U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTERAGENCY AUTISM COORDINATING COMMITTEE

SUBCOMMITTEE FOR
BASIC AND TRANSLATIONAL RESEARCH

STRATEGIC PLAN QUESTION 4 PLANNING GROUP

CONFERENCE CALL

THURSDAY, OCTOBER 18, 2012

The Strategic Plan Question 4 Planning Group convened via conference call, Noah Britton, *Co-Chair* presiding.

PARTICIPANTS:

NOAH BRITTON, M.A., *Co-chair*, Question 4 Planning Group, Bunker Hill Community College

GEMMA WEIBLINGER, *Designated Federal Official*, National Institute of Mental Health, (NIMH)

TIFFANY FARCHIONE, M.D., US Food and Drug Administration (FDA)

ELIZABETH BADEN, Ph.D., Office of Autism Research Coordination (OARC), (NIMH)

ANSHU BATRA, M.D., Our Special Kids

EXTERNAL PARTICIPANTS:

CONNIE KASARI, Ph.D., University of California, Los Angeles

LINMARIE SIKICH, M.D., University of North Carolina

BETH MALOW, M.D., M.S., Vanderbilt University Medical Center

MATTHEW GOODWIN, Ph.D., Northeastern University

TABLE OF CONTENTS

PROCEEDINGS:

Ms. Weiblinger: Good morning, everyone. My name, as the operator said, is Gemma Weiblinger and I'm temporarily acting as the designated federal official in place of Dr. Susan Daniels who is currently out on maternity leave.

Welcome to the IACC's conference call to discuss the update of its strategic plan with specific focus on Question Number 4, "Which treatments and interventions will help?"

I will now turn the call over to Mr. Noah Britton who will lead the discussion. Noah?

Mr. Britton: Hi, thanks. So, we have Beth and Connie and who was the last person who joined? I didn't catch it.

Dr. Goodwin: Matthew Goodwin.

Mr. Britton: Oh, hi Matthew. Thanks for calling. Well thank you all for your help. Your recommendations have been really great and I really enjoyed reading them. I know how much of a burden this was so thank you very much.

I guess the big thing I just want to say is how did you all feel about what me and Anshu sent

out as far as information? I'm interested in your opinions on this.

Dr. Beth Malow: Was there a more recent email than a week or so ago? I just want to make sure --

Mr. Britton: I don't think so. Anshu sent out her stuff at the very beginning and never sent any sources, and I sent mine on Friday.

Dr. Malow: Oh yes, okay. So no, I thought that was very helpful. Actually Anshu had sent me a template that I could use for my information which was great. So it sounds like based on what everybody has sent in that we've gotten a lot of the areas pretty well covered.

Mr. Britton: Yes, I think so too and I'm happy about that. What about the other two?

Dr. Kasari: This is Connie. I don't believe I received Anshu's.

Mr. Britton: She sent out just a template and it had her ideas on it and I think that's the extent to which she's going to send anything for what do we need.

Dr. Kasari: Oh, I see. Okay, so that was very early on. Right.

Mr. Britton: Yes, exactly.

Dr. Kasari: Okay.

Dr. Malow: Do you need that, Connie? I'm sorry. Connie, I have that here if you want me to send it to you.

Dr. Kasari: I think I recall. I think it was -- you know, I thought that was from last time.

That's interesting. Okay.

Mr. Britton: She may be planning to do more but I haven't heard anything so my guess is since it's getting pretty late that she's not going to.

Dr. Kasari: Okay. Yes, go ahead.

Dr. Malow: Yes, I thought Anshu had indicated to us when we were sending everything in that she was going to try to put everything together into a document.

Mr. Britton: Right. She's going to put everything that the five of us sent her into "What do we know." But as far as "What do we need," that's information I'm compiling. So, I was like okay, I guess that's all she's saying for "What do we need." So I can use that as far as her input.

And a lot of you sent in a lot of great stuff

for “What do we know” which was awesome. And I was just wondering as far as “What do we need” was there anything that you didn’t include that you felt might be important? Some of you specified a section for “What do we need” versus “What do we know” and others of you just sort of included everything together. I’m just wondering is there anything you want to add or anything you feel like is particularly important to include in “What do we need” with I am going to right.

Dr. Kasari: Well, I think that there were overlapping ideas in “What do we need.”

Mr. Britton: Right.

Dr. Kasari: And at least from the perspective of what I know best which would be the early intervention and social skills and including Jeff Wood on comorbidities it looks like we need more rigorous designs.

Mr. Britton: Right.

Dr. Kasari: We need to look more closely at active -- so we had a lot of overlapping ideas.

Mr. Britton: Right and I think those would probably be the things we focus on most. Keep

going.

Dr. Kasari: But actually on the "What do we know" sort of backing up. So what Anshu had sent, this is why I thought it was older, is I guess I had a different perspective –

Mr. Britton: U-huh.

Dr. Kasari: on what we know about early intervention.

Mr. Britton: Yes.

Dr. Kasari: And so you guys will read those and kind of think about those and put those together, is that correct?

Mr. Britton: So, Anshu is going to compile "What do we know" and I sent her -- my input on this is I sent to all of you and hopefully she will include everything we sent. But honestly she's going to be the one writing that and then she'll send it out probably on Monday I hope after all of us have seen it. But then it'll go to OARC and then to the larger committee for review. So it is possible she'll write something that's only what she wrote. I have no idea.

Dr. Kasari: Okay, because I would totally

argue that the second paragraph under Early Intervention is not completely accurate, that in fact we do know -- but this is where I think I need clarification. Yes, comprehensive interventions haven't targeted any of these core deficits, things like joint engagement, joint attention.

Mr. Britton: Mm-hmmm.

Dr. Kasari: However, we do know that targeting those things does actually have an effect long-term on kids' outcomes.

Mr. Britton: Did you send that information to us?

Dr. Kasari: I did.

Mr. Britton: Okay.

Dr. Kasari: In mine I reviewed what we know and I also sent a paper that we just wrote kind of reviewing the last not 18 months, but the last 2 years of social skills intervention.

Mr. Britton: I'll be sure that she makes sure to read that.

Dr. Kasari: It may be that we're interpreting different models.

