, but you know, the short-term objectives, I know we're not suppose to change these, but the short-term objectives, it can be handled in different ways. We can certainly get started.

You can have a feasibility phase to a longer trial.

Dr. Dawson: Yes.

Dr. Hirtz: You can only do what you can do, in a short amount of time, I agree.

Dr. Dawson: Yes.

Dr. Insel: So, how do you want to report this out to the IACC? How do you want to cost it out, given that it's a little vague in the actual implementation of it?

Dr. Wagner: I'm thinking that most things are not ready for big, large multi-site trials yet and most of the things that we want to explore and and they could either be done by funding the smaller study first, and then a larger one, or like Deborah said, two days.

But either way, what we might want

to cost out is the first phase for now, and have the next one -

Dr. Hirtz: We need to be clear in the language, and not funding for this under-powered phase three trials, that that's not what the pilot trial should be, and that I think we should increase the budget to be more I agree on your language, but I think we should increase the budget anyway. We could allow for multi-site studies.

Dr. Insel: This is also -

Ms. Granpeesheh: This is Doreen from ARI. I just wanted to throw in that we're doing a single site study right now that's costing $1.5 million per year. So, I agree, I think that the site with $600,000 is not high enough for the number of kids needed for these studies.

Dr. Insel: I think this goes back to Liz's point as well, that in each of these, we want to have some exploratory component to look for the individual who responds in a particularly good or not so good way, so that you can ultimately come back and design your

next perspective study, based on the variety of - knowing that this is such a heterogeneous syndrome, we're not just interested in the means. We want to look at individual patterns.

So, you're only going to get that if you can get the numbers. You get the size up, to be able to see the variation in response.

So, I want to again, push us along, mindful of the time. Tell me what you think the IACC should see for this item on the school age and adolescents, launch three randomized control trials. What's the number?

Dr. Hirtz: Why don't we say nine million instead of the $4.5?

Dr. Insel: Okay, with that. Onward, standardize and validate three model systems, such as cellular and/or animal and replicate features of ASD and will allow identification of specific molecular targets or neural circuits amenable to existing or new interventions by 2012.

Ms. Fallas: Jennifer Fallas from

the DoD. We estimated about three years, $1.8 million for three studies.

Dr. Wagner: Okay, our estimate was $1.8 million for three to four studies, depending on the size of the study.

Ms. Mumper: Liz Mumper with ARI. Our estimate was actually $1.5 million per study, per year. I'm sorry, $1.5 million per study, spread over four years.

Ms. Tanski: This is Tish Tanski. We came up with $1.5 million over three years per study.

Dr. Insel: So, the variation is between $1.8 million and that would be $4.5? Are you comfortable with that as a range?

Okay, let's move on. Test safety and efficacy of five widely used interventions that have not been rigorously studied for use in ASD by 2012.

Mr. Dunaway: This is one I hope that we fund and I hope we do a large study, because there's so many things out there where people are saying, you know, this is the best thing, this is the best thing. You can go on

the internet and see all sorts of stuff, and I'd like to see good science be done and I'd like to see it done with a lot of different people, maybe a lot of different institutions.

I just want to know that we could start giving people, you know, the best that science has to offer when it's when it talks about what people can do, because we want to empower our parents and I'm hoping that we really go to put what we need into this, so that it gets done and it gets done in the best way possible, with hopefully, the most participants. Thank you.

Ms. Mumper: Liz Mumper from ARI. We agree, we have a huge interest in this area. This, I think, is an area where the single subject design and the attention to individualized treatment is helpful.

I might ask Doreen to come on the line and help us with costing this out. My estimates have been that whatever the traditionally designed study would be, to do the single subject design, you end up multiplying by about 2.5. Doreen, would you

like to comment on that?

Ms. Granpeesheh: Yes, sure, and on this study particularly, we just spent $2 million on a study of hyperbaric oxygen which was multi-site and then we did a single subject one as well, which also cost quite a bit, so my estimate on this was that if we're looking at five different interventions and we have what, three years over the course to do it and nutrition aside, because nutrition itself would be a much more expensive study, I would be looking at $1.5 million per study per year.

Dr. Insel: Yes, NIH has at least one nutrition study. Anyone know, basically can you give me, even ball park, what that cost is -

Dr. Wagner: It's a little different because it's not an intervention trial per say, it's a CHALLENGE study. So, it's not going to be parallel. I don't know how much it costs.

