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STRATEGIC PLAN UPDATE

Working Group 4 – Question 4 – Which Treatment and Interventions Will Help?

Conference Call 2

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Proceedings:

DR. SUSAN DANIELS: Hi. This is Susan Daniels at the National Institute of Mental Health Office of Autism Research Coordination welcoming you to today to the conference call of the IACC Strategic Plan Update Working Group for Questions 4 which treatments and interventions will help.

We'd like to welcome our public audience as well as members of our working group and Dr. Kevin Pelphrey who is the chair of this working group. I think that we won't go through specific introductions today since we did that on the last call but I'll go ahead and read roll call just to make sure we all know who is on the line. So starting with Kevin Pelphrey.

DR. KEVIN PELPHREY: Yes I'm here.

DR. DANIELS: Thank you Jim Ball?

DR. JAMES BALL: Here.

DR. DANIELS: Thanks. Samantha Crane?

MS. SAMANTHA CRANE: Here.

DR. DANIELS: Thank you. Geri Dawson is not going to be able to join us today. Tiffany Farchione? Melissa Harris? Elizabeth Kato? Alice Kau? Louis Reichart will not be able to join us today. Rob Ring?

DR. ROBERT RING: Here.

DR. DANIELS: Thank you. Tim Buie?

DR. TIMOTHY BUIE: Here.

DR. DANIELS: Connie Kasari?

DR. CONNIE KASARI: Here.

DR. DANIELS: Thanks. Christie Kavulic? Alex Kolevzon? Elizabeth Laugeson is not going to be with us today. Alex Leonessa? Beth Malow?

DR. BETH MALOW: I'm here. And I'll be in clinic staffing so I'll come in and out as I can.

DR. DANIELS: Thank you that's fine. Nancy Minshew? Sam Odom is not going to be joining us today. Mustafa Sahin?

((Crosstalk))

DR. DANIELS: Fred Shic?

DR. FRED SHIC: Here.

DR. DANIELS: Thank you. Phil Strain? Dennis Sukhodolsky and Zach Warren? Okay so we've gone ahead and finished the roll call and anyone who's currently listening but trying to get into the speaking line please feel free to just jump into the conversation and let us know you're here. And as people speak on the call please indicate who you are so that people in the listening audience can tell who's speaking.

So we appreciate everyone joining us today. For today's agenda we're going to be working on looking at progress that's been made in the field in order to provide information that we can use in the Overview of Progress Section of the strategic plan update which this group will be writing as a group.

So we're going to start with some follow-up from call one. We did have a question from Beth Malow about the content of the AIRP program. And our staff has looked into that and we've got a little bit more information about some of the projects especially on co-occurring conditions that were funded in 2013.

We have that information that if it is needed during the writing process we're happy to share it with you and get additional details from HRSA but the way we have it listed in the portfolio analysis is the way it's reported in the database systems which is a single project and so it doesn't have a lot of very specific detail about all the subprojects but we certainly can provide that information for the working group as you need it. So, you know, as you go along if you need that information let me know. Are there any...

UNKNOWN FEMALE SPEAKER: Yes, SAMHSA

DR. DANIELS: Yes thank you too for asking about it. There are a lot of different subprojects in that. It's a very large project and so it might be worthwhile to review that information. And so we can pass around some information about that especially for those who might be writing a section and co-occurring conditions and treatments for those. Are there any other follow-up questions people have from the first call?

(No response.)

DR. DANIELS: So then for our first agenda item for today we want to take a few minutes to talk about public comments that we received in response to a request for public comment that was put out by the IACC. And the request for public comment was structured so that we could collect input on each of the seven areas of the strategic plan to find out what issues the public thought were most important to make sure are included in any updates of the plan.

And so I've given you a document. This is something also that members of public and access on our Web site that there is a list of themes that are office identified from the comments that were shared. And we also have the full text of the comments on our Web site. So does anyone have any comments about any other theme areas or any

particular points that struck you as you reviewed comments that came in?

DR. BUIE: I think it's actually - this is Tim Buie. I think it's a very nice clear list a request from patients and families of patients because I think very often families don't know who they're seeking on the caregiver side to talk about issues of nutrition or supplements or complementary therapies. And there are generally developmental pediatricians are focused on those issues and it's not something they have great comfort with. And at least identifying that whole list kind of points to the similar questions that they'd like better research on these topics, they'd like more information about some of these issues and interventions.

There isn't a great clearinghouse for that information for families to access. And I think that is a big need even though there are some places trying to fill them. The information that's coming from some sites are, you know, more anecdotal than databased. And that's really a lacking piece of information on the community I think.

DR. DANIELS: Yes that's true, good comment. Do others have some comments on this as well?

DR. KASARI: Well this is Connie. I'm struck just by how many interventions they would like to have tested or kind of strong feelings about particular therapies. So, you know, I think it just, you know, suggests that there's a lot of heterogeneity out there in terms of what people want to see and how people think about these different interventions so yes I think the comments are really informative.

DR. DANIELS: Thank you. It's true that I think for this working group it'll be a challenge to encompass all of these different areas in our chapter in a comprehensive but readable format

because there are so many different areas that we need to cover. But it was good that we got feedback on a lot of them through the public comment. Anything else that…

UNKNOWN FEMALE SPEAKER: I was just curious Susan at staff how many comments did we get?

DR. DANIELS: I don’t have that in front of me. There are a lot of comments. It's actually 1100.

Unknown Female Speaker: Oh my goodness, wow.

DR. DANIELS: So it’s not just…

UNKNOWN FEMALE SPEAKER: That’s great.

DR. DANIELS: …for this question but…

UNKNOWN FEMALE SPEAKER: Yes.

DR. DANIELS: …for the entire request for public comment which actually that's the largest number of comments we’ve ever received from one of these. We periodically do request for public comment. In the past we’ve usually had on the order of 500 to 600.

So I think that it probably helped too with the way that we were able to put the Web form together this year and get it publicized. So we really, really appreciate the comments that came in from the public and the people were invested in trying to help us understand their perspective. Anything else that you - yes go ahead.

MS. CRANE: This is…

DR. DANIELS: Yes go ahead.

MS. CRANE: This is Sam Crane from (ASAN). One thing that I find interesting about the comments about prioritizing early intervention is that, you know, there's a need that's sort of jumping the

gun a little bit in terms of saying well there's an assumption that early intervention is going to be more effective.

But for a lot of these interventions we don't have that evidence base on timing so I think that, you know, as part of talking about early intervention it might actually help to develop more of an understanding of, you know, which interventions work better when they're earlier and which interventions actually work better when you start them when the child is a little bit older.

DR. DANIELS: Thank you. Other thoughts?

DR. PELPHREY: Just playing with that idea - this is Kevin Pelphrey. Just playing with that idea a little bit that what came that she mentioned was such a win for our field to really emphasize the importance of early intervention. But I'm starting to hear that emphasis and the exceptions of that idea actually used to argue you can imagine kind of against adult interventions and older adolescence interventions a lot of times and talking with people around issues of insurance coverage.

But I think to then this point is really important and also it could be helped along by science, mentioning the science in our report that suggest that adolescents is that and young adulthood are periods of reorganization that we can take advantage of from the neuroscience literature that's coming up about that cognitive neuroscience in particular.

MS. CRANE: And then this is Sam again. Actually that reminds me of another situation where in addition to just adults where we're seeing real harms from this attitude where if you look at research on communication based approaches, communication interventions, things that are intended to improve communication ability almost all of the randomized controlled trials

that we see are on people under age 5 or 6. And if you if you only look at that then you're not actually necessarily going to be capturing the population of people who don't speak until after age 5 or 6 or by the time that they reach that age they're still not speaking. And that's going to be an important subpopulation because those are the people who have the most significant communication challenges.

There are a lot of people who, you know, aren't speaking at age 2 who actually aren't going to have very specific - significant communication challenges in the long run. They just are taking a little bit longer. People who don't speak by age 6 have the most significant communication challenges and their brains are in a different stage. They're no longer in the intense language learning stage where an early intervention is going to cause really rapid growth.

But we really can't ignore the population of non-speaking kids over the age of 6 because these are also going to be the group of people who need the most help. And they might need different kinds of help than the things that work for kids that are at the early language learning stage.