Mr. Britton: Yes. And she may, you know, again the fact that she didn't include any sources makes me think that she's waiting for sources from the rest of us and we'll compile based on that, although, she did write that as a MEDLINE search for clinical trials in ASD. I do wish she had said exactly what she was basing this on. But yes, I'll make sure that she reads what you sent. This is Connie speaking?

Dr. Kasari: Yes.

Mr. Britton: Okay.

Dr. Kasari: And I gave you more detail than you probably ever wanted.

Mr. Britton: We need as much detail as we can get.

Dr. Malow: I'm sorry, this is Noah, right?

Mr. Britton: Yes, this is Noah. Hi.

Dr. Malow: Yes, so -- this is Beth. What I can do is I can go back to what I sent Anshu and kind of bullet what we don't know, because I kind of mixed it in, if that would be helpful to you.

Mr. Britton: I mean I think -- let me find exactly what you wrote. But I think yours was

particularly clear to me.

Dr. Malow: Okay, good.

Mr. Britton: As far as what we need. And if I have any problems on that I'll get in touch.

Dr. Malow: Okay, that sounds great.

Mr. Britton: Sure, yes. Thank you very much. It was very clear and yes, tons of details from everyone which was wonderful.

Dr. Sikich: This is Lin Sikich. I thought one thing that we still pretty strongly need are more objective outcome measures readily implementable across sites.

Mr. Britton: Yes. It's a tough thing I think we all agree on that. That's a tough thing to do properly. And people have been trying for a long time and still are arguing and will probably continue to argue forever.

Dr. Sikich: Hopefully not forever.

Mr. Britton: Well, hopefully not but the way science works it never ends. But yes, it would be nice if we could get some better outcome measures and make sure that they are implementable across sites.

Dr. Kasari: That was a big issue that Jeff Wood also raised, Lin, and one that I raised in terms of sort of behavioral interventions.

And I think that we really have to be very careful about those outcome measures and what is considered change and what's considered meaningful change. And it is a struggle but we've got to get better at this.

Mr. Britton: Yes.

Dr. Sikich: And it's something that also would be, you know, I think one of the charges for this committee is also to state that there needs to be -- that there should be a real push for a consensus about what kind of measures we need to develop and really that issue of what's meaningful change. Change versus, you know, demonstrated change.

I think the other thing that for me reviewing the pharmacological studies is that we're -- there's been this big shift towards pilot studies really being there to test feasibility and to -

Mr. Britton: Um-hmmm.

Dr. Sikich: to at some level decide whether to

move forward with a bigger trial.

But the field is still really, I think publishers and many people are still unsure of when do we decide that evidence of feasibility, evidence that maybe there's some sort of signal here even if it's not statistically significant is reason --

Mr. Britton: Mm-hmmm.

Dr. Sikich: to move the trial into a more rigorous, larger study versus, you know, when do we say we're going to disregard these pilot studies because they didn't show significance. Or we're really going to believe this pilot study that did show statistical significance even if we're a little skeptical or it doesn't clearly make sense.

At some level I think it's actually a huge need from medication studies because there are so many different hypotheses out there --

Mr. Britton: Mm-hmmm.

Dr. Sikich: and there's so many single gene disorders where people are coming up with well, let's try this, let's try that. If we're really

coming to some sort of a guideline or suggestions for things to think about as you decide whether to move stuff forward into clinical trials.

Dr. Kasari: So, I think that's a great point for medication studies in particular, but I think you could argue for behavioral interventions that the research traditions that we use by doing this very tightly controlled laboratory clinical study and then trying to move it out into the place where you want it to have an effect takes way too long. And that some people would argue that we need to actually test things in the community.

I think that's different between drug studies and community behavioral studies. And I think both of those points should be made. They're both important points. One, you don't want to move too fast. The other one, it's not that you want to move fast, you just want to test it where you think it's going to have an effect rather than take 10 years to get it there if you think it's that important.

Mr. Britton: Unfortunately a lot of the behavioral and social stuff that's implemented in

the community because a lot of it has been tested in the community is not rigorously tested in the community. And so --

Dr. Kasari: I'm talking about a rigorous test.

Mr. Britton: Right. I mean, well what I'm saying is that the community studies that are out there do need to be more rigorous in how they're done.

Dr. Kasari: Absolutely. Absolutely.

Mr. Britton: And so that I think is even more salient in the behavioral studies. But again that's something that I'll mention --

Dr. Kasari: Right.

Mr. Britton: -- to make sure. And I don't agree that we need to move the process along more quickly because it's quite dangerous to implement studies that may or may not be harmful to the population. But I do think that we need to have more RCTs and more effective tests on stuff that we're already doing in the community.

Dr. Kasari: Right.

Mr. Britton: And make sure that that stuff isn't harmful and that stuff is somehow useful to

people.

Dr. Kasari: Well, right. So then you're starting to talk about harmful interventions. But I think most behavioral interventions like a social skill in the school setting is not very harmful.

Mr. Britton: Well, that can be argued. I'm not going to get into it but it can be definitely.

Dr. Kasari: Okay.

Dr. Malow: This is Beth. I have a couple of thoughts based on what you guys are saying which I think is excellent.

One is that I think in some areas like the area I reviewed with the medical comorbidities we actually need some really good pilot studies before we can even move into phase III trials.

Because the literature is so limited and we need some very carefully done pilot trials that will help us prepare for phase III trials, whether it be the outcome measures or the agents or the drugs or the behavioral interventions. So I would argue for both phase III trials but also the pilot studies that will prepare us for those trials.

I've been working with -- I don't know if you guys are aware there's like a NeuroNEXT Network in neurology at NINDS that is set up to support and fund pilot studies. But I think that the other institutes and the whole coordinating council, the idea of doing pilot studies I think is important.

And then the other point I wanted to make is maybe when we talk about developing these outcome measures we could talk about partnering with other organizations. Like I know, and I don't want to single out Autism Speaks but I know that they did a -- I just pulled up slides. They did a translational medicine research initiative to come up with outcomes in clinical trials for individuals with ASD that was held last March in Washington, D.C.

So in generic terms maybe it could be put in that partnering with foundations and community groups and industry perhaps to develop consensus on these outcomes measures for clinical trials, whether they be behavioral or pharmacological would be a good idea.