Participant: Are you talking about the stronger ones?

Ms. Granpeesheh: Yes, I'm collaborating on that one. This is Doreen, and I believe it's going on now, beyond period, and I think we've already passed five million on that.

Dr. Dawson: Well, that was done in the context of a start center grant, right?

Dr. Granpeesheh: Yes.

Dr. Wagner: Yes, that's right. But I don't think we can use that as a model, because it's not really an intervention outcome treatment study.

Dr. Dawson: It's a challenge, right?

Dr. Wagner: Right.

Dr. Insel: So, we started off with a basic figure of about $500,000 per subject, for some of these other trials. What you're telling us is that these would be more complicated. They could be the ABAB design or other kinds of intervention designs that would not be your typical RCT, and that may be more expensive.

And there are what the - the

IACC is asking for five, as opposed to where we were before, which were three randomized trials or - I guess we had three yes, we had five trials for infants.

But for the infants, it was going to be about $15 million, is what we ended up with. So, what's a figure here that we ought to put in play?

Ms. Granpeesheh: This is Doreen again. Just because the language in this says to test safety, and I'm not sure that a single subject design would be acceptable right now for safety.

But in any case, my suggestion would be that this be somewhere in the range of the other ones, where we're looking at the randomized control trials, so, close to $15 million.

Dr. Wagner: I think that makes sense. I think that's right.

Dr. Insel: The heads are nodding here as well. Is there anybody else who has a comment on this?

Participant: Fifteen.

Dr. Insel: I'm not hearing any comments. We're going to move onto the next panel and that is, where can I turn for services and a short-term objective is a state-of-the-state's assessment of existing did I miss one?

Dr. Yeargin-Allsopp: Yes.

Dr. Insel: Sorry, I skipped a page. We're going to have to pick up the pace here. Complete two multi-site randomized control trials of comprehensive early intervention that address core symptoms, family functioning and community involvement.

Ms. Mumper: Liz Mumper from ARI. I've got two samples here, a definitive trial to identify early behavioral intervention as effective and what can improve it, at $1.75 million per year for five years.

Identify if teaching parents behavioral techniques will be effective, $700,000 per year for five years.

Dr. Dawson: Yes, again, the ACE network that was recently funded, which is a multi-site randomized control trial of

comprehensive early intervention was $2.5 million a year for five years, and I'm assuming we're talking direct cost, by the way.

Dr. Insel: We're talking total cost.

Dr. Dawson: Yes. Participant: Oh, wow.

Dr. Insel: So, that sounds like around $15 million.

Dr. Dawson: Yes, I'm thinking direct all along, sorry.

Dr. Insel: Welcome to the Government. Now, I know so, this $15 million, Liz, is that about where

Ms. Mumper: Yes, that's great. That's good.

Dr. Insel: Okay, long-term objectives. Complete randomized control trials in humans on three medication targeting core symptoms by 2014.

Mr. Dunaway: It's Wolf again. This is another one where I've actually seen people that have had medication and then the

medication is done really well. I mean, it doesn't do well in all cases, but this is one I feel is important because I've seen people go from not being able to work and not being able to be productive and then have the medication and be able to be productive and have fewer tantrums and be able to deal with things in the work environment and community a lot better.

So, this is one of the areas that again, I think is important and I guess I keep saying these things because as a consumer, I want you to know that there are some things that I've actually seen work and this is one that I think we should, again, put special emphasis on.

Dr. Insel: Thank you, that's great, because again, I think we've got enough experience to know a little bit about how to cost out a more typical RCT. We've been using the $500,000 figure per site or per study,
for three different projects going on. That sounds like about $1.5 per year, is that

right, and how many years, five years? So, that sounds like $7.5 to me, but tell me if I'm - am I in the ball park?

Ms. Tanski: Yes, Tish Tanski, Autism Consortium. That's actually a little low. We're doing something now that is just a pilot and our costs look like about $800,000 a year. I'm not sure if that's a special population issue or not, but I thought I'd throw it out there, for three years.

Dr. Insel: Deborah, Ann or Lisa, do you have a sense? What do you think?

Dr. Wagner: Well, again, it depends on the course of the trial and how many sites you're going to need. So, I think what you were suggesting before is probably the minimum of the range, $7.5 would be the minimum of the range.

