Affecting the Aging Trajectory: *Regulatory Constructs for Gerotherapeutic Drug, Biologic, and Device Development*
Hybrid Public Meeting
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Transcript – Afternoon

XPRIZE Healthspan and ARPA-H PROSPR Awardees: Evidence Being Built at Scale

Introductions by:

- **Jamie Justice, PhD, Executive Director, XPRIZE Healthspan, XPRIZE Foundation**
- **Andrew Brack, PhD, Program Manager, PROactive Health Office, ARPA-H**

XPRIZE Healthspan Presenters

- **David A. Brown, PhD, Chief Scientific Officer, Stealth BioTherapeutics**
- **Zahi A. Fayad, PhD, Lucy G. Moses Professor of Medical Imaging and Bioengineering, Icahn School of Medicine, Mount Sinai**
- **Blake B. Rasmussen, PhD, Professor and Chair, UT San Antonio Long School of Medicine**

ARPA-H PROSPR Presenters

- **Brianna Stubbs, PhD, Director of Translational Science, Buck Institute for Research on Aging**
- **James Peyer, PhD, Founder & CEO, Cambrian Bio**
- **George A. Kuchel, MD, CM, FRCP, Director, UConn Center on Aging, University of Connecticut**

Susan C. Winckler:

Let's go ahead and get started. We will kick things off again for the virtual attendees and I'll eventually get your attention to the room. We have one more rapid fire session before we turn to a series of conversations. And so what we are going to hear are six snapshots of [00:00:30] work driving medicines or products in the gerotherapeutic space. And in fact, I'm just going to have Dr. Jamie Justice tell us about who we will hear from to give us a little background on XPRIZE Healthspan Global competition and the participating presenters. So Dr. Justice, give us some foundational information and then we'll turn to those three.

Dr. Jamie Justice:

Okay, absolutely. So today we're going to hear, I have a couple of case studies that are from our competition. So we're going to hear first from, excuse [00:01:00] me, from David Brown, who is the Chief Scientific Officer for Stealth BioTherapeutics. We also have Zahi Fayad, who's for Mount Sinai,

who's going to also talk about an approach that they're using in our competition. And finally, Blake Rasmussen, who is in San Antonio. So at the Barshop Institute there. And again, these are selected at semi-random. They're all US-based investigators. They all represent very different approaches to the competition and [00:01:30] to the field. And I think they're very representative of approaches that either regulators might see or that are really indicative of testing types within the field. So again, if you missed it this morning, that's me. I'm still here.

And the XPRIZE Healthspan, again, it's a competition $101 million prize purse that's actually given out over two milestone points and it's to incentivize the [00:02:00] advancement of proactive accessible therapeutics that can improve function and increase health span. So we have heard from a lot of people this morning who have helped contribute to this prize. If you're here and you're an advisor or a judge or a team or have some way contributed as a partners or as our ecosystem or a sponsor, please raise your hand. Pretty much everyone here, those online, feel free to raise your hand too. It's been a really large initiative. We've had to make a lot of decisions. We've made these decisions as informed as possible [00:02:30] from the scientific community, from patient voice and from major partnerships and scientific advisors. Again, those decisions for our prize means that our teams are going into one year trials this year.

We have asked our teams to demonstrate that their therapeutic can restore muscle cognitive and immune function. So as relevant to the talks this morning, this is a subset of some of the things of interest within intrinsic capacity. It is a multi-endpoint [00:03:00] by intention. It is function based. And at the end of this competition, we've also already heard from Nic Schork. So maybe this response threshold idea makes a little more sense in that context. And so thinking about a way for global competition in different populations, under different settings, with different therapeutics is that this was a very rigorous and challenging way for us to have our teams demonstrate this. And again, we are awarding [00:03:30] in 2030, the teams are starting trials this year, but we actually launched this program in 2023. Last year in 2025, we did our first big announcement where we awarded 40 teams, but about a hundred teams were qualified to continue in the competition.