Mr. Britton: I don't think I totally

understand what you're suggesting. So you're saying that one of the things I should add into what we need is to partner with community organizations to confirm scientific results. Is that what you're saying?

Dr. Malow: Well, or partner with foundations and industry to develop a consensus for outcomes measures based on the evidence or whatever. In other words, I think that these meetings and these consensus groups that come together can be very useful in adding to the evidence that's been accumulated.

Mr. Britton: The problem with that is it leaves a lot of room for bias and for -- I don't know the technical term for it but for that organization

Dr. Sikich: Conflict of interest.

Mr. Britton: to have way more say in the process than --

Dr. Malow: No, I mean I agree. And I think it has to be a partnership. I agree. I mean it probably needs to -- I guess what I'm getting at is I think there is some usefulness if others on

this call agree. I mean that's why I'm bringing it up.

I think there is some usefulness to saying we're going to have NIH sponsor a 2-day meeting where we're going to talk about outcomes measures in behavioral interventions or pharmacological interventions for individuals with ASD. And we're going to include some folks from industry, include some folks from this foundation, that foundation. You know, and I agree it has to be managed. We don't want to introduce bias or conflict of interest but I think bringing people together can be helpful.

Dr. Sikich: My concern is that we're not even -- that the meetings like that that have been held that I have been at largely rehash existing measures.

Dr. Malow: Okay.

Dr. Sikich: And I can choose between the existing measures.

What I think really needs to happen is a move towards developing completely new kinds of objective assessments.

Dr. Malow: Okay.

Dr. Sikich: That aren't based on parent support.

Dr. Malow: Right.

Dr. Sikich: And really are trying to be things that are more objective and that are really looking at what we think are core behaviors.

I would say that in my perspective one of -- we've been talking for 10 years

Dr. Malow: Um-hmmm.

Dr. Sikich: about existing measures that are out there. And I don't think anybody's particularly happy with the existing measures that are out there. But we have had fairly limited progress towards really trying to develop new, more objective measures.

Dr. Malow: Right, I see exactly what you're saying. Now, my question to you is what's the best way to get those measures developed? Is it -- I mean maybe it is just doing RFAs or program announcements. But is there any merit, and if there's not tell me there isn't. Is there any merit in having any sort of consensus conference

where people would talk about let's move from these parent-based measures into these other measures and then sort of get people encouraged and fired up at the end of those meetings to go and do just that.

Mr. Britton: I think you're making a really good idea -- suggestion. And that this is sort of what the IACC is thought to do but in practice is not something that we have done.

Dr. Kasari: Can I –

Mr. Britton: And I think it would be really valuable to make that something we do. Unfortunately that would be a Congressional issue rather than a IACC choice. Sorry, go ahead.

Dr. Kasari: I'm sorry, this is Connie. So we've been doing those kind of consensus or those workshops for, I don't know, 10 or 15 years. I've been to several of them. And in fact there's an RFA out for measurement on this exact issue and has been out for a while. So I think that they've done exactly what you said. But of course those are all in development. And I think people are really trying to work hard on this issue. There

has been movement in the behavioral field but it's just for progress.

So I think we're going in the right direction. I know it's a medical -- the psychopharm studies are still on parent report and CGI and those kinds of things. And I think people recognize -- I think we need more work there.

And part of it's an expense issue, you know, doing multi-sites and doing something quickly. But I feel like we're addressing the issues and there is progress.

Dr. Sikich: I think that I agree with Connie. I just think that it needs to stay on the radar and stay as something that continues to be felt to be important. I have some concerns that because that RFA has been out for a couple of years now.

Dr. Kasari: Um-hmmm.

Dr. Sikich: And I don't know how many projects are actually funded by it.

Dr. Kasari: A few have been.

Dr. Sikich: That people will say either we can't do this or it's not important for the government to still invest in this.

Dr. Kasari: Yes.

Dr. Sikich: And that's what I don't want to have drop off the kind of viewpoint. And also this idea of trying to move beyond things that are laboratory tests into more real life.

Dr. Kasari: So I agree completely, Lin, that we need both outcome measures and we also need to define what change is and what's meaningful change. So how do we know that it's a meaningful change. Is it something that is, you know, improves life and functioning? And is not just a score but may or may not have any meaning.

Dr. Sikich: And that's something that I don't perceive that there have been clear-cut conferences about.

Dr. Kasari: Yes.

Dr. Sikich: Of really kind of trying to grapple with this idea of what would be clinically meaningful, what would be personally meaningful for a family, for an affected individual.

Dr. Kasari: Um-hmmm.

Dr. Malow: I agree and maybe that's the difference, Connie, is that we've had these

meetings about outcomes and people have tried to bring up let's move from these parent-based measures to something else. But it hasn't really -- I mean the focus has not been we're going to actually focus our conference on what these measures are. I don't know. You know better than me.

Dr. Kasari: Yeah, yeah.

Dr. Malow: But I agree with you it's very important. I think it needs to stay on the radar. And if putting it in the report at some level helps it stay on the radar I would be for that.

Dr. Sikich: Yes, I agree.

Mr. Britton: Thank you for that. That is good to know. Matthew, I haven't heard anything from you. I'm just wondering if there's anything you feel is particularly important about including in "What do we need" or even "What do we know".

Dr. Goodwin: I mean for the area of technological intervention I sort of sent quite a bit of [Inaudible comment] and suggested what we need.

I think there's an opportunity for us. I mean

this conversation is exactly kind of in that vein. But to think about what are common themes across each of our different areas. And it seems like we're all saying very similar things. I mean we need better measurement we need more consistent measurement across people. We need multiple levels of measurement and to understand mechanism well enough so we can start doing more treatment targeting. So I'm not sure.

Mr. Britton: Okay, I was just wondering if there was anything you had to add. That's great. I see what you wrote here.

Dr. Malow: Can I make a comment along the lines of Matthew? I'd love to hear what you have to say, Matthew, about this but I think one of the outcomes measures that could be developed with technology is like a lot of times we base a child's level of agitation or anxiety or whatever on these reports, on these parent reports, on these clinician CGIs.

And I think that the field is really getting exciting with some of the things you've been developing, your colleagues have been developing

with being able to measure autonomic function, for example. You know, I just wonder if that could be worked in. Maybe not the specifics of that but the idea that you could use technology in a way to develop some of these more objective outcome measures.