DR. KASARI: This is Connie Kasari. I appreciate those comments. I think one of the themes is interventions on minimally verbal individuals which usually signals past age 5. NIH actually has funded a large, actually two large ACE programs on minimally verbal kids. One of those is specifically on interventions.

Another one has an intervention trial. There are a couple of other randomized trials on older minimally verbal individuals now on treatments and kind of trying to think outside the box. So I think that there has been significant…

MS. CRANE: Are you referring to trials on improving language based miscommunication or other treatments?

DR. KASARI: Language-based communication.

MS. CRANE: Okay.

DR. KASARI: And so I think...

MS. CRANE: I'm sorry, so I was just looking at what has been published so far and I hadn't seen that.

DR. KASARI: Yes. Well I think they're not quite up to the, you know, I think we stopped at what…

MS. CRANE: Yes.

DR. KASARI: …2013 or something? So there have been some newer ones. I still think it's a good priority area but there has been movement on that I think in response to public comments. So it's just - that's just an FYI.

MS. CRANE: Who is speaking because I want to follow-up with you about that afterwards?

DR. KASARI: It's Connie Kasari.

MS. CRANE: Okay, Connie, thanks.

DR. DANIELS: Any other comments about public comment?

(No response.)

DR. DANIELS: Well great. And those public comments will be available to the working group and to the entire committee, you know, going forward as you do the writing and work on the strategic plan update. So you can always refer back to the comments. We'll also be talking about

those comments in the IACC meeting on October 26 so we'll have time to consider them further but appreciate you all having a look through them.

So the next portion of our discussion will be to talk about progress that's been made in the field in terms of accomplishments and also thinking forward to what we need to do. So I want to go through this in some kind of order just so that it's easy for us to put the notes together in a way that's going to help the working group.

So I want to start with behavioral and social interventions. And the kinds of issues we want to talk about are what kind of progress has been made in the field, what are some of the barriers and opportunities that have emerged, progress that's been made in translating research to practice and different needs and gaps that can be addressed through research. So if you can comment on that with regards to behavioral and social intervention. The floor is open.

DR. KASARI: So Susan is this just in general or based on what? On - so we have the - we have the studies there were chosen from up to 2015 right? So are we talking about more recent than that?

DR. DANIELS: Yes.

DR. KASARI: Okay.

DR. DANIELS: So we're talking about probably more recent. So with the IACC they selected some research advances to highlight in their summaries advances publications which I provided to you just as a reference. But we're just asking you all as experts in the field if there's some particular areas that you think, really significant changes of happened in the field that might even be more recent that have changed our thinking about where the science is going or presented new

opportunities that we need to take advantage of in the next strategic plan update.

DR. KASARI: Right.

DR. DANIELS: So what you think about that so feel free…

DR. KASARI: Okay.

DR. DANIELS: …comment.

DR. KASARI: Yes so I would say - and this is Connie again. I would say that in the last year or so we've seen more studies that are done in community that are randomized controlled trials and of significant size so more studies in actual community centers or in schools.

So I think that implementation science approach has actually happened in terms of testing different interventions in the community so I think that's an advance. I think we still need more but that's an advance. I also think we've had a little bit on the minimally verbal kiddos which is an advance. And there have been many, many treatment trials now with parent mediated interventions and most of those are for young kids.

DR. DANIELS: Do you have any comments about particular findings that have moved us forward that might present new opportunities for research?

DR. KASARI: Yes I think that in the implementation ones in the community that we're getting significant results that are similar to lab-based ones. So I think that that's promising. And newly verbals are finding that we can move kids past age 5 to actually use spoken language if not just more communication generally.

And with the parent mediator I think that's the area that's the most kind of perplexing

because I think depending on the type of intervention that's done and the age of the child actually matters as to whether or not the trials are coming out with significant findings.

So we have a number of trials of really young children that don't show a difference between a particular intervention and a control group so that's kind of interesting. And it may have to do with just not understanding that sort of developmental trajectory the children are going through, what those needs are for parents or for kids, you know, probably lots of different factors. So I think it's an area that still needs significant attention.

DR. DANIELS: Are there any particular barriers that you see in this area that funders could be addressing or that researchers could be addressing?

DR. KASARI: Well I think that trials need to be, especially randomized trials need to be of significant size and that doing lots of little tiny trials I think is not as useful as going ahead and fully powering. Sometimes, you know, they're just not powered to actually be that informative.

So that's, you know, I think that's really true of sort of the telehealth types of interventions which I think are really important if we're going to kind of throw the net wider and reach a lot of families that don't have access to a research center. Those need to be well-designed and well, you know, empowered. And they also need a significant intervention that works. We don't know that we're there yet.

DR. DANIELS: Thank you.

DR. RING: Hey Susan this…

DR. DANIELS: Yes?

DR. RING: …Rob Ring.

DR. DANIELS: Yes?

DR. RING: I couldn’t agree with Connie more on these last couple of points and just really the, you know, the opportunity costs of pursuing, you know, fundings that may not be as well supported, you know, by, you know, trial design and statistical power can be significant.

It's not to say that the smaller trials that, you know, have increased in number are informative but there are risks associated with it. But I think a lot of this could be attended to by, you know, forcing a rethink on, you know, the best practices when it comes to the size and design of studies out there. And this would be true of all modalities of therapeutic interventions not unique to behavioral interventions so as the modality. It's true of all cases.

DR. DANIELS: Yes it’s also a theme that came up in the last strategic plan update as well but I think would be fine for you all to reiterate here. Go ahead.

MS. CRANE: This is Sam. I mean one of the trade-offs is that when you have much larger trials it's harder to investigate, you know, highly personalized or contingent interventions that are aimed at a very specific subgroup of people or people who haven’t responded to other kinds of interventions. And so, you know, we want to be able to get, you know, really good powerful studies but we also want to be able to tailor interventions to specific needs and sometimes…

((Crosstalk))

MS. CRANE: …that can lead to smaller studies.

DR. RING: This is Rob. I agree with that completely and it may have arrived prematurely in the conversation in terms of Susan your anticipated order of things. But I think it's going to come up across many of our points of discussion. It's, you know, unless we find a way to reduce the complexity of the autism heterogeneity, understand and get our arms around that, better define subgroups, that ontology subgroups that lie underneath the autism umbrella, you know, we can power all the studies we want up to statistical confidence but we still may not be able to overcome the lack of fundamental knowledge around that heterogeneity.

And so these points I think all talk to each other in some way. They're not independent from one another. So that promise of personalized interventions and that, you know, desire to have greater confidence in the findings that come out of studies really in many ways will be realized through better understanding and reducing the complexity of the heterogeneity out there. And that comes through biomarkers and other points of discussion later on but it's just a very tricky challenge moving forward but I think it's doable.

DR. KASARI: Oh well I…

MS. CRANE: The other…

DR. KASARI: Oh, go ahead.

MS. CRANE: Go ahead, go ahead Connie.

DR. KASARI: Well I was just going to say that, you know, I agree that heterogeneity is it shouldn't be a problem for trials. But and there are - I think we need to be a little more sophisticated methodologically to handle some of the heterogeneity. So one of the models is to do an adaptive treatment design or a smart design in which one can look at children who are responding

or non-responding in the population that you're interested in.

And so I think then you get into thinking about personalized trajectories for individual kids. Those have to be powered but they do provide the kind of information you're talking about. I think we need to kind of think outside the box a little bit more on our treatment methodologies.

DR. RING: Amen.

MS. CRANE: So the other thing that I would raise is - this is Sam again is that, you know, we have to look at not only, you know, there's the laundry list of specific interventions that people want tried but sometimes we're - we've seen studies on interventions where they've studied it but they haven't actually even really looked at the right outcomes or the outcomes are not necessarily the same ones but people really care a lot about.

So, you know, in communication interventions for example I don't know about the ones that Connie was just mentioning that I haven't seen yet but a lot of them measure the, you know, any increase in spoken vocabulary or spoken, you know, verbal behavior how many times the person says something. But a lot of the times what we're really more interested in is an increase in functional communicative capacity. So if someone is going to be using, you know, an iPad or a text to speech system to communicate a very robust text to speech system is going to be really important to us whether or not the person increases the number of spoken verbal behaviors that they have like on some level doesn't really matter that much to that person's long-term ability to communicate whether they're using, you know, signing or typing or speech. And so that's something that we want to make sure that we're focusing on a lot.