Dr. Insel: Okay. So, we go from say, $7.5 million to $10 million would be a reasonable range.

Dr. Wagner: Yes.

Dr. Insel: Develop interventions for siblings of people with ASD, with the goal

of reducing risk recurrence by at least 30 percent by 2014. Comments on what this would cost?

Ms. Tanski: I have an estimate of $2 million over five years, to do one study.

Dr. Insel: Do we have anything currently that we can use as a good model?

Dr. Dawson: Yes, at the University of Washington, we launched a trial of 200 infant siblings who were going to who are going to be randomized into intervention at eight months pre-symptom and that project is probably around it's hard, because it draws on all the cores and everything, but I guess I would think it's around $800,000 a year for five years, 200

infants randomized.

Dr. Kau: Including direct?

Participant: No, okay, and add indirect to that.

Dr. Dawson: Okay. That's probably the only example we have currently. It's hard to draw because it's one project within the eight centers.

Dr. Insel: How is this different from the short-term objective of the five RCT's for early interventions on infants and toddlers?

Dr. Dawson: Well, the difference there is the infants and toddlers actually already have a diagnosis, or at least close to a diagnosis, whereas the prevention study that launched a UW, start where all of the infants at risk are provided with an intervention before any symptoms are apparent.

And so, you're really trying to preempt and then it's a stage model, where infants that go on to continue to have develop symptoms, get a more intensive second phase.

Dr. Insel: Geri, what's a reasonable cost to get this done?

Dr. Dawson: Well, like I was saying, it's $800,000 direct for five years to do the study on 200 infants. So, you know

Dr. Insel: So, I'd say $1.2 million.

Dr. Dawson: Yes, I would say for

one study of 200 infants.

Dr. Wagner: A year, right, Geri?

Dr. Dawson: Yes.

Dr. Insel: So, $1.2 per year, that's only one study. But that would be six million in total.

Dr. Dawson: Yes.

Dr. Insel: People okay with that, for starting?

Dr. Dawson: Yes.

Dr. Insel: Now, we're moving on. Next panel is where can I turn for services and we're going to start with the short-term objective, a state-of-the-state's assessment of existing programs for supporting people and families living with ASD.

Dr. Dawson: And I'm sorry, I'm going to have to sign off.

Dr. Hann: Geri, this is Della. I need to speak with you about some administrative issues. If you could just call me back, that would be really helpful.

Dr. Dawson: Okay, I'll call you.

Dr. Hann: Thank you.

Dr. Insel: Okay, costs for doing the state-of-the-states?

Dr. Wagner: We have an estimate of $60,000 building on a current effort, that maybe you know more about than I do.

Participant: What happened?

Dr. Hann: Do you know anything about this, because this is something that Alan was working on? Do you want to turn your mike on? Thank you.

Participant: I'm actually not able to comment on this, sorry.

Dr. Insel: But the estimate is about $60,000. Now, okay, and that's a one year effort?

Dr. Hann: But that's just our contribution. CMS and other agencies too are providing some funding for that. So, that's why it's not just $60,000 a year. But Bonnie, do you have any sense?

Dr. Strickland: I was just going to say, this might be an areas where we could do a lot of collaboration because we're just launching a project now from combating autism

and there's a large piece of that, it's an evaluation effort. That's about $500,000 a year for three years.

But it's supplemented by state grants at $300,000 a piece. But I know that CDC Marshalyn and Catherine, don't you also have an evaluation going on? I mean, maybe we could cobble I mean, we don't really want to cobble anything together, but I think these are initiatives that are already existing and we could look at the overlap with a little bit of effort, I think, that we could launch at least the beginning with existing resources.

Dr. Yeargin-Allsopp: Our human development and disability division does have some activities. They didn't have enough time to get any figures to me, but I can get some after this call. But I think we can build upon some of the existing efforts, but that's not helpful right now, in terms of an exact figure.

Dr. Insel: Sampson has done a state-of-the-states for we don't have anybody here from Sampson, on other areas. This is

really a one year, single figure project. We ought to be able to almost cost this out to the nickel, because it's been done so many times in other areas.

But we can assume that the $60,000 is only part of it, I think, that's fair to say. Why don't we put in a place holder here, if you're comfortable with that, of let's say, $300,000 to actually this is just to do a book between now and a year from now.

Dr. Yeargin-Allsopp: Yes.