Dr. Goodwin: I may be not fully understanding exactly what the report is going to look like that Anshu's going to put together to go to the committee. I sort of just got a terse one-liner at the very end of my section.

But I totally agree with this. I mean, so what has been documented so far is really more computer-based instruction. But we're starting -- we have several studies underway and many that we'd like to do trying to get more objective, quantifiable measures of some of the constructs that we're all interested in.

So sleep, seizure activity, motor movement impairment, anxiety. These are all things that we have objective measures now that we can do in situ. I think that's a very promising area but we don't have literature yet to sort of say

definitively where we succeed and where we fail at that with this population. So with that caveat I absolutely think that should be included in this summary report.

Mr. Britton: So, so for the, can you summarize the things you just said in one sentence that I can think about for including?

Dr. Goodwin: So I think that we have new technological capabilities that enable us to get more quantitative outcome measures [Inaudible comment] interested in.

Mr. Britton: Yes.

Dr. Goodwin: And we can do this unobtrusively in a natural environment. So that's autonomic nervous system responding, that's physical activity detection. Sleep. Seizure activity.

Mr. Britton: Yes.

Dr. Goodwin: And emerging are affect indices.

Mr. Britton: Okay.

Dr. Malow: I think that's perfect.

Mr. Britton: Okay.

Dr. Goodwin: So when I think about anxiety, when I think about therapist-child relationships, when I

think about medication outcomes, when I think about sleep and seizure, these are all things where we're asking people questions with global surveys and we're doing behavior ratings, and we don't have a lot of direct physiological or physical activity measurement. We could be doing more of that with these new technologies.

Mr. Britton: Great, great. That's very helpful, thank you.

Dr. Goodwin: Thank you.

Dr. Sikich: And I think that we probably will also be able to move forward, for instance, eye tracking sorts of studies where it can really get more of a measure of social functioning. And some of the voice recording strategies which right now are geared only towards very young kids could be something that could be done for larger, for a more extended age range. So it again would be something that would be much more objective than just a parent report.

Mr. Britton: Can you tell me what you mean by voice recording? I'm not familiar with this.

Dr. Goodwin: [Inaudible comment] is a good

example.

Dr. Sikich: Yes.

Dr. Goodwin: [Inaudible comment] has done some work that's published in this area. So these are ways to use sort of small microphone packages embedded in vests in young kids that can do very dense data sampling and pattern recognition for sort of words heard and words spoken.

Mr. Britton: Oh, I see. Okay.

Dr. Goodwin: It's targeted to youth. And so --

Dr. Sikich: Four and under.

Dr. Goodwin: Right.

Mr. Britton: Okay.

Dr. Sikich: But that would be the sort of thing that if the programs were developed and the technology advanced where you could identify the affected person and key either people in their environment you could actually measure how much they initiated, how much they responded, how complex the utterances were, how many were request-based, how many were not request-based.

Mr. Britton: Okay. I see.

Dr. Goodwin: Another way of note to think

about this is we have emerging capabilities to instrument spaces and instrument people that give us a finer level of objective granularity than surveys and human coding, say, live or on video.

Mr. Britton: Right.

Dr. Goodwin: These are great methods. We learn a lot. I would never suggest that we replace those with technology but we can add them with technology. That could be a very powerful potential --

[Several speakers]

Dr. Malow: I think the other thing to say in all of this is the idea of how do you integrate. So let's say you're going to collect some parent measures, and you're going to collect some clinician CGIs, and you're going to do an autonomic or eye-checking or continuous performance test or whatever it might be.

I know it comes up when I submit grants where I have several of these measures that people always want to know well, how are you going to put it all together and how are you going to integrate it. Because I don't think we're going to

invalidate the parent report. I mean, I think the parent report and the clinician report are still important but I think figuring out how everything fits together is also going to be very important.

Dr. Goodwin: One thing, you know, I grapple with this in my own work is are we explaining different levels of variance or are some measures more or less valid than a given phenomenon. And I think until we have replications of multiple different people using the same measures, having the same constructs with a variety of different participants can we really answer that. But either way that's a gain.

Dr. Malow: Right, right. No, I'm not saying that we're ready to know that because I agree, the validation studies have to be done. But I guess what I'm saying is as we do these studies I think there does need to be an emphasis on collecting --

Dr. Goodwin: Multi-level.

Dr. Malow: -- different levels of materials. So I mean like I guess this would be a question for Connie. You're not suggesting we would throw out parent report. It's more like where do you put

the other measures in to get a comprehensive picture, right?

Dr. Goodwin: That's what I mean by -- I mean I'd like Connie to respond to that but that's -- when I say different variants explained, I mean a parent's report and a direct behavioral observation and a physiological data stream, all three may indicate something about, an approximation of the construct you're interested in but give you different information.

Dr. Kasari: Yes, we've actually done studies where we've gotten teacher report, parent report, to report observations, peer report, and it doesn't all match. And one of the things we need to ask are we need to get child's report.

Dr. Goodwin: That is hard.

Dr. Kasari: But in the context in which they are in terms of the behavioral interventions. So yes, I had comments about that in my little review.

So I do think that we can't be too simplistic here because we're trying to measure something that's very complicated. So from whose perspective

are you interested. You know, it's probably good to sort of triangulate these things.

Dr. Goodwin: I actually think too, another suggestion that is sort of implicit I guess in what we're talking about are RFAs or RFPs that were targeted on measure development for treatment outcome studies. That can take a variety of different intervention approaches.

Dr. Kasari: That is right.

Dr. Goodwin: But we come up with some standardized tool kits of methods that we all agree to be using.

Dr. Malow: I like that, yes.

Dr. Sikich: But I think NIH is actually -- the last study section I was at NIMH said at least that they have tried to put together these outcome tool kits for various disorders. I have not looked at the one they've put together for autism. And so I can try to look at that and see what they've put together. But I know that there is movement towards that. And I think that's also part of what NDAR is trying to do.

Dr. Goodwin: In bioinformatics. But they're

all assuming that somebody else has collected data to put in there. So I think we have to think about data collection devices and methods.

Dr. Sikich: But the tool kits are supposed to be the data collection methods and the outcome devices that should be used.