DR. KASARI: Absolutely. So I think what you're referring to are what are the meaningful outcomes and to think about what that outcome or that endpoint is for a treatment trial. And at this point we have no agreed-upon outcomes that are really meaningful. So I think that's a problem when you try to compare these different interventions. But Sam I'm happy to send you a paper that I think that…

MS. CRANE: Yes I think I'd be very interested in seeing it. I didn't - that's not the only context in which I see this happening. I just it was…

DR. KASARI: Right.

MS. CRANE: …it was on my mind and…

((Crosstalk))

MS. CRANE: …an example of an outcome that I could I would consider meaningful versus non-meaningful.

DR. KASARI: Yes. So in general that's probably an issue for us because I think it is hard to think about the outcomes of some interventions that just seem so meaningless. So you get a change, you get a significant effect but it may not have a lot of meaning to the individuals or to practice or sustainability of an intervention in a context. So I do think it's something we have to tackle at some point.

MS. CRANE: I 100% agree.

DR. DANIELS: So outcome measures -- this is Susan -- is on the little outline that I've provided for the group, the questions or topics. I know that that was something that you all discussed a little bit last time and has come up over the last few years as we've been doing strategic plan updates. And there were a number of

issues related to outcome measures, treatment response and personalized medicine that you've all brought up including just developing markers and metrics to measure treatment response.

Kevin had brought up sex differences in treatment response, non-responders to treatment, stratification of patients using various methods, how we're going to research outcome measures and quality of life and long-term outcome measures, inclusion of individuals on the spectrum and planning intervention research in determining outcome measures and intervention as prevention. So as long as we're on the subject if others have particular thought that you want to share on any of these types of topics please go ahead.

DR. SHIC: Well I think - this is Fred. In relationship to the, you know, incorporating the feedback from individuals with autism to these treatment programs I think it's kind of traditionally been, you know, part of the protocol to try to understand the perception and the value of these different treatment interventions for individuals with autism when they can provide that feedback directly. It's - I don't know if we've made a lot of progress in terms of systematically incorporating that into the way that these research projects evolve over time or in fact even insofar as how we designate, you know which areas of research need to be focused upon.

I mean thinking in particular about adults with autism there kind of needs and the things that we as researchers want to focus on when we conceptualize autism maybe core deficits, quality-of-life they sometimes may be at odds. And with the individual needs of individuals with ASD, especially those who can really kind of try to express what it is that they want.

And I wonder if that might be an area that we can kind of think about like Connie had mentioned, thinking outside of the box of how that - those

perspectives can be incorporated more systematically into research projects and planning for which research projects to fund.

DR. DANIELS: Does anyone have any ideas about that or thoughts about what kinds of things would need to happen in order for that to take place?

DR. KASARI: Well I'm thinking about it. I think it's - you raised an interesting point Fred because I do think we want to take into perspective of the folks that need intervention. And I'm not quite sure how to do that but I do think about social skills interventions in particular.

And so sometimes I mean for my own experience doing work in schools with kids on social skills sometimes we enter kids in because they have autism but they don't all have a need for a social skills intervention, you know what I mean? So we sometimes have kids in there that are already very high on whatever outcome it is and we don't exclude on the basis of that. I think with adults they sometimes don't want social skills interventions but some do right? So this…

DR. SHIC: And so…

DR. KASARI: …they can kind of self-select into this. But with kids we often we can send them to their parents and then they say sure whether or not they need something. So I think that I don't quite know what I'm saying but I think it is kind of personalizing the intervention through a need. It's not always the need.

DR. SHIC: And Connie I think you bring up this…

MS. CRANE: This is Sam. Oh.

DR. SHIC: Oh.

MS. CRANE: Go ahead.

DR. SHIC: Go ahead. Sorry I was going to say that - please go ahead Sam I'm sorry.

MS. CRANE: Sorry I'm bad at taking turns. I'm autistic. So Connie - what Connie was mentioning is really true to a lot of our members' experiences. And a lot of social skills interventions this goes back to what is a meaningful outcome right? So social skills interventions might teach a person the scripts they need to sort of be considered socially acceptable and follow, you know, what people consider the rules that they should follow but they're not necessarily going to improve a person's social outcomes like whether they have meaningful mutually supportive long-term friendships and relationships.

Whether the - they can, you know, learn - when to say no and when to not go along with people and when to not cooperate. And that in some cases we even see people saying that, you know, social skills they learn through social skills interventions hurt them in meaningful ways. They learn that they were supposed to just go along with people or they learn that it wasn't okay to be different or break the norm in situations when maybe that was actually what they should have been doing. So that's important.

DR. SHIC: And I think that it's, you know, because there's such - there's so much variability in the response I mean on multiple levels right? So Connie was alluding to that some adults with autism they basically self-select into these social skills groups because some want it and some don't want it.

And so I think, you know, the focus has been on those individuals who want it. What about those individuals who don't want it and what do they

need? What would they prefer? Why do they look at this and say like this is not something we need?

And with the kids, you know, this the fact that some kids aren't finding value in these particular programs that we've developed for them and Sam as you said, you know, that some kids are actually finding these programs deleterious when they look back and just kind of gauge how it's impacted their lives.

You know, and I wonder if this all could be wrapped up in this idea of, you know, that I think maybe Connie was alluding to also that we need a real science of personalized medicine that can allow for these group designs to kind of stand as an overarching structure but really to make this mature in the sense that we really just need the - we really - we need the personalization to be built into the group structure in a way that these studies can still be interpreted despite the massive heterogeneity that Rob was talking about.

And I wonder if - that's the - one of the areas of need that kind of crosses over in these, you know, when thinking about the interventions this conceptualization of kind of organizing heterogeneity as a core feature of the personalization process and the group design.

DR. KASARI: Right I think that that's it. It's trying to understand heterogeneity. It's also trying to understand active ingredients of the treatment. So we're talking about the individuals with autism as having heterogeneity, different needs and so on. So not a single treatment's going to work for all individuals.

Not - some individuals don't need an intervention at all but we also don't understand the interventions very well. So what are those active ingredients that those components that are important, you know, that's the mechanism for whatever the outcome is that is hopefully

meaningful if that makes sense? I think there's a lot of work on that front that needs to be done.

DR. SHIC: And especially I think focusing on the motivational piece and the perspective, this kind of perspective of value, how is this valued by the individual who is in the treatment? How is it valued by the parents, how is it valued by the, you know, families and communities?

And they're all at different levels and kind of this hierarchal structure of really defining value I think is something that and honestly it seems like it's maturing as well.

MS. CRANE: And it - and again I don't want to ignore the importance of outcomes measures in this context as well, you know, the - if you're measuring the number and frequency of prosocial behaviors or, you know, the behaviors that you've decided are pro-social you might get very, very different results than if you're looking at things like how many friends does this person say they have?

How much time do they spend with friends? You know, do they feel lonely, you know, or do they feel that they're in conflict a lot? You know, what are the social goals of this person?

You know, a lot of autistic people, you know, all they really want is, you know, one or two very good friends and once they have that they're really happy. And, you know, not all of these social skills interventions are necessarily going to help with that.

DR. SHIC: I do think that the area of kind of understanding markers is really important. But I think, you know, as just the context for those markers it's equally important to be able to link those up to as you say the things that really matter.

And I think that we are, you know, there's a lot of things that are very exciting to us, you know, neurophysiological measures, neurochemical or even, you know, serum levels of various chemicals that we know affect mood or self-regulation or but I think that's - that we haven't kind of come up with a really standardized way of considering these measures.

And I think that that's one of the challenges and really to always, you know, look at these measures keeping in mind exactly the point that everyone's raising that it has to be something of value.

I was wondering, you know, is - I was going to actually just go back a little bit to some of the comments that the - that were made on the - by the public. And, you know, I was struck by, you know, there was - it seems like there was a reasonable amount of dissatisfaction about how kind of an integrated or not really chaotic but just kind of non-unified the different areas of research were.

And there seemed to be a real desire to kind of unify all of these themes that we're talking about under more systematic and more just in a more organized fashion. And I was wondering if anyone had some thoughts about, you know, is – are there some as we're talking about the active ingredients of treatments are there some active ingredients of research in treatments that we should be really focusing on as well?