Dr. Insel: And if that's off by a great deal, we can fix it by the time of the IACC meetings and I don't think it will be too far off.

Dr. Rice: This Cathy from CDC. So, one would be the development of it and the second would be the dissemination. So, the $300,000 seems more about the development of the book.

But we would want some clarification, was this meant to be dissemination of providing the printed

materials or just having a web-access PDF type file?

Dr. Insel: Right, this is to develop the assessment, that is to have it will be a 300 page book.

Dr. Yeargin-Allsopp: Like a White paper.

Dr. Insel: Yes, has a list, and CMS is already well on their way to doing this. So, this is one of the things that Ellen Blackwell is working on and it's been done for development disabilities. It's been done in many other places. It just hasn't been done for autism.

So, that's why I'm saying, I think we can get very precise numbers. But I don't think $300,000 is too far off.

Dr. Yeargin-Allsopp: Okay.

Dr. Insel: Support two studies that assess how variations and access to services affect family functioning in diverse populations.

Participant: We were thinking that these were relatively small studies, three

year studies, and about $150,000 per year each. So, it came out to $900,000.

Dr. Insel: Anybody else have thoughts about this?

Dr. Yeargin-Allsopp: I would support that.

Dr. Insel: Okay, so, $900,000 for - this is really in the domain now of services research.

Dr. Yeargin-Allsopp: Right. Dr. Insel: And long-term objectives, four methods to improve dissemination of effective interventions in diverse community settings.

Dr. Yeargin-Allsopp: So, at CDC, we can use our experience with learn the signs early and if we use two sites, about $500,000 per site, per year. Then we come up with an estimate of $6.3 million.

We would be partnering with HRSA. Bonnie, are you still on the call?

Dr. Strickland: I am.

Dr. Yeargin-Allsopp: So, I don't know what your thoughts are about this.

Dr. Strickland: We haven't costed it out, Marshalyn, but I think that we I agree with you. I think that's probably about right.

Dr. Insel: Other comments or anyone else who has experience in doing this? Marshalyn, again, $6.3?

Dr. Yeargin-Allsopp: Yes.

Dr. Insel: And that's over how many years?

Dr. Yeargin-Allsopp: Well, it says through 2013, so, five years.

Dr. Insel: Okay. So, that's about $1.-something per year, 1.25.

Dr. Yeargin-Allsopp: Right, you do it per year, okay.

Dr. Insel: Okay, all right. Test the efficacy and cost effectiveness of three evidence based services for people with ASD of all ages in community settings by 2015.

Dr. Yeargin-Allsopp: Okay, we have an estimate here as well and we came up with two sites, about $750,000 per site. We were thinking of this as a supplement. So, I

don't know how much it would be if we were starting a new effort. But it's through 2015. So, it's about $9.5 million over five years, I guess, is what we estimated.

Again, this is building on some infrastructure. So, it may be more if we didn't have any infrastructure.

Dr. Insel: Ann?

Dr. Wagner: Yes, we had an estimate of $6.75 million, so, based on $450,000 a year, if we were going by what our previous interventions studies were costing, that was a little bit low. But somewhere in there.

Dr. Anderson: This is Kai Anderson from CMS. Can anyone comment on what types of services we might be talking about, because if we're talking about pharmacological therapies, then that will actually cost probably less because we can do alternative research using existing services and databases, or are they more behavioral services or interventions like that?

Dr. Insel: So, this is just to

repeat, because you can't hear. You're talking about housing living community support?

Dr. Insel (talking to Denise Resnick): Okay, so, these are services to maximize functioning, which would be support employment, housing, a range of things like that, education. So, this is really where rubber meets the road. This is really the key stuff.

Mr. Dunaway: And are there going to be more of these at some point or are you going to learn from them? I'm asking because this is something that's desperately needed out in the community now, and I'd like to know if we learn what we hope to learn from this, are we going to be able to ramp it up relatively quickly, so that it can start to help people that are out there, because, again, I do a lot of motivational speaking and I work with parents and all of that and these are the questions I get asked most often.

"When my kid gets out of school, do they just fall off the radar? Does the

country stop caring about them? What happens when they have needs that go beyond the 12th grade or college?"

I'd like to be able to walk away from here and say, down in Washington, they heard you and that maybe we have things coming down the pike that are going to be able to help people. I mean, that's why I ask these questions.