I mean, the idea at least as it was presented last week was that this is something where NIMH with its experts have said these are outcomes that we should have to measure these kinds of constructs, these kind of ideas in these disorders or these symptom domains.

Dr. Malow: This is Beth. I like this. I think the thing I would see maybe that you could add is a sentence when you talk about the new technologies or the development of these things that go beyond parent report is to say and then these new outcome measures will be integrated into parent report. Or you know, so basically there's a sense that we're going to integrate everything together that I don't want to get lost in the shuffle.

Mr. Britton: Right. Okay. That's important.

Thank you.

Dr. Goodwin: Just one parting word on this, Noah. I want to make it clear that the literature that I was reviewing was really using technology for educational purposes. What we're talking about now is using technology as outcome measures.

Mr. Britton: Right, right.

Dr. Goodwin: And that -- progress is being made there. But you know another point you could make is a lot of the people who are developing the technologies are not working with people who are intervening with children with autism. So if we were successful at getting tool kit development RFAs then I would think one of the things you'd really want to do is be pairing those technologists with those clinical providers than having these two functioning independently from one another.

Mr. Britton: That's a great idea.

Dr. Goodwin: It works great for a tech person but as soon as you hand it off to a teacher, to a parent, to a clinician that's where the real science starts.

Mr. Britton: Right.

Dr. Goodwin: And -- it doesn't work so hot.

Mr. Britton: Right, right. Absolutely and I know a researcher who's doing that but I haven't heard of many others. And it is important. And also including autistic people's opinions on this of course.

Dr. Malow: Oh, while you say this I just wanted to mention --

Mr. Britton: Sure.

Dr. Malow: -- individuals with autism. I meant to put it in the email and you sent out your fabulous review but I didn't want to offend you. If we could use family-first language and avoid saying "autistic" if others agree.

Mr. Britton: Well, the problem with this is that that offends autistic people who don't see person-first language as being helpful.

Dr. Malow: Oh.

Mr. Britton: It's equally offensive.

Dr. Malow: Okay, as long as you're thinking of that. Because I'm very careful in everything I write whether it be a paper or grant or whatever

to say individuals with autism.

Mr. Britton: This brings up an important point that isn't talked about much on the IACC or in research world which is that there's an enormous divide between people doing interventions and what autistic people want, and of course there's a ton of variation within both of those groups. But I think that's going to be one of the biggest things that would hinder having some sort of universally approved even outcome measure let alone intervention or intention of intervention.

And so I'm going to do my best to include everyone's opinions on this and say there's little agreement in terms of what people want changed versus what people feel is an important aspect of their personality that they don't want someone to force them to alter.

Dr. Malow: Right.

Dr. Sikich: How is that position reflected in this committee?

Mr. Britton: What do you mean?

Dr. Sikich: Is there an advocate or a person with autism who's representing their thoughts

about intervention?

Mr. Britton: That's me.

Dr. Sikich: Okay. Sorry.

Mr. Britton: I'm sorry I didn't give you biographical information. That's myself, John Elder Robison and Scott Michael Robertson. Yes. And so it is a minority of the committee and we do have our own opinions. But yes, we are working.

Dr. Malow: Okay. Thank you. Actually I should disclose that I have two children with autism if you need a family member.

Mr. Britton: There's a lot of family members on the committee as well.

Dr. Kasari: So I think that Beth and Noah, I think you guys have both identified the variability in opinion based on a parent's perspective.

Mr. Britton: Yes.

Dr. Kasari: And a person who can talk about it and identifies with autism. So I think it's not the disagreement, it's just the variability in perspectives that comes with the territory.

Mr. Britton: I suppose. There are definite

disagreements, you know, and this is going to be something that is going to impact my review definitely where I'm going to say this thing I'm thinking about first is although this is something that may be effective in accomplishing a goal is this a goal that's worth accomplishing. And some people are going to say yes and some people are going to say no and I'm going to mention both perspectives.

Because stuff like anxiety I think everyone agrees is an important thing to get rid of and the comorbidities are things that pretty much everyone agrees is important to get rid of. But stuff like flapping behavior is something most autistic people feel is an important aspect that they want to retain.

Dr. Malow: Well Noah, I think the way to do it is just in the same sentence or the same paragraph that you talk about, you know, we're going to make sure all of these measures are complementary, like we're not throwing out the parent report, we're just going to enhance it with these other measures.

I think you could just have a line that says something like we also will be mindful of different people view, including those with autism or if you prefer to say autistics.

I mean I think there's a way to put it in that follows that general thread which is we're going to use a multifaceted approach that includes input from a variety of areas. Just like we're going to include input from a variety of technologies, parent report, clinician report.

Mr. Britton: Yes, that's a good way to phrase it.

Dr. Malow: I think it could be done.

Dr. Baden: Noah, this is Elizabeth. I do think Anshu is on the line now and I know there were several questions for her earlier in the call. So Anshu, if you are still on the line?

Dr. Batra: Yes, hi. Thank you, Elizabeth. I'm sorry you all, I had an emergency this morning and I'm stepping in later.

Dr. Farchione: This is Tiffany. I'm also stepping in a little bit late. I had a conflict with another meeting that also ran over but I'm

here now.

Mr. Britton: Hi.

Dr. Batra: I just want to thank everyone for participating in all this. And Noah, thank you so much for stepping in. And if you could sort of get me up to speed in terms of what questions are still pending and what.

Mr. Britton: Well, I guess the big thing we've been talking about is the stuff that people feel need to be included in "What do we know" and "What do we need." And there's some good information that I can email you that Matthew was mentioning and everyone was agreeing.

The big things we all agree on are we need better measures we need more studies done within the actual community where they will be used. And we need a better toolkit of analytical methods.

And include -- sorry, what?

Dr. Batra: Diagnostic tools?

Mr. Britton: Right.

Dr. Farchione: No, outcome measures.

Mr. Britton: And with specific reference to new technologies which have shown up in the last

few years that can be useful as objective measures. And these should be included along with parent report and individual report just to make sure we have better methods of analysis.

And Anshu, I was wondering what you -- also your questions for this call were because this was mostly your idea I think. So I'm curious.

Dr. Batra: Okay, right, right, thank you. Yes, so I thought it was important for everyone to have a place where we could all ask questions.