DR. BUIE: I mean it's a good question. This is Tim. On the medical side heterogeneity is such a difficult issue when you're including patients. And, you know, we're going to come to this shortly but when you look at the dietary studies for instance or the medical intervention studies you're looking at treating people with a whole variety of ways that they present and they aren't necessarily presenting with the same problems that bring them to the choice for the treatment that's

offered them. And they may not have anything that is very clear to the treatment.

And I think that what a lot of the families are asking about is they'd like at least a good effort put towards establishing those norms. When we look at a GI questionnaire there is not a single validated GI tracking questionnaire for progress over time.

There's not anything that's out there for us to use. We use one that people are published and so we choose it as the standard but none of the tracking tools for these therapeutic interventions are very well-established. So it's hard to design the study I think to give really hard science to success. And, you know, narrow into what are the symptom (competences) that are going to most likely to respond to certain interventions?

I – and I think everybody has struggled with trying to develop a framework for setting those research trials up. Maybe that's because we're coming to this from so many different specialties that it's easier if you do this as a bench researcher or through some systems pathway. That's - I wonder if we could get help from systems biology people to sort of tell us how to follow through with this in a more systematic method so that the data collection gets more similar.

DR. RING: Yes and this is Rob. I, you know, I think we're sort of aggregating around this topic for a reason, you know, particularly the topic of measuring outcomes and clinical endpoints and perhaps to make both the supporting comment and maybe a comment of obviousness.

But, you know, from a strategic point of view if we even look above the level of, you know, conduct of specific trials and the probability of success of an individual trial and being able to test and answer a particular question about an intervention or not from a strategic point of

view, you know, the lack of or the underdevelopment shall we say of validated clinical endpoints regardless of the target we may be talking about, it could be a GI clinical target, it could be a behavioral target. It could be seizure, it could be sleep, it could be anything that could ultimately be the focus of some therapeutic intervention.

The absence of having really strong clinical endpoints is really dampening a lot of the enthusiasm among funders across that funding, you know, landscape. It's not just NIH or it's not just nonprofit foundations looking to prioritize where they want to fund research. It's also, you know, the venture investment in entrepreneurs working on cool ideas. It's large companies that would like to develop medicines and medical foods and therapeutic technologies.

And it's the FDA, the regulatory body that oversees the pathway to the market that many of these interventions have to travel. They all, you know, see great risk in the absence of having good validated measures. And until we really tackle that forcefully we're I think holding back a lot of when that could be put into the sales of this field from a funding point of view.

And so I just probably stating the obvious just from a strategic point of view and not just a tactical execution of clinical trials. If we don't get our arms around this it's going to really continue to dampen initial investment in this field regardless of where it comes from.

DR. SHIC: Now the big question is of course what does that even look like? What do those outcome measures - I mean do we need to be thinking about just a singular easy to interpret measure of positive progress? I mean I think I've seen the biament used in pretty much every clinical trial involving kids but I wonder, you know, as far as change measures go, you know, do -

have we made progress in saying these are the best measures of change?

And have we made progress in viewing these measures as not, you know, kind of solitary units that can't be broken apart and again to look into, you know, what makes these measures good measures or is that - it's the reason why this hasn't been explored as much is because in some ways it seems like it's unexciting science? And so for that reason it doesn't have the kind of excitement to it that other, you know, more experimental studies or proposals, research proposals would?

DR. KASARI: So it's an important topic.

(Silence.)

DR. MALOW: This is Beth. You know, I wanted to mention, you know, it begs the question of whether we need to do more research or fund more research in the outcome measures. And I know I was looking at an RFA or it may have been a program announcement in the past around NIMH and NICHD working at outcome measures in neuro development or developmental disabilities in general not focused on autism. So I know, you know, I know those have occasionally come up.

So that, you know, might be one thought is to focus on research that would actually solidify the outcome measures. I'm not as familiar going back historically in the field. That may have been done before but that's one thought that comes to mind listening to this conversation.

DR. RING: This is Rob. I can offer an example of how this was in part tackled when I was at Autism Speaks previously. And actually this was work that started collaboratively when I was still at Pfizer and Geri was the CSO. Geri Dawson was CSO of Autism Speaks. We recognized this need for validated outcome measures, you know, many years ago as well and started an initiative aimed at

trying to assemble experts in endpoints, clinical trials experts, you know, in all of the allied disciplines that would feed into the development and validation prioritization of endpoints out there including FDA.

And, you know, the biggest question for us as an organizing principle around that because we would - essentially we funded the working group, these working groups to develop consensus statements on the state of validation for endpoints supporting particular labeling paths.

And so this was a medicines development heavy sort of focus but it could be easily applied to any modality. And to start that we had to really ask the question what do we view as the clinical targets for therapeutic interventions whether or not it's medicines or technologies or medical foods or any number of different behavioral interventions?

And they may differ as you look at the modality but I would argue that many of them are going to be the same because it's that endgame that clinical target that at least in the medicine development world would define the label and define all of the research to deliver on.

And we at that time agreed that we'd focus on three targets that we thought were of great perceived impact for the greatest number of people out there. It wouldn't hit everyone but they were the social communication deficits. They were anxiety associated with autism and they were some of the repetitive behaviors.

And we organized efforts around that but that could have easily been sleep architecture. It could have been easily GI issues. It could have been easily seizures. It could have been any number of them.

So I think - or they could have been just global measures of improvement that are unique to autism. But regardless of where you go and how you organize it I think there has to be some agreement on what we think are from a prioritization point of view the most tractable clinical targets out there for measuring change in in the here and now and start there.

DR. DANIELS: So it sounds like you've got a good discussion on outcome measures and it probably will be an area you might want to consider for one of your three objectives for this area. But I'd like to unless anyone has a pressing comment to make on the same topic I'd like to move on to something else so that we can make sure we have enough time to cover other important issues that you all might have input on some input on.

So if it's okay we'd like to move on to talk a little bit about what's been going on with medical pharmacological treatments and the status of that science, what have been the important advances we've made in the last few years, some of the barriers that remain in that area, ideas about future directions.

DR. RING: This is Rob. I'll make one comment. And I think it's very encouraging, you know if you just look through the lens of current clinical trial activity as a way of seeing where the direction of clinical research on medical treatments is headed. You know, there's been a really very encouraging shift, you know, in clinical development activities aimed at peripheral associated symptoms of autism, those that are not core to the diagnosis. There's been a shift from that to core features.

And what I mean by that is that the lead clinical trials from a medicines point of view in this space right now are Roches phase oppression 1A trial which is focused on social communications

and the Source B (Lynn Sicages) network trial on oxytocin looking at core symptoms.

If you looked the clinical trial activity in the medical, you know, treatment area just, you know, five to ten years ago they were almost all focused on, you know, the ABC irritability endpoint as the primary interest. So the good news here is I think there's a real shift in treatment development on the pharmacology side from peripheral symptoms or associated symptoms into the core domains of autism which hasn't been really done previously.

DR. SHIC: And to follow up on Rob's point I mean I've been seeing that as well just through some of my own work. And I should say that and not to beat a dead horse, no one is as invested as in these new measures of being able to gauge change or new - more powerful outcome measures than these drug companies that are invested in these new compounds to really understand the mechanism and specific targets that might be affected by new compounds that are rising or compounds that might be related to drugs that they are developing.

And I think that it's really an - kind of an amazing time for pharmacological research. It is a first generation of compounds that we're seeing that are specifically targeting core symptoms of autism rather as Rob said than peripheral symptoms.

MS. CRANE: On the other hand this is Sam. You know, one concern we would have is again drug companies aren't necessarily always going to be going for the symptoms that they - that are the most meaningful to autistic people themselves. They might be going for symptoms that, you, that they think that they can affect.

So, you know, repetitive behaviors would actually be a good example of that. You know, it is a core symptom of autism but on the other hand

autistic people themselves don't really care that much about repetitive behaviors. Unless they're extremely disruptive to our lives or extremely out of control we're not necessarily that concerned about, you know, taking a medication that will reduce our repetitive behaviors. We might be more concerned about taking a medication that will reduce anxiety which is getting seen as a non-core symptom so…

DR. SHIC: So…

MS. CRANE: …that's the concern.

DR. SHIC: Yes sorry I was just going to clarify that. I really meant that core social and communicative symptoms...

MS. CRANE: Yes.

DR. SHIC: …like these compounds. Those - that's new. That's very new.

MS. CRANE: Yes, no that's I'm just sort of…

DR. SHIC: To make - that's a really good point.