Dr. Insel: Well, this has come up at almost every meeting that we've had of the IACC, that has led to this list. I think where they were on this particular item and this came out of a workgroup that talked a lot about the need for services and the assessment of services was, the lack of information about the cost effectiveness and about which of the services are actually working best.

And so, the research mission here was to come up with projects that could tell us about essentially, the return on investments. What's working, and because we're putting money into supported employment, how much is that saving us from disability

costs and other costs?

Mr. Dunaway: A job could work real well, I could tell you that.

Dr. Insel: So, what I think

Mr. Dunaway: Or a mentorship.

Dr. Insel: Well, I think a lot of us have that sense that there is also a feeling from the workgroup that we actually don't have the numbers for much of that and so, for policy makers, to the extent that we can provide numbers, it helps to actually push the agenda.

Mr. Dunaway: I agree.

Dr. Insel: Our task is just to figure out what that's going to cost, to get those numbers, and what do you think?

Dr. Wagner: So, let's say $7.5 million, so, we'll make it

Dr. Insel: Speak up, so, what would this be?

Dr. Wagner: I would say $7.5 million.

Dr. Yeargin-Allsopp: Well, mine was a little bit higher.

Dr. Wagner: Yours was, that's true.

Dr. Yeargin-Allsopp: Yes, so, I mean, I said $9.5. So, should we make it like $10 million?

Participant: Okay with me. Dr. Insel: We're on the last objective under services. So, what again, let's provide this range of $7.5 to $10, because I think it's going to depend a lot of which services we're talking about and when this actually kicks in and the scope of the effort. But that will give them a range to think about.

Dr. Yeargin-Allsopp: I agree.

Dr. Insel: Home-stretch, gang. We've got to get this done in the next 15 minutes. So, what does the future hold? Short-term objectives, develop and have available to the community, research community, means by which to merge or link databases that allow for tracking the involvement of individuals in ASD research by 2010.

This is really just linking databases question.

Dr. Yeargin-Allsopp: Well, isn't this NDAR? I mean, it sounds like NDAR to me.

Dr. Wagner: Well, I think it says the means to - and others

Dr. Yeargin-Allsopp: Right, and how much does that cost?

Dr. Wagner: Well, but we're not talking about building a new NDAR. We're talking about the technology it takes to link NDAR with other kinds of databases. I think that's what this means.

Dr. Yeargin-Allsopp: Okay, yes.

Dr. Wagner: That's my interpretation.

Dr. Insel: Yes, and I think that's about $500,000 per year, yes? Della knows the numbers better than here again, we probably can do this down to the nickel.

Dr. Hann: To build the actual technology, it's about $500,000, but then to maintain it, because someone has to maintain

it over time, is another probably $100,000 a year. But that cost would continue out, because you have to maintain it.

Ms. Tanski: That's pretty consistent with what we are doing in Boston. We spent actually, we spend more, $600,000 a year on the development side.

Dr. Hann: Yes, actually, for maintenance costs for it alone are $750, to be honest with you. But we're just talking about this piece, in and of itself, that's where the $500,000 plus $100,000 over time.

Dr. Insel: Yes, and actually, it's that building out NDAR has been $3 million $3.2 million per year. We're in our third year. So, that's not but this is just for the link.

So, again, the figure sounds like $600,000, is that what you're saying, Della, $600,000? Are people okay with that?

Dr. Hann: Yes, that's it.

Dr. Insel: Okay, launch at least two studies to assess and characterize variation in adults living with ASD by 2011.

Dr. Yeargin-Allsopp: This sounds a lot like the one on the previous one, doesn't it?

Dr. Wagner: Well, this is more characterization. It's not intervention.

Dr. Yeargin-Allsopp: Right.

Dr. Wagner: But I think we thought this again, could be sort of shorter term, three year studies, $150,000 a year. So, $900,000.

Ms. Juliano-Bult: I was thinking of these as the study

Dr. Insel: You need to identify yourself.

Ms. Juliano-Bult: Hi, this is Denise Juliano-Bult from the research branch at NIMH. Normally, studies like these would be preliminary to developing services intervention. So, they're kind of like first step towards figuring out what kinds of services are needed in these areas.

Dr. Insel: So, this goes back to Wolf's comment about, this is more the description of what it is people are living

with and trying to find a way to quantify that.

Dr. Yeargin-Allsopp: Right.

Dr. Insel: So, and you think that for $900,000 this could be done?