In particular, I -- for Matthew I had some questions after reading your submission. And I was just trying to understand a couple of things.

One was -- so what does exactly the Cohen's d for the value mean? How is it determined and what's the significance of that?

Dr. Goodwin: It's a standardized effect measure between, typically between two different groups. So it's take two groups, subtract their means from each other, divide it by the pooled standard deviation across the groups and it gives you a standardized metric of effect size.

And if it's helpful to you I can send you an

email with Cohen's small, medium and large effect size measures. It's the most commonly used Cohen's d and Hedge's g are most commonly used in meta-analysis.

Dr. Kasari: And they're also used very, very often in pharmacologic trials. And typically something less than 0.2 is a very small, probably not significant effect. Something in the range of 0.3 to 0.6 or 0.7 is a medium effect. Something between 0.7 or 0.8 to 1, 1.2 is a very large effect.

Dr. Goodwin: That's right.

Dr. Batra: Okay, so that was my next question. So how much of a difference in -- so I'm taking it as sort of standard deviation, you know. And so how significant a difference does there need to be to say that that is a positive effect or another effect?

Dr. Kasari: The other way people typically do that is by looking at confidence intervals and seeing whether they cross zero or not. So if you look at 95 percent confidence intervals do you have both positive and negative numbers or do you

have just negative numbers if you're looking for a decrease in something, or just positive numbers if you're looking for an increase.

Dr. Goodwin: The values that I gave you based on this meta-analysis is a Cohen's d of 0.47. So that's a medium effect. And it's got a confidence interval range of 0.8 to 0.86 which suggests again that these are precise measures of medium magnitude.

You get variations so that's why I was giving you the plots too. Some studies show bigger effect sizes and some show smaller. So this is an average over that body of research.

Dr. Batra: And the only thing that's, you know, it seems there's a lot of inconsistency between the studies. And so how do you design a randomized control trial for these computer programs? What's your vision of a trial to demonstrate effectiveness?

Dr. Goodwin: Well, so you would want to have good sampling procedures so that the folks in the intervention group are pretty appropriately matched to the folks who are in a control group.

And what I -- and you would randomize who is going to get the real intervention and who is going to get not nothing but -- and when I say not nothing, I would like to see a technological intervention in both sides, but one has something that you think is an active ingredient and the other one doesn't.

So just doing a computerized -- doing a technological intervention compared to a non-technological intervention you may get effects just from the novelty of the platform delivering the technology.

There are different kinds of studies you could do. You could compare that against sort of computer interaction versus human interaction. But I think what would be more interesting is computer interaction versus computer interaction where you have different aspects of a program that you think is a key ingredient included in the experimental group but not included in the control group.

Dr. Batra: So, in the review that you did there's so much variability in terms of the age of the individuals, in terms of their IQs. And so

looking at these different computerized technology programs, you know, which ones looked like that they were effective? Because then you have to face --

Dr. Goodwin: Yes. So the last paragraph of the first two -- so, the last paragraph on the first page and continuing on the second page is what I think would be useful things to think about designing future studies in this area. So RCTs, the fact that we need more homogenous groups, we need larger sample sizes. Most of this is with folks with higher IQ quotients. So I think we could do more with more severely affected.

Many people use many different kinds of measures several of which the – sort of develop their own so they're not standard. We don't know anything about the psychometric properties. And so on.

Dr. Batra: This area, looking back at the last update, this is [Inaudible comment] sort of an area of need, especially for individuals who are non-verbal, looking at what is out there to help that population. I guess in their expertise have

we come across any computer programs and technologies that really addresses that population.

Dr. Goodwin: So the ones -- I mean I have certainly. I mean TeachTown is probably one of the better with evidence. There's a lot of technology out there but very little of it has empirical validation. So we see a lot about the iPad and all these apps in the news, and everybody's got the next best technological intervention for autism. Very few are data-based. Focus on those that we have empirical evidence for.

But I definitely think an area for future work is trying to include people who are more severely affected. No question.

And this is, again, maybe you were not on the line when we were having this conversation but what's reviewed here are sort of educational technology interventions. There's also much we could be doing using technology and developing technology for better quantitative outcome measures of non-technological interventions.

[Pause]

What I did not provide in here too, and I didn't know again the format of the report that you'll give to the committee, is sort of the why rationale. Something to think about in that why rationale is many folks with autism if given the choice to select their own activity will gravitate towards computers, DVDs, iPads, interactive media. There seems to be an affinity for some of these technological interfaces. That's really helpful to get a child who you have a hard time engaging their attention.

And then once there you could present very stimulating materials in a very consistent way. We don't have enough therapists and teachers to help the individuals with autism who could benefit from those skills. So the extent to which you could have a technological intervention that's performing as well or better than a human you could scale that up. You could make those tools available to more people.

And then the fact that these technological delivery, you know, intervention delivery systems are computerized, they collect data. So you can

gather a lot of information about where people are succeeding or failing within that program that helps you not only make that program better but potentially learn something about core differences in the participants using that system.

Dr. Batra: That's a good point.

Dr. Kasari: I would also argue -- this is Connie. Anshu, hi, I would also say that we talk about non-verbal kids more as minimally verbal kids because most kids have some language. And the technology or the devices are really important but we also need the strategies and the interventions around that to help kids engage with those. So in other words, we don't just give them something and expect --

Dr. Goodwin: That's exactly. I mean I would never want to replace a human in the loop -- tools they could use together.

And what's especially important, and this meta-analysis did not I think in my -- I don't think it did a good enough job pointing out that we have very little data about generalizability of skills acquired during the intervention off

computer.

And that -- we need much more of that if these interventions are going to stick. And humans are going to be the ones that are facilitating that.

Dr. Kasari: And that may often be kind of this idea that you start where there's more engagement with the technological kind of program and use it to transition to more human contact into the community, into the personal relationships. I mean, I think it depends. I think we just know. There aren't interventions that combine the two really.

Dr. Goodwin: We need to do those. Those are important studies.

Dr. Kasari: Yes, I agree.

Dr. Goodwin: And the other thing, sort of saying a technological intervention is like saying a pharmacological intervention. You know, there's a lot of different drugs that do a lot of different things. There's a lot of different technologies that do a lot of different things.