MS. CRANE: You also mention that they had…

DR. SHIC: Yes.

MS. CRANE: …in the - in the past been focused on repetitive behaviors and the something we are glad they're moving away from.

DR. RING: Yes this is Rob. I don't really see much, you know, spending a lot of time looking at and kind of understanding both where large companies are wanting to go and where a lot of the entrepreneurial and small company activity is focused. I don't see much really interest in that repetitive behavior domain. And it probably is a reflection of them, you know, the level of

maturity and understanding the real unmet needs of this space coming along.

And, you know, I think what's encouraging is you are seeing, you know, beyond, you know, the social communication domain you are seeing companies that have spent years looking or working in the area of sleep and attention and anxiety and even in the GI areas starting to rethink all of the investments they've put into developing molecules for typically developing populations who do struggle with those symptoms redirecting them towards potential utility in the autism community. I think that's very encouraging.

You know, I think that they're going to run into the same challenges as anyone is, you know, if there aren't - is if there is no way of bringing that actually to the market, you know, through FDA who will be the arbitrator of whether or not the outcome measures are considered valid then they will abandon those efforts and go elsewhere and so that, you know, sort of reinforces that strategic point I made earlier. I do think there's a lot to be encouraged about in terms of the newer technology coming into the story but it will run into that same wall if we can't prove that they work, you know, and it's going to be a problem.

DR. SHIC: Rob would you say that the - like that - this difficulty is summarized by looking at what it takes to get novel therapeutics into disseminated into the - a population and then focusing on those barriers that are prevent that are roadblocks kind of all different levels to that dissemination process?

DR. RING: Absolutely. I think, you know, you have to review whether or not NIH is funding into these areas or nonprofits are funding into them or companies or doing it out of desperation themselves. These are all - these all share a common reducing the risk the scientific risk of

moving that science forward and unless we can address those bottlenecks or as it's commonly called de-risk those bottleneck areas it's going to continue to thwart the advancement of science in this area.

And I think there's, you know, there's a lot of very and, you know, the state of the science and autism is maturing to a point where I think the field can reasonably move forward therapeutic ideas that are going to have great value to the community. They're not going to help everyone, you know. And I think that as, you know, managing the expectations out there among the community about treatment development it wouldn't matter if it was a behavioral intervention or a technology or a drug. They're not going to work for everyone but understanding who they're going to work best for and in combination with what other treatment are they going to achieve their best efficacy is really where, you know, the field needs to go right now.

DR. PELPHREY: Two - this is Kevin. Two ideas that we might want to plant as we develop our chapter that I'm thinking about from kind of taking in a lot of the comments that have been floated. One is on the nature of outcome variables and outcomes in general. I think we all know that our outcome measures are measures of a single point.

And we hope that in comparison to a previous measurement of the same phenomenon that we'll see an increase or an improvement or a decrease of its symptoms. And, that's kind of the commonly accepted notion of outcomes.

When I think about that from the point of view of what we know all about how the brain is organized and how it develops across the lifespan and I think about an outcome let's say processing a certain category of object can be an outcome so you process social objects and nonsocial objects.

And in autism the common finding is that social objects are processed more like non-social objects and we don't see the type of specialization for social objects that you might see in typically developing individual. And so that can become a target, you know, for example in imaging SMRI signals from a temporal cortex and an ET signal and M170 something like that. That is measuring an outcome in the sense of a long period of development or it could be measuring the result of the 16-week intervention and can be measured reliably and validly.

You know, we know a lot about that process. But it seems like we know enough about that type of process to know it's not actually a particularly good outcome measures because we're not just trying to change what the brain has laid down because that would be a very temporary change but rather - and this is the point of my comment we're trying to change we're equipped to learn with the tools needed to form new social representations. And we know enough in cognitive neuroscience to know that's really a different set of reasons. They're interconnected to those ones we've been measuring.

And the point I'm trying to make is not specific to those details. That's just the details that I know enough about to articulate an example but rather the broader point of what we need to be measuring is processes of learning you know, for example there are very elegant numerous studies about computational models of social learning and neural computational substantiations of them with imaging, you know, kind of the very cutting edge of cognitive neuroscience that deals with neurosystems involved in the process of laying down your representations as opposed to looking at the results of those representations long laid out.

And so if our outcome measures become have we given a person a tool that would allow them to face the social world or any component of the world that we're interested in improving in a way that augments their ability to learn more from that aspect of the world that becomes I think a very interesting target and one that might be much richer as far as mechanistically understanding particularly how a treatment can continue to be successful.

And it also opens up the interface between medication studies and behavioral interventions because you could think of the target of the medication as affecting those systems for example that would improve a category of learning and then sharing it with an intervention that is targeted at that category of learning.

And so you see what I'm getting at? And it's kind of a subtle difference but one that I think in cognitive neuroscience we're getting more and more interested in that difference between process versus the measurement of existing representations.

MS. CRANE: So this is Sam. And one of the things I would urge again is to make sure that any study even studies along those lines also include measurement of something that we would call, you know, at the end of the day, you know, is the person having more effective social interactions because they're using this new cognitive model or, you know, is this new cognitive model simply, you know, something that they're doing but maybe it's not necessarily going to be affecting their social interactions all that much.

And one example that I could give a sort of metaphor is there is a lot of different ways to do the long division. And if there's, you know, one way that's very, very common among typical people most typical people find that easy then you might think that, you know, the best way to teach a

person who is not doing very well at long division is to teach them how to do it the way that most people find easy.

But, you know, some people for one reason or another might be able to use to achieve certain kinds of social outcomes and make certain kinds of social judgments using a different cognitive (unintelligible) what is seen in more typical children.

And we don't necessarily want to say that that the best way for the best outcome for the kid is to have a cognitive process that's closer to what a neuro- typical child is. It might be that, you know, they might actually improve their social functioning through a social - through a cognitive process that's actually very different from what other people use.

DR. PELPHREY: Yes that's a really important point. So imagine the situation where you have an intervention that has individuals who respond and don't and you think that the individual who are responding are those that are coming to do something computationally more typically but in fact you weren't able to measure this because you didn't have…

MS. CRANE: Yes.

DR. PELPHREY: …the right tool but actually they're building a system that's entirely different from their neuro- typical peer who did need the intervention to do it the same way. And the kids who didn't respond were actually the ones who were trying to build the system we were trying to create for them but they just didn't - it just didn't take. And so…

MS. CRANE: That's exactly…

DR. PELPHREY: …if you knew that....

MS. CRANE: …right.

DR. PELPHREY: …you would be much closer to personalized medicine. And my point is simply that we're already there in basic cognitive neuroscience of being able to do that type of work. And in learning science people have been doing it, you know, kind of NSF funded work along those lines for a decade but it's not yet being applied to autism in part, you know, because I think it's incredibly risky but I think that we might have an opportunity to kind of push that.

But I also think I've been told in response to making some more comments like this although this has lessened over, you know, the course of a couple of years that that kind of notion of trying to go after process and, you know, for example using a medication in the context of a behavioral intervention is really far out there as far as something would ever receive FDA support or approval and to just be aware of that that there's not an existing model for thinking about that.

And that might be for really good reason, you know, that it would work but it might also be for more of a less glorified reason that it's just not in place yet and maybe we could affect that by suggesting something along those lines.

MS. CRANE: This is Sam again. Another thing that I have encountered as a barrier to investigating medication is that, you know, we've seen people who had even more barriers when they were trying to test out a medication on an adult population than when they were trying to test the same thing out on either non-autistic adults or autistic children.

And I don't want to have this sound like it's talking about long term outcomes. I'm thinking of a medication that like a sleep medication that you could use them on adults, you could - but you could also use it on children.

And you simply, you know, are starting with adults because adults are a safer population to test out a medication on and they're are more capable of providing, you know, meaningful consent without having to use a proxy than children are.

And so we had a call once from a person who wanted to research on medication for autistic people. It was a medication that was targeting a biological practice that they can - that they believed was probably autism specific so you could not test this medication on non-autistic people.

And although it actually had been used on non-autistic people to treat other things so it had been, you know, safety tested that way. But they wanted to test the medication first on autistic adults. And they wanted those artistic adults to be able to give their own consent to participate in the drug trials.