Dr. Yeargin-Allsopp: Well, I think it would take a little bit more because this sounds more like some of the epi studies, some of the RFA's that we've had, like looking at the prevalence of ASD in adults and we usually have those types at about - you know, maybe $500,000 to one million a year.

So, I would think it would cost a little bit more than $900,000, maybe if we said one million a year?

Dr. Wagner: Okay.

Dr. Yeargin-Allsopp: For two grantees, two million a year times what? This is only for three years.

Dr. Wagner: Right.

Dr. Yeargin-Allsopp: Maybe six million?

Mr. Dunaway: I think it's kind of

Dr. Insel: I'm worried about

putting a little bit of rigor in here. I'm not I mean, these are as I understand it, these aren't true epi studies. These are meant simply to it says here, to assess and characterize the variations in adults living with ASD, so that social and daily functioning, demographic, medical and legal status - is it that expensive to do that?

Mr. Dunaway: I think what this is really trying to say is that, they're asking you to try to quantify that autism experience, try to get a sense of what it's like to live with autism, as best you can, as outsiders and then based on what you find, then build your models or your scientific research around what you found.

Dr. Wagner: But I do think there are people who have been doing longitudinal studies of fairly large cohorts. Not a lot of them, but there are a few with adults that you could track them. So, I didn't think it would have to be a big epidemiological effort.

Participant: Well, and I think the other thing is talking about the situation and

trying to just understand something like a range of service needs for folks and maybe better ways to try to match services to what people need.

Dr. Yeargin-Allsopp: So, just an example or just a convenient sample to do this, then yes, it would cost a lot less.

Dr. Kau: If there's a treatment goal in the earlier, can we combine the both - both goals, because to do the treatment, you need to

Dr. Yeargin-Allsopp: Right, that's what I'm wondering about, because it sounded to me

Dr. Kau: So, why two different studies?

Dr. Yeargin-Allsopp: Right, maybe we can just combine those and

Dr. Insel: Well, maybe, but don't worry about it because we're not designing RFA's here. We're really just trying to tell the IACC what each of these things on their wish-list would cost and it's we'll worry later about how to pay for

everything.

Dr. Wagner: So, we can make a note of it.

Participant: Given that we have been sort of low-balling some of these things, why would like $1.5 million? And I don't think it needs to be an epi study. I think it can be done

Dr. Yeargin-Allsopp: Okay, I agree, $1.5 million sounds fine to me, Tom.

Participant: Okay.

Dr. Insel: Okay. So, then we go to these two clinical trials to test the efficacy and cost effectiveness of intervention services and support and this is the piece that really gets at the daily functioning, and now, this is for adolescents and adults or seniors living with ASD.

So, this, I assume, we're back to now, the RCT kind of numbers. We've been talking about roughly $500,000 per year for those, and this is asking for two such trials. Is that about so, if that's a million per year over five years, is that about the right

range to be thinking about or is there something special about these kinds of trials that are done as cost effectiveness? This is more kind of like what's it called? I guess it's called effectiveness research.

Dr. Wagner: Right.

Dr. Insel: That's the new rage, that is there any reason to think that that would be more expensive, less expensive or can we use the figures we've been working with?

Participant: I think we can use the figures we've been working with.

Dr. Insel: Then we're at about $5 million?

Dr. Wagner: Yes.

Dr. Insel: Okay, unless anybody knows more?

Dr. Yeargin-Allsopp: No.

Dr. Insel: Okay, comparative effectiveness, that's the figure that keeps getting used. Okay. Long-term objectives, develop at least two community based interventions with individual specificity that improves outcomes as measured by educational,

occupational and social achievements by 2015.

Do we have something like this, that can serve as a guide for -

Dr. Wagner: Yes, we do have one.

Dr. Insel: what it would cost?

Dr. Wagner: We have the David Mandell study, which is about $700,000 a year. So, we put $750,000 per year for one study, would be $3.75 million for five years.

Dr. Insel: And would we need two set studies or is one study going to be able to get to intervention?

Mr. Dunaway: I'd like to see two, I really would and I'll tell you why. This country is different, different regions of the country, different there's a whole lot of difference in the country.

So, I would suggest that we at least have two. I'd like to see more, but two at least.

Dr. Insel: And that's just what it says, at least two community base interventions and for those you who do this

kind of work, I'm assuming that you need different studies to do different interventions.