That means that they went on to run short proof of concept studies. Some of them, if they're using a new drug, that might have been PKPD studies. Some have already done testing and so they already had some evidence they could bring forward. Others [00:04:00] were actually trying new combinations because combination therapies are really common in the field, and we do see that. Right now, our judges are doing the judging of the finals applications. We're meeting in Canada on June 10th through the 13th, I believe. I'll double check my dates, judges. It's like deciding the Pope. They're going into the room after doing a very rigorous review, looking at de identified data, [00:04:30] considering the competition, considering this large data set and evidence base and they'll identify the 10 teams who will be awarded, but additional teams can continue. Again, this is an open competition using centralized resources.

And who's showed up? So again, why we're having this meeting is because we've already heard, it's not that we're waiting for consensus by any means. Right now, what we have is we have teams that are already in clinical testing. [00:05:00] We have a field that is well incentivized to develop. We have work that's come out of proof of concept and preclinical studies. We've heard about the interventions testing program, cannot say enough about the drive and the impact that the National Institute on Aging has had to incentivize the field. But again, for XPRIZE competition, what that means is we've already had 789 global teams register for this competition over the last two years. Out of those, we had 111 that were qualified [00:05:30] to start those early stage proof of concept studies. We just closed our application

period. I was hoping for maybe 40 teams to submit applications. We have 65 with human data from early stage trials, who are vying for the ability to be one of those top 10 teams or to continue self-funded.

What we see is not one drug or therapeutic. I think this is very important. Another reason that we reached out to Reagan-Udall [00:06:00] Foundation is that this doesn't sit in any one center or anyone's desk. What we have are teams, these are from the top 40 teams and we see very similar representation in our applications that just came in. We have about a quarter of our teams that are testing drugs. These are almost equally split between repurposed and new novel therapeutics. We have about a quarter of our teams testing biologics of various combinations and types. From monoclonal antibodies [00:06:30] to again, totally novel multi-protein, to we even have now going into finals, we now have five applicants with epigenetic reprogramming as their primary therapeutic. We have cell therapies, plasmapheresis-based transfusion, anything you can imagine. We also have a category that we call multimodal, which is like lifestyle interventions plus.

Again, these combination therapies are very common. So how do you apply some of the basics [00:07:00] you should already be doing, exercise, diet, sleep, and combining that with a novel therapeutic of some kind. So again, we have about a quarter of our competition that's featured there. And then finally, we have things that are more in the unregulated space. So these are nutraceutical supplements and others and that category continues to grow. And we provide any of them with an equal footing as long as they can demonstrate it, it's allowed. They have to have their own safety and we provide the framework for testing. [00:07:30] And so I wanted to give a snapshot of groups that have very different approaches, very different modalities, who have some clinical evidence behind them that I think would be relevant to just showcase some of what is being established in the field. And with that, I'm going to announce our first team, which is led of speaking today with David Brown.

Susan C. Winckler:

Great. Thanks.

Dr. David Brown:

Thank you to the Reagan-Udall [00:08:00] Foundation. Is this on? There we go. Thank you to the Reagan-Udall Foundation for having this. Thank you, Jamie, for the opportunity to present our work. I'm Dave Brown, Chief Scientific Officer for Stealth BioTherapeutics. I'm here representing our XPRIZE team. The name of our team is the Mitochondrial All-Stars. So we are fascinated by mitochondria. The Stealth BioTherapeutics was founded based on the idea that targeting mitochondria could significantly improve health span. So this fascination by mitochondria is pervasive [00:08:30] for us. We see the mitochondria as an energy grid. Many of you may be used to seeing the static black and white image of mitochondrial cross section, which is certainly interesting, but mitochondria are much more dynamic and as exciting as I hope is conveyed in the movie to the right-hand side as an intracellular energy grid. As has been alluded to today, mitochondrial dysfunction is a central driver for aging and age-related diseases.

So something that we're very interested in working on. Our company has decades of experience [00:09:00] and a number of different small molecules at various stages of development. The one I'm going to talk about today with our XPRIZE grant is called elamipretide or elam for short. Elamipretide is a mitochondria targeting peptide that binds to the inner mitochondrial membrane. So this is where all the

business takes place inside mitochondria. You can see a rendering of the electronic transport chain here in this with the elamipretide depicted in blue. This is a very well studied molecule. So we feel like we have science [00:09:30] and the process of science on our side as it's been tested in a number of different models of aging and disease. It's also well characterized in the clinic, having been tested in over 1700 individuals with over 400 patient years of data. It's the first and only FDA approved therapy.