And the Human Subjects Review Board has basically said, you know, we don't think that it's - that you can get consent from an adult population of autistic people which, you know, as an artistic person I found really, really surprising. So I give consent to healthcare all the time.

But they were told, you know, that they had to either, you know, go after autistic children and get the consent of their parents or, you know, go after people who had no developmental disabilities.

And I don't know how often that's happening but it was really troubling because we want people to be able to test medications. We want people to be able to test medications by starting on adults because that's, you know, that's in some ways a safer population to begin testing.

DR. DANIELS: So some great discussion points on this topic. I'm wondering if we can move to another topic while we still have folks on the phone to get some other input. Do you have anything to share about treatments for co-occurring conditions or anything related to complementary, dietary or alternate treatments, not necessarily that those would be the treatments of choice for co-occurring conditions but anything in that area because I know that we have a couple people on the phone in particular that might have interest there?

DR. RING: This is Rob. I'd make at least one point. I've been really struck by and this is not unique to the autism field but it - the autism field now has examples moving through its clinical development stories but the emergence of therapeutic gains and other digital tools that take us beyond sort of a lot of the noise we hear out there among app users. You know, I think one of the most common questions I got when I was CSO at autism speaks was from parents was which app should my child be using and which works the best. And it's not really an easy question to answer.

But there are examples so I take Achilles labs as an example of a company working to integrate some of, you know, some traditional cognitive interference test and gamify these in a way that makes the game itself a delivery vehicle for therapeutic intervention in a way that we haven't seen before. I think that this is a trend that we're going to see a lot more of moving forward but it raises some questions but I think it would be - Fred would probably have a lot to say in this area but this is an area I think we should be watching very interesting one.

DR. SHIC: Yes I was holding out for the technology stuff...

MS. CRANE: Right.

DR. SHIC:…for the technology section afterwards but I think that that's, you know, it's we don't have the infrastructure. The problem is it's almost in some ways a split crossed funding agencies because the technologies that we need in order to really control this space don't exist right now. The standard randomized controlled trial approach it's going to work for, you know, maybe ten, 20 apps or ten 20 kind of rigorously best case computer algorithms or programs or systems but it's not going to work for the 2000 apps that are out there right now.

So it's - it is managing the complete insanity of complexity out there with the understanding that, you know, that is in some ways reflective of the breadth of needs in autism. It's just it's very complex but also understanding that there's also, you know, predatory models out there. There's questions of accessibility. There's questions of actually, you know, research strategies, how do you know if something was working or not?

I mean I'm really struck by and - this is going a little bit off-topic and thinking about the advances that have happened over the last few years. A think we've seen some really great advances in thinking about technology and that in autism research specifically because really solid strong commissions have been coming to this technology to attach to render inside vendor perspectives surrounding studies.

And that's something that I think is a momentum that needs to continue and carry forward because I mean I'm thinking about the AAC field right? So Connie's one study looking at AAC is probably the most but I don't want to give it to many props or I'll seem biased but and single-handedly expanded the number of participants in the entire field of AAC research by about 30%. And this is, you know, one of her studies.

And finally, you know, the application of a very rigorous methodology to this but there's a question. You know, AAC is for Connie her project was focused on very, you know, a variety of AAC devices. So I mean I think we're they all iPad base Connie?

DR. PELPHREY: She's having a hard time getting back in.

DR. SHIC: Okay.

DR. PELPHREY: So we're trying to get her back on the line.

DR. SHIC: Right but - so the I was basically my point is that, you know, there's a rigorous methodology that's coming in. And that's absolutely critical to show that there is some substance behind these new research areas of therapy. And we're going to need a few of those but we also need to realize that the strategies that we have right now aren't going to be enough in the future.

And so we have to really think creatively about organizing, you know, systems that are alternatives to the standard randomized controlled trial. I mean I don't have an answer but I think that that might be an area that we want to focus on. And that could apply across multiple areas, not just technology systems but a whole host of alternative complementary measures and also, you know, standardized methodologies right, which behavioral intervention is best? These are questions that I think, you know, is a question of active ingredients.

Kevin brought up learning, essentially learning to learn right? So the self - the science of self-sustaining change in therapy and how can we promote that and are there alternative pathways so mechanisms that can be leveraged to help individuals succeed and in essence trying to

identify that cocktail of therapeutics that will work best for individually? I think these are all things that, you know, unless we start to tackle them directly we're not going to make progress in figuring out how we're going to really develop these personalized medicine programs.

DR. DANIELS: So this is Susan. We're - as long as we're on the topic of technology-based interventions we can also talk about robotics, AAC -- any of those -- if you want to comment on what have been the biggest advances in recent history in this area.

And you've already commented a little bit about some of the barriers or challenges but do you have further comments on that please go ahead.

DR. SHIC: And I think that the application of very rigorous methodology maybe in some ways when you look at that it's not the most exciting thing right, this idea that we just needed these larger populations, very controlled trials people who really understand treatment to be conducting some of these studies maybe that isn't just the most exciting topic for, you know, new research but oh my gosh is that necessary, is that so incredibly valuable to the fields to give it form and to give it, you know, some believability? I think that that is - has been the greatest progress.

We've seen some advances in, you know, thinking about robots right, so more randomized controlled trials. The days of, you know, NF3 and NF3 these are largely relegated to technical advances rather than, you know, research, clinical research projects now and I think that that's a good trend.

In terms of the technology itself for robots we're seeing the advent of what's sort of called closed-loop systems for therapy this idea that a robot basically from beginning to end or as large as, you know, as much as possible act - acts

autonomously to deliver some type of skilled training.

And I would hesitate to call it therapy at this point because I don’t think we're nearly there yet and I don’t think that we'll ever honestly achieve, you know, this idea of having a robot teach skills to kids. I - it just doesn’t really make sense right. This is dangerous honestly a little bit wanton. So…

MS. CRANE: I embrace our robot overlords.

DR. SHIC: Yes exactly.

MS. CRANE: That’s great, yes.

DR. SHIC: But they're so fun but and I think that they can complement existing treatments and that’s' something that we're starting to understand as well, what are the active ingredients of that robot? Is it because robots are just so cool or is it something else entirely different?

Is it as Kevin was mentioning these different pathways that are available to individuals with autism in terms of their neural responses to social versus nonsocial avatars because that actually provides some advantages for teaching or is it an anxiety related? These are things that we're still disentangling and I think we’ve been making very good progress on the robot field.

MS. CRANE: Was the robot simply more consistent and able to, you know, do - respond to things to certain stimuli exactly the same way over and over and over in a way that a human can’t?

DR. SHIC: Yes. And that’s definitely been one of the areas where robots have been touted as having advantages. But I - it’s because I haven’t seen treatments, you know, like longer treatments

that have been organized around this thing. I wonder if it would be very different from like discrete trial training which has been around forever and does work for some set - some subset of the autism population. And it depends on the skills. It depends on the individual and it depends on liberal functioning.

And I also wonder, you know, in that case does a videogame like Rob was mentioning is that - does that tackle the same type of advantages? And so I think we need to still explore right because the advantage of the robot is its embodied form. That's the single, the physical body presence. That's what distinguishes it from other automated systems. And why is that important and is it important? And I think it's important to lift this out of the area of computer science honestly and move it into as - forward as a clinical problem or as a psychology study something that…

DR. RING: Right yes.

DR. SHIC: …deals with large populations so that we can be more consummate of these results because the people who developed the technology they're not invested in the results clinically in the same way that a clinical researcher would be. You know, they wanted to design the core technology. And once they've done that there's really especially depending on where your funding is coming from not great incentives to turn that into something that's going to run over the course of five years, you know, in five years you could develop, you know, 12 different new robot prototypes.

DR. LEONESSA: So if I can step in here one second. This is Alex Leonessa from Virginia Tech.

DR. DANIELS: Hello Alex.

DR. LEONESSA: So when I was at NSF I did fund several projects in the area of social robotics so

for the particular task to help children so with the several different level of autism. And the area of social robotics in the last couple of years has taken really some giant leaps and I've seen and I can provide documentation to show how therapies themselves have made statements whereby using some of these social robotics approaches in one session they were getting improvements and differences that they didn't see in like months and months of therapy.

And so some of the people that do this kind of research and this kind of approaches are not actually computer scientist themselves. They just so because he was mentioning about the use of the technology and move away from actually building the robots. Funny thing is those people actually use robots that have built but other people for the purpose of therapy.