So, if Ann, you're telling us it's $3.75 or something like that, so, it's about $8 million to do this, right, over five years?

Dr. Anderson: Kai Anderson from CMS. The way I'm reading this, because of all of at least two community interventions, it almost sounds like they're asking us to develop a demonstration, in addition to the evaluation part, in addition to the research. Is that is anyone else looking at that the same way, which would actually bring in more cost implications.

Dr. Insel: Anybody here at the workgroup, to know what they were asking for?

(No audible response)

Dr. Insel: I don't think we know, but we could

Dr. Yeargin-Allsopp: We could put in a range.

Dr. Insel: Well, maybe the thing to do would be to find out I know that David

Mandell, who was the person who was mentioned by Ann, is he was one of the people in this workgroup and my guess is that when he was thinking about community based interventions, he was thinking about the kinds of things we're doing, like a CMS demonstration project, but on a much smaller scale.

Dr. Hann: This is Della. I think the key to that one actually, is with individual specificity and I think that's the piece of it, it's taking probably some things that we already think may be working and stuff like that, but figuring out how to tailor them better to the folks who need them.

Dr. Insel: So, I think that if we put in $8 million, should there be an asterisks there to just check on that? I don't know that we have enough information here about whether there's a demonstration project needed in this. I'm not sure what that would cost.

Dr. Anderson: I think that makes sense.

Dr. Insel: Okay. Do you have even

a ball park figure of what it would cost?

Dr. Anderson: A demonstration?

Dr. Insel: Yes.

Dr. Anderson: Big bucks.

Dr. Insel: Yes, 100 times this?

Dr. Anderson: Yes.

Dr. Insel: Okay. So, it's closer to a billion?

Dr. Anderson: Really big bucks, yes, in terms of I'm coming from the CMS demonstration, we're all for that.

Dr. Insel: Yes, right, well, you guys have real money. That's the difference. We tend to think about millions. You tend to think only in billions.

Okay, develop and have available to the research community, means by which to merge or link administrative databases that allow for tracking of the involvement of individuals living with ASD, research and healthcare, education and social services, and this one goes trails out to 2018.

Dr. Tanski: This one happens to dove-tail almost exactly with an RSA that we

have out now, that's looking at encouraging folks to find ways for getting into large databases, linking them and be able to do that kind of thing, not specifically for autism, but in the realm of mental health services research.

And so, I don't know if any are going to come in for autism or not, but the main point of the mechanism is to develop sort of the info-structure for being able to do that kind of data merging.

So, we're probably able to supplement and encourage someone to include autism in what they're looking at merging. It will probably broaden beyond what we normally see in mental health, into things like the education system, to merge that like the services data. But it can build on something we already will have, by the time this is finalized.

Dr. Insel: So, Ann, what's the reasonable cost estimate here?

Dr. Wagner: I got this from Denise, so, $300,000 is what she was

estimating to that would it to supplement. That was to supplement one.

Dr. Insel: Anybody else have some ideas about this? It says for linking administrative databases.

Participant: So, the data is already collected.

Dr. Insel: The folks at CMS? Kai, do you have any idea of what this costs to do?

Dr. Anderson: I don't think it costs more than that to just simply merge the databases. But if you wanted to do something with it, I don't know if we're just talking about merging a database and making that available to the public to use.

Dr. Insel: Right, yes, it's building a new database, based on administrative databases that are out there. So, it's essentially providing that as a resource for investigators who want to mind all of the Medicare data, want to mind all of the HUD data, anything like that.

Dr. Anderson: Maybe three to $500,000.

Dr. Insel: Okay. So, we're in that range. After all the money we've just been looking at, that's pretty small potatoes.

And that is it. We've done 35 of these. We've got a few minutes just to sum up and to see if there any points that you want to add, as additional items for the IACC, to give them some feedback on the costs.

Remember, we started by saying that this doesn't have to add up to any specific number. If this is two billion, that's fine. If it's two-hundred-million, that's fine as well, maybe not as fine, but that's also a possibility.

What they wanted were just budgetary requirements for each of these, remembering that some of these may change between now and the time when this becomes more final, because we've still got the draft plan out for public comment, and so, any part of this is still up for modification and revisions. But this will certainly give them something to work with.