So we at some point have to be very specific about what's the platform and what's the intent

and what's the skill you're trying to teach. I would not equate all technology interventions to each other.

Dr. Kasari: Correct.

Dr. Malow: This is Beth. I opened yours, Matt, and it's excellent. And I'm just thinking in the report about what we know and also where we want to go. I think to make the distinction that we brought up earlier between the technologic kind of ways that we can use technology to get children and adults with autism to interact better but also as correlates for some of these outcome measures that are lacking.

And I think kind of making that distinction that there is two kind of separate areas where the technology can be useful.

Dr. Goodwin: Yes, the technology that I have just trying to base this on data-based [Inaudible comment] have any published pharmacological measures of interventions yet. I think that's very much a direction we need to go.

Mr. Britton: Is what direction? You were breaking up a little bit there.

Dr. Goodwin: It's what I've said before, that outcome measure development, quantitative.

Mr. Britton: Yes. Okay. Great.

Dr. Batra: Sorry, you were breaking up. I didn't hear that.

Mr. Britton: He was saying we need more objective outcome measures developed and we need to do research to make sure we have better outcome measures that are objective and based on technology.

Dr. Sikich: Can I ask a question? This is Lin Sikich. How will this report take account of things that are kind of nearly finished or ongoing but there aren't results yet? For instance, there at least two, the trial of arbaclofen in autism, the database has just been locked. And so that study has been done. We don't know the results yet, the data analysis isn't completed but probably by June next year we will know those results.

There is a very large study for instance of memantine right now going on in autism that will probably take 2 years to finish. Both of those

studies are focused on social relatedness, so really one of the core symptoms of autism.

There's a study that is just starting looking at oxytocin for core symptoms but it probably won't be done for 5 years. But there, you know, those kinds of studies that really have as a primary outcome measure core symptoms are going on, some are nearly finished. How would those be reflected or will they be reflected?

Mr. Britton: I'm going to say they probably can't be just as a scientist. Go ahead though, whoever was going to speak.

Dr. Batra: I think that we could put something that these are studies that are ongoing and we'll have to see what the outcomes are. And I think we can just mention it. I don't think we can really comment a whole lot on it.

Mr. Britton: Yeah.

Dr. Sikich: It just seems to me that it shifts a little bit from what we need. It's kind of like what do we know what's in progress, what do we need --

Mr. Britton: Well, we're not writing on what's

in progress though. Do you want me to say something like what we need is to finish this study? Because I think we already know that. I don't know what else --

Dr. Sikich: I think just a sentence to acknowledge that they're going on.

Mr. Britton: Oh, okay.

Dr. Malow: This is Beth. I mean the other thing that could be considered if we feel these are important things like to incorporate these technological measures into some of the studies that are ongoing is some of the institutes will occasionally put out an RFA to enhance, you know, to provide more funding to an ongoing study.

I mean, in other words if these are long studies that are 5-10 years in duration the idea of saying we will give you some additional funds to add on a specific outcome measure. I don't know. If they feel it's important.

Dr. Sikich: Basically a supplement.

Dr. Malow: Right, a supplement. Exactly.

Dr. Goodwin: That's a really nice idea.

Dr. Baden: Noah, this is Elizabeth in the

Office of Autism Research Coordination. And I just wanted to jump in quickly to say that for things that are ongoing but are aiming to fill gap areas I do think we would like you to mention those.

But clearly we can't indicate anything for results because we don't know yet.

But if you just mention that they're ongoing and what they're trying to address like core symptoms in this case I think that would be really good.

Mr. Britton: So you're saying something useful would just be to say there are more studies that are ongoing now trying to address social connectedness? Is that what I should put in?

Dr. Baden: Possibly and even if you want to mention some of the specific ones. And if you have an idea of the end date or when results might be available.

Dr. Sikich: And I can send you that, Noah.

Mr. Britton: Sure, that would be great Lin. Thank you. Anything else, Anshu?

Dr. Batra: Yes and Lin, you had mentioned in your email that you were also going to be looking

at other alternative --

Dr. Sikich: Yes. Most of what I found actually has been covered except for kind of pilot studies has been covered really nicely by Beth. I think it was Beth who did that with the melatonin studies.

Dr. Malow: Yes and then I also brought up the AHRQ reviews that I think pertain --

Mr. Britton: Yes, thank you for those.

Dr. Malow: You know one thing I did put in my review is there is -- so the medical comorbidities section which I've kind of led is there is a big supplement coming out in Pediatrics in November that will have a lot of articles. So I don't know how to handle that because I guess it will be after the deadline. But there's going to be some very good things in there. So I don't know if that --

Dr. Batra: [Inaudible comment] Do you know when?

Dr. Malow: I can find out. But you know, it's really -- I mean the medical comorbidities have just not received a lot of attention. And there's some really nice articles in there. I mean I could

find out when in November.

Mr. Britton: Sure.

Dr. Sikich: Any of those online ahead of print?

Dr. Malow: The problem is I talked to Jim Perrin who was the author of the supplement. He's the new president of the AAP. And he said they've been embargoed. So I don't know how to handle it.

Dr. Kasari: They're coming out November 1st, Anshu. I've got one in there.

Dr. Malow: Oh, good.

Dr. Batra: So maybe we can look at that and see if we can --

Dr. Malow: And I sent the title. Anshu, I think I sent you the title, the table of contents. So you have that.

Dr. Batra: Yes, I have that but it would be nice to just get -- if there's any way to just maybe get a quick one or two, one-sentence summary on what's the --

Dr. Malow: Oh, the abstract. Do you want me to email Jim Perrin again and copy you and see what's possible?

Dr. Batra: That would be helpful, yes. That would be helpful.

Dr. Malow: Okay, I'll do that.

Dr. Batra: Yes, and you know, the other thing I was interested in is what other, other than pharmacologic interventions to address the comorbidity, but you know what other interventions other than just medication might be --

Dr. Malow: I included -- I mean part of it was there's a really nice review of behavioral interventions for sleep but it was, I don't know if it was done before 2011.

You know, the one that -- one of the ones that's coming out in the supplement actually includes a lot of different, like it includes acupuncture, massage, behavioral. It's actually one that our ATN committee wrote. So that would be nice if it could be included because it goes beyond pharmacologic.

Mr. Britton: Okay.