And after one session, you know, I've seen videos actually were children would engage, you know, the audience, make eye contact to actually address them personally and acknowledge, you know, that they were in the room with them and I mean it was amazing results. I think this (unintelligible) and there have been some clinical studies and there have been, you know, more long-term studies in the use of social robotics for autism. I mean if you search it I'm sure you'll find plenty of research. I can make a couple of names of researchers that are very well known in this area.

DR. SHIC: Absolutely there's great researchers who are working this space. And I don't mean to disparage the field at all. I'm just pointing to the - to a gap right? So there is not something that's equivalent to Connie's study of AAC devices combined with behavioral interventions to really look at the difference between AAC devices and behavioral interventions by themselves. I mean the idea of the large randomized controlled trials for robots I haven't if it's out there I haven't seen it. You know, the end of 30 versus the end of 30

over a period of what we need know to be an effective intervention at, you know, the effective level of intensity right so ten weeks, three times a week at least I haven't seen that, you know, and I haven't seen…

DR. LEONESSA: No I understand that. I understand that. I mean it's also true that it's a much newer approach so, you know, the researchers are getting up to speed with all of these technology. I mean therapies themselves are actually getting interesting using the technology during their own sessions. So they actually want something off the shelf so that they can just use and include in their sessions in their therapies to improve their effectiveness.

So but it's overall, you know, a fairly new field. And I mean I've seen really big improvements in the last few years, a couple of years two to three years, perhaps that has become as social robotics has become, you know, more widely accepted and used. But, you know, the kind of clinical studies that you're talking about, you know, I can think of one perhaps that gets close to it but not quite still at the level you are referring to.

DR. SHIC: Well that's because, you know, if you make it - I mean anyway that's not a good place to talk about the funding divisions between but I mean definitely there's amazing researchers who are working together to try to patch up this area but I think just more concerted attention towards the need of the rigor and it - I think it just it's probably a very necessary step.

DR. LEONESSA: No I agree.

DR. SHIC: There are really a lot of good work out there yes.

DR. LEONESSA: I agree. I'm only saying that I think social robotics as an intervention should

definitely be mentioned and considered. That's how I like to just go on record with that.

DR. DANIELS: So in terms of…

DR. SHIC: Yes no social…

DR. DANIELS: So in terms of social…

UNKNOWN FEMALE SPEAKER: Hello? Hello?

DR. DANIELS: This is Susan. In terms of the barrier to translation are you thinking of it more as a workforce gap, a funding gap or a gap in coordination between funding agencies or anything else that you want to say about that?

DR. SHIC: I mean I would see it as really all of them. You know, I think the - there is - we should always be wary even though I'm a computer scientist I love robots. I'm part of the NSF Expedition Team and its amazing science. It's great work. But we also always have to be cautious about this because, you know, so as an example there was - I visited a school in a foreign country that with average incomes about maybe about $15,000 to $20,000 a year. And the question was that was posed to me is which, you know, what are all the cool things that we could do with a $30,000 robot for our school?

And I kind of looked at this and I said well, you know, do you really want to invest $30,000 in a robot? Is that going to necessarily give you the gains that you think there is because the honestly the research out there doesn't support that this is going to necessarily be a huge advantage right? We still have yet to be able to say a single statement like put a robot in a classroom is this going to improve learning by kids with autism?

And we can say that it will improve it for some kids. We can say that most of the kids with autism who enroll in these studies that deal with

robots they’re very excited when they interact with the robot. We can say that. Engagement levels are high, participation is high, affect is very positive.

But can we say that that long-term outcomes will be better whereas we could say, you know, let’s hire this speech language pathologist for a year and a half of that would make a demonstrable change in these kids' speech.

DR. KASARI: So Fred?

DR. SHIC: And there's a trade-off…

DR. KASARI: Fred.

DR. SHIC: …that we need to be attentive to.

DR. KASARI: So can you guys hear me? This is Connie?

DR. DANIELS: Yes we can hear you.

DR. KASARI: Oh my God this has been it’s crazy because I’ve been talking at you guys but I was in the listener mode, not the speaker mode for some reason when I called back in, sorry. So I missed a lot but I think Fred you're raising issues about I think what I heard was that the robots and the AAC devices really are augmentations to the behavioral treatment in a way that I think you’re suggesting about robots and certainly was the way we used AAC it was an augmentation to a behavioral intervention. So it wasn’t by itself. We're you suggesting that it - that we would…

DR. SHIC: No.

DR. KASARI: …test it by itself? Oh.

DR. SHIC: No, no I mean I think it’s exciting that there’s greater autonomy the starting to be built into these robots. And actually great work

by Zach Warren has kind of moved and (Sarkar) has really moved the discussion forward on mostly autonomous systems for teaching specific skills. But yes, no I think it's really as an augmentation to existing therapy. And so the question of, you know…

DR. KASARI: Yes.

DR. SHIC: …do you bring in…

DR. KASARI: Yes.

DR. SHIC: …a robot or do you hire speech language pathologist for a year and a half?

DR. KASARI: Well but I think you could test those. Those are empirical questions.

DR. SHIC: Exactly, exactly.

DR. KASARI: I think they're - if you think they're important. So I think our task is to decide, you know, what is it that we don't know? What is it that kind up and coming that might be interesting? And maybe robots are interesting. They're very expensive so you have to think about that and…

DR. SHIC: Well they don't have to be expensive. That's another question.

DR. KASARI: Okay? Well I mean I don't want to get into all the sort of funding and stuff but I think any of those things are interesting with augmentation.

DR. SHIC: But to make it rigorous to do the studies right I mean I think that…

DR. KASARI: Absolutely.

DR. SHIC: …important. That's still necessary until the strategies that we have that may, you

know, provide additional information at scale exists which they currently don't exist and I mean alternative strategies to an RCT for finding out whether systems of measurement are, you know, or affect - treatments are effective. I mean...

DR. KASARI: But there are other…

DR. SHIC: …people have been thinking about this for a long time. Yes?

DR. KASARI: there are other methodologies besides just a straight randomized controlled trial. Again I think that one recommendation should be that we should be much more sophisticated in our methodologies for scientific testing of intervention. You can still randomize but you can do adaptive treatment, everybody gets something. I think we have a lot of randomized trials and some of them are very weak so just doing an RCT doesn't mean that we've done really great science.

DR. SHIC: Strong science.

DR. KASARI: We need to think about those methodologies so one place where I think we could strengthen our research is by, you know, more sophisticated strategies.

DR. SHIC: I agree. Yes I just - but and I think some methodological dissemination and development funding to develop methods…

DR. KASARI: That would be great.

DR. SHIC: …I mean that's what - that's something that's necessary yes.

DR. KASARI: Yes.

DR. DANIELS: Great. Well would it be okay for us to try to circle back to complementary dietary alternative treatments and co-occurring

conditions? I know Tim was on the line and thought he might have some comments in that area and maybe some others as well?

DR. BUIE: Sure. This is Tim again. On diet, you know, most of the studies that have been published thus far that are blinded controlled studies have not been favorable to show benefit over a placebo period. And I think yet despite that dietary responses one of the things that's been noted anecdotally really quite robustly.

And so one of my concerns is exactly the heterogeneity of who has been investigated, who is enrolled in those studies and are those things that we could identify in candidates to make them have a better outcome? We've concluded a study where we looked at GI symptoms in kids who went on to dietary restriction rather than selecting kids who are without other sort of driving characteristics.

And so it may be that if we narrow the focus on to local problems we'll be better about identifying who's going to respond to that type of therapy? That's yet to come. There's not data yet I think to support that and I think that's one that is still a great enough interest that we should probably comment on what we know in the dietary arena but I think at this point there's still not a lot of positive commentary to say that it has been beneficial.

There is so much interest in supplementary type therapies. And I would include them in terms of complementary but there's a lot of crossover in what are sort of deemed complementary therapies and supplementary therapies that are offered for a particular comorbidities like mitochondrial dysfunction or methylation type defects, et cetera. And a lot of those are under study and there's very legitimate researchers starting to publish on these things. But again most of them have very, very limited publications to sort of

make broad recommendations that I don't think we can do yet. But I think I again they're probably worth acknowledging and sort of stating where we are in the state of the research on those topics.