I also wanted to provide some time

for any of the members of the IACC who are on. I know Lyn was on before. I don't know if anybody - if she is still with us or anybody else is with us, to also provide some feedback, so let's start with them.

Lyn or anyone else from the IACC, are you still with us?

Ms. Redwood: Tom?

Dr. Insel: Yes, I can hear you. Go ahead.

Ms. Redwood: I'm so sorry. I've been working here from home and I had it on mute. I just want to first thank everybody who is there that has taken their time out today and dedicated it to this cost estimate. It will be really helpful information for the IACC.

But I would like to just get everybody to step back and just look at the budgeted numbers just make sure that there's balance between genetics, environment, treatment – I just see that there are some areas that need to be so funded and I just want to make sure that we have a really broad,

balanced, diverse research portfolio. I also wanted to voice my concern about the trend of just supplementing existing database because I feel like that creates the status quo of our system and I really want new ideas and new researchers who maybe are in other fields to get involved in autism research, so I think we need to strike a balance between the existing studies we have and utilizing them better and also having new studies and I'm a tiny bit concerned about linking the databases to studies in other countries, things like Denmark and Norway, because their lifestyles and environmental exposures, medications, vaccine use, they're all really quite different than here in the United States. I really think we need our own databases here too. So I just wanted to throw out those points and I really want to thank everyone again for all the time put into this.

Dr. Insel: Well thanks, Lyn, for those comments and for sticking with us throughout the day. Anyone else from the IACC available?

Let's see, are there any comments from around the table or on the phone?

Dr. Mumper: I just want to in the spirit of sharing new paradigms, Deborah mentioned the value that might be gained from looking at things like Rett or Fragile X.

For our paradigm, we are very interested in looking at what work has already been done in the field of like, cancer or Alzheimer's because we are very convinced that there are some common mechanisms here at work and that if we look at mechanisms of other chronic diseases and step out of the sort of, typical genetic profile, I think that it could very valuable.

In terms of decreasing costs and coming up with potential interventions that are going to be available to the autism community sooner, I would rather not re-invent all those wheels and I would rather borrow heavily from translational research and our colleagues in other fields, that inform these very basic physiologic processes that people with autism have. So, that's my final comment.

Dr. Insel: Thank you. Any other comments? Wolf?

Mr. Dunaway: My only concern is just that we understand that a person with autism - in autism, there's a lot of granularity. There's a lot of differences between people.

It's always been said to me when I've heard it, is that if you meet one person with autism, that's what you've met, one person with autism. There's a lot of uniqueness in autism and it's going to be difficult for us and you won't be able to – like the nice lady on the phone said – about there being differences in different cultures and different countries.

A person with autism, everybody learns to survive in their own unique way. So, when you're doing these studies, we have to remember that each autistic individual is just that, highly individual, and if you lose sight of that and just start placing numbers in databases, you lose sight of the fact that each of us are individuals, you'll lose sight of

the fact. I just want you all to remember the granularity and the individuality.

Dr. Insel: This is a point that is emphasized a lot in the draft plan and it's, I think, part of what has been a big barrier to progress, is that we keep doing what has been called average science instead of personalized or individualized science.

So, we're looking at bringing 50 people who meet some criteria together and looking at the mean difference or mean effect, and that may not be the way to get at the kind of granularity you're talking about, which is what we really need.

And so, it may require different kinds of designs and different kinds of approaches. I think we heard a little bit about that today, but we've certainly heard it within the IACC and we heard it in every one of the workgroups, they stressed this as well.

It's actually interesting, Liz's comment, because some of the same issues are coming up now in a big way, in areas of cancer, where we realize what we thought was a

single form of cancer is actually 50 different kinds of cancer and we have to figure out 50 different kinds of treatments, often.

Any other comments? Della, anything for us that we need to think about before we adjourn?

Okay, well, thank you so much. This has been a bit of a whirl-wind. I know we had to rush through a lot of this, but it's really critical that we provide the numbers that people have asked for.

This is a place where I sometimes think the perfect is the enemy of the good. We - none of these numbers are going to be entirely accurate, but they are going to give us a starting point and I think in aggregate, they'll give the community a sense of what the cost of the plan would be if we were going to try to do all of this.

Thanks very much and we appreciate your coming here, sometimes from far away. Safe travels, and thanks to everybody on the phone or on the webinar. We're adjourned.

(Whereupon, the above-entitled

matter concluded at approximately 2:30 p.m.)