Dr. Batra: I felt it was really important because that's what families, that's what parents and that's what individuals are really looking

for, other options.

And I think one of my comments I wanted to make was that I think looking at these reviews and that there's been so much emphasis on medications.

Dr. Malow: Right.

Dr. Batra: And I think that the public out there is really speaking of other options as well and what are the other things that have been looked at. And if there aren't options that have been looked at whether we need to.

Dr. Malow: Well actually I just pulled it up. So the good news is the behavioral interventions for sleep problems in children with ASD is from 2011 and I included that in my summary I sent.

And then the one that's coming out in Pediatrics actually has even more interventions. So maybe if both of those were included that would help. So, I'll find out what we can do with the supplement.

[Pause]

Dr. Batra: And then there's a couple of things.

[Pause]

Yeah, I had a couple of questions for Jeff but I'll just email him and see if he can quickly answer them about the CBT practices.

And Connie, I think one thing I really wanted to highlight from what you had submitted is really just the findings about the early intervention and how it impacts language and 5-year data. I think that's a real important thing to sort of mention. Again might be something for early intervention.

Dr. Kasari: Yes, I think there's been a lot of movement in the behavioral interventions actually. I think it's been positive.

Dr. Batra: And Noah, in your submission you you mentioned something about mindfulness being an intervention that's been looked at.

Mr. Britton: I haven't found anything else on mindfulness but I will admit I haven't looked for everything that exists. So there could certainly be more. If you want I can try to find more on mindfulness.

Dr. Batra: I guess again just having some additional things like that would be --

Mr. Britton: Yes, definitely. I think that

should be the biggest focus truthfully as you saw in my review.

Anshu, do you have any other questions as far as what I said here?

Dr. Batra: Well, yes. I think just a comment in terms of a lot of the movement-based interventions. I thought that was quite interesting. And what additional studies or support do we need to look at more of movement-based initiatives.

Mr. Britton: Yes.

[Inaudible comment]

Unfortunately some of those were the very first RCT ever done on that intervention.

Dr. Batra: That might be something we might want to put in the, you know, that we need.

Mr. Britton: Yes, yes, yes. Yes, definitely. Working on some more of that, yes. More of the stuff that I sent you cause that's important.

[Pause]

Mr. Britton: Anshu --

Dr. Batra: Again I'm not sure [Inaudible comment]. It just seemed like there would be a lot

of focus on drugs to address the core symptoms.

And it felt like we were turning away from looking at the underlying causes of abnormal neural connectivity and behavioral development as opposed to just the [Inaudible comment] interventions to treat.

Mr. Britton: Are you saying then that we would need more CBT stuff in contrast to the interventions?

Dr. Batra: Well, not the CBT stuff but looking at other interventions that are different from drug or medication.

Mr. Britton: Yes, I think one thing we do need is to focus on other interventions besides drugs. Because we've been doing a lot of drug interventions.

Dr. Batra: Movement-based interventions, you know. Physical rehab type programs. I think Tiffany had mentioned the TMS as a [Inaudible comment] mentioned has been looked at. You know, more sensory motor-based interventions.

Autonomic, looking at maybe autonomic controls, again, these are things that I don't

think have necessarily been looked at in the past.

[Pause]

Mr. Britton: So Anshu, do you have anything else that you're planning to send me for my section on "What do we need"? Because obviously you had some stuff at the beginning. I was just wondering if I should wait for more.

Dr. Batra: Absolutely. Yes, I'll send you some stuff hopefully so that we can get it completed.

Mr. Britton: Okay, great.

Dr. Batra: And then what I'm doing right now is I'm in the process of integrating all the information, submissions and --

Mr. Britton: Right.

Dr. Batra: -- to everyone. And that way everyone can comment.

Mr. Britton: That would be wonderful. I'll do the same thing as soon as I get the stuff from you that I can integrate.

Dr. Batra: Elizabeth and Gemma, so we need to submit everything to you, sort of a near draft by Monday, correct?

Dr. Baden: Yes, that's correct.

Dr. Farchione: Okay, so when -- because I know you guys had talked about doing your parts and then I was going to sort of edit for content and brevity. When do you think we'd be able to get your section to me?

Dr. Batra: So I'm hoping, again today is Thursday, so I'm hoping over this next -- I should be able to get it to you and get it to everyone I'm going to say by tomorrow if not early Saturday. And that way, will that give you enough time to kind of review it and see [Inaudible comment]?

Dr. Farchione: That's going to be really difficult because I have a lot of stuff going on this weekend and I'm leaving for the Child Academy meeting on Monday so I'm already squeezing a lot of things into my weekend. If you could try to get it to me by like say midday tomorrow that would be --

Dr. Batra: Okay. Yes, that --

Dr. Sikich: Is this Elizabeth talking?

Mr. Britton: That was Tiffany.

Dr. Farchione: Tiffany.

Dr. Sikich: Okay. I'm sorry. I don't recognize people's voices yet.

Mr. Britton: Yes. Tiffany, I'll try to get it to you by midday tomorrow but obviously I don't even have Anshu's input yet. So I'll do my best.

Dr. Farchione: Okay.

Mr. Britton: And obviously Saturday would be the latest. But hopefully I'll have it in by tomorrow.

Dr. Farchione: Okay. When you guys say that you need it by Monday, what time Monday are we talking? Like end of business Monday? Because I could also be working on revisions. Because I'm flying out Monday morning. I could also be working on revisions on the plane.

Dr. Baden: If you could have it by the end of day Monday that would be okay with us.

Dr. Farchione: Okay.

Mr. Britton: Great. Perfect. Thanks a lot.

Dr. Batra: Do the experts have anything, any other last comments?

Mr. Britton: I guess, Anshu, I just want to make sure that the cautionary stuff I mentioned in

my review gets in. That was the big thing, just the focusing on the negative impact of stuff. I really want to make sure that's in there.

Dr. Batra: Right. No, I know. I appreciate -- yes. I think definitely.

Mr. Britton: Great. Thank you very much. Perfect. Thank you, experts. Appreciate your help. Bye.

Dr. Farchione: Thank you.

Dr. Kasari: Thank you.

Mr. Britton: I guess we will email you soon.

(Whereupon, the Strategic Plan Question 4 Planning Group call was adjourned.)