MS. CRANE: This is Sam. I'll add also that, you know, we have to make sure that we're not just studying comorbidities as comorbidities but also, you know, including people with co-occurring health conditions and other studies. I know that there's a lot of studies that exclude anyone who also has epilepsy.

And I'm not talking about, you know, studies on epilepsy but studies, you know, on communication interventions or behavioral interventions or really all of these, you know, a whole bunch of other issues. People with epilepsy are being excluded but there's so many people with epilepsy in the autism population that, you know, we risk missing important interactions and we risk missing information on how, you know, are autistic people with epilepsy responding more or less to other kinds of interventions? I don't know if that fits into that category but it's important to me.

DR. BUIE: I'd like to jump back to something unless other people want to say things about the dietary interventions. One thing that I think is the most prime area of research currently in the GI community and the immunology community is micro biome assessment and differences in the intestinal and micro biome and the metabolomics of microbes to contribute to both symptoms as well as potentially core autism issues.

And I think there are a number of groups that have published talking about the differences. There are fewer groups that have talked about sort of the pathways how these differences might affect autism and affect immune state and affect the core functioning of these guys but this is a prime interest in our community. They really want more information on this.

And what may drive variances in the micro biome including dietary interventions including digestion errors or problems enzymatically or whether probiotics might have a value or other interventions such as fecal transplant may have of value this is just an exploding area and I think it's probably hard for people who are more neuroscience based to get interested in this but there are really good clear pathways written about the what's going on and how they may affect symptoms. And so I think this is something that we need to spend time on and definitely write about and really try to come to consensus about if we can.

MS. CRANE: So are there unaddressed, you know, lesser address co-occurring conditions that I think we - we're seeing anecdotally a lot in the community but I'm not seeing as much research on it as I think we would hope. And one example is connective tissue disorders. And connective tissue disorders in addition can affect a person's ability motor skills.

So a person who is, you know, having muscle tone issues that can affect motor skills and that in turn can affect, you know, all sorts of things from functional and adaptive skills to ability to communicate to the person who's having a hard time developing oral motor skills. And we're, you know, we're seeing a lot of people noting that there is an incredibly high overlap of autistic people and people with connective tissue disorders and we're not seeing that much interesting on it.

DR. DANIELS: Anything on this? I know that Beth unfortunately had to step off the call so she won't be able to comment but may send in some written comments. We have not - I don't know that we have - well we do have some folks that could talk about educational interventions to some extent. I know that Department of Ed is not on but any comments about classroom interventions,

educational interventions that you want to give on the phone? We can always of course go back to the working group and get more information on that.

DR. KASARI: Connie again. I would say that we don't know very much about academics or kids with autism and very few studies on reading math, executive function in the classroom couple, you know, I think that's a big area of need.

DR. DANIELS: Anything else that you can think of that we should make sure to note?

DR. KASARI: Well I think just interventions in schools in general. You know, I think most people are still doing their randomized trials in clinics and not in the environments in which they want those to be applied. So I think the more sort of research that's done in context would be in advance.

DR. DANIELS: Great. And we also will have help from question five's group and they're going to be talking about implementation science so they'll…

DR. KASARI: Right.

DR. DANIELS: They'll help us out a little bit on that side as well. And then I also had a category for occupational physical and sensory-based treatments. There is a new study that's going to be coming out soon on sensory-based treatments that we can share with the group when it's available but anyone have any particular thoughts about those areas?

DR. BUIE: Well I would want to add feeding difficulties and feeding disorders. I think they probably fall under the occupational receipts category and maybe other people are dealing with them. But they are a predominant problem beyond food selectivity although there may be some sensory issues there.

MS. CRANE: Yes definitely very, very much sensory. Sorry that was…

DR. DANIELS: I'm sorry, what did you say?

DR. BUIE: Yes. I think beyond sensory issues there is certainly…

((Crosstalk))

DR. BUIE: …other phenomena there that are going on. That's one of the things that makes one consider acid reflux or allergic esophagitis or a number of other medical conditions as well. And so at least focusing on identifying those eating disorders I think is of value. And that's a very common condition especially in the younger kids.

MS. CRANE: We've seen a study that was trying to research feeding issues in teenagers and it got push back from the funder because the funder believed that it was no longer relevant to that age group which I thought was absolutely shocking though because the, you know, teenagers also do need to eat.

DR. BUIE: They do.

MS. CRANE: There are autistic people continue who to have eating issues well beyond early childhood.

DR. BUIE: Absolutely positively. And we have a number of individuals who were doing well enough but then through either selectivity or other symptoms have needed gas trophy placements, et cetera well to their teenagers where they really made it through as younger kids. And so I think that's true. And we've usually used those as ancillary supports till we can try to get to the other basic eating problems for those individuals but it's a problem in all age groups totally agreed.

MS. CRANE: And I would add to that, you know, that interventions should not just be about addressing selectivity in the first place but also, you know, investigating nutritional approaches that work for people who are selective. So, you know, there might be nutritional regimens that you can use to at least improve someone's health even if they remain very selective eaters.

DR. DANIELS: Kevin do you have any comments on this from the eating disorders perspective on some of your research?

DR. PELPHREY: No not really, nothing that is particularly relevant here. I keep having a suspicion that we're following up in our network is focused on growth but a lot of the growth that miss on diagnosis end up with diagnosis of eating disorders but, you know, that's just a comment more than any particular recommendation.

DR. DANIELS: Oh sorry, I muted myself. We're getting close to the end of the hour. I want to go to the last part of our list of topics here talking about some general themes that you all mentioned about how to accelerate research and increased uptake of and access to evidence-based interventions. Do you have any comments on concepts that we should consider for possible recommendations to help us to be able to reach populations with evidence-based interventions?

DR. KASARI: Hello?

DR. PELPHREY: Short of saying that there's a need I don't have any particular recommendations.

DR. KASARI: Well I think we should have more research in low resource context and, you know, more diverse populations which means we probably need to be adding community more. And this may be taken up by the services group but I think we can recommend that as well. So that would be one recommendation. To get things out into communities

faster is to actually do them in communities from the beginning and do reverse trials in communities.

DR. DANIELS: I think that you had also have mentioned dissemination of information about which evidence - which interventions have an evidence base and what's the latest to parents and providers. Any thoughts about more you would want to do with that?

MS. CRANE: No I think that, you know, part of another barrier to some evidence based interventions is people will test out an intervention that's at such a high intensity level that people can't manage it. And that might be one thing that people consider on the front end is, you know, am I piloting in intervention that is really actually, you know, doable if it were to be scaled up? Will people, you know, have to, you know, is this a full-time job to carry out this intervention as a parent or is it something that people can do pretty easily?

DR. KASARI: Good point.

MS. CRANE: And prioritize the easy one.

DR. DANIELS: Any last thoughts on that? Well we're coming to the end of the hour. I think that you've all had a really robust discussion. We really appreciate you providing thoughtful comments on a lot of these areas. In terms of next steps our office will go ahead and try to incorporate some of these comments into the notes that we have. And we'll be working with our Chair, Kevin Pelphrey to come up with an outline for the progress chapter that you'll be writing and then being in touch with you to see who we can recruit to help with some of the writing and editing of these areas. And of course the entire working group will be able to see whatever is produced.

On our next call we're going to be talking about the three objectives that we will be creating for this area. So before that call takes place please just keep in mind what you think might be three areas that you could prioritize for further work. And you can feel free to if you have suggestions that come to you and you want to email them to me I can try to put together a list of those before the call and then we'll have time to discuss that.

One last item that I should've talked about was the aspirational goal which sorry, I think that I will actually just table that for the next call because I don't have that right in front of me right now. But we'll talk about the aspirational goal and whether it's still appropriate in light of all the recent updates that we've had in this area but I'll do that on the next call. But anyway I'll be in touch with you with follow-up information and information for the next call and feel free in the meantime to email if you think of other thoughts you'd like to add in that didn't come up on the call. Thanks so much for joining us.

DR. PELPHREY: Sounds good.

DR. DANIELS: Appreciate your time.

DR. PELPHREY: Thanks Susan. Thanks everybody.

DR. DANIELS: Thank you.

UNKNOWN MALE SPEAKER: Thanks.

DR. DANIELS: Have a good weekend.

DR. PELPHREY: Bye-bye. Have a good weekend.

DR. DANIELS: Bye.

MS. CRANE: Bye.

(Whereupon, the conference call was adjourned.)