Mitochondria targeted therapy. It was approved last September under Subpart H, so the accelerated approval pathway for an ultra-rare disease. In addition to what I'll be talking about today, the company has [00:10:00] some really encouraging data in aged populations and in particular in dry age related macular degeneration, a leading cause of blindness where we saw some really encouraging phase two data where we saw some photo receptor protection in the phase three trials currently enrolled. So we have a lot of preclinical data that goes behind and that went behind our XPRIZE semifinals award. What you're seeing on this slide first on the left-hand side is an image of an electron micrograph [00:10:30] of a young mouse and then compare that to the old mouse, to the middle image. The mitochondria in this section that are round, you can see they're full of white spots. Well, this is where all the energy is made.

And so if you have a hole or a vacuum within these mitochondria, it tells you because structure and function of mitochondria are so closely related to each other that there's something different about aged mitochondria and that's where people like us see a real opportunity. In this case, in this non-clinical study in mice, you can see on the right-hand side of the image, [00:11:00] the aged mouse that was treated with elamipretide, normalizing the function. We've also seen in humans. So before the XPRIZE even started, the University of Washington did a study in older adults where we know they have mitochondrial dysfunction. They looked at the rate of ATP production in the older adults and you can see on the right-hand graph here, the rate of ATP production when the individuals were treated acutely, this is one time with elamipretide and improved the rate of energy production by [00:11:30] the mitochondria in these aged individuals.

So this was very encouraging for us, and this collaboration to work on the XPRIZE is one that's for us building on a 10-year collaboration as these studies were done at the University of Washington. We've also published studies showing that elamipretide can reduce markers of inflammation and so we fit the criteria for the XPRIZE competition. So we formed a team, the Mitochondrial All-Stars. We were introduced at the All-Star or at the semi-finals [00:12:00] award e-banquet in New York as a basketball team, which was a huge compliment. Probably the first and only time we go to New York and get mistaken for basketball players, but we had a really nice team here. So on the Stealth BioTherapeutics side, we have mitochondrial expertise, decades of expertise doing clinical trials, including supporting investigator initiated trials. And then on the right-hand side of this graph, we teamed up with our colleagues at the University of Washington. Dr. Dave Marcinek is the Co-director of the [00:12:30] Nathan Shock Center there.

Dr. Sumi Jayadev is a Neurologist and a part of the UW Alzheimer Research Center. And he's got an excellent research scientist that rounded out our All-Star team. So what we ended up doing in our XPRIZE semi-finals study was a study that we called SHAPE, Study of Healthy Aging and Physical Function with Elamipretide. In this case, we did a four-week treatment. This was a single arm open label treatment, where everyone got elamipretide once [00:13:00] a day for one month. So it was a 40 milligram dose. The age that we enrolled was 65 to 80. The objectives here was first and foremost just to demonstrate that we can do a trial like this to position ourselves for the XPRIZE finals. So this is a phase 2A investigator initiated study. We kicked off in June of 2025, got an IND exemption in October and then started enrolling immediately after that, just finishing up last month. The primary objective, of

course, was to [00:13:30] evaluate the safety and tolerability. With the secondary objective being to look at the muscle inflammatory and cognitive function as per the XPRIZE competition guidelines.

Here are a little bit of the data from our semi-finals study. First and foremost, elamipretide was well tolerated. It's built on a very robust safety profile that we know about this. The most common thing that we see as it's a peptide was injection site reactions here. And we saw some interesting findings. So what you're looking at here is before [00:14:00] and after the one month of elamipretide treatment for knee extensor strength, six minute walk test and then cognitive function. And so you can see in each case the individual scatter plots of the 23 individuals who are on this, as well as the mean composite change over the course of one month. These were very interesting findings, of course, but come with the obvious caveat that this was a single arm open label study. So we can't account for any learning effects or things like that. Where we see that though is this could be a really good support for the initiation [00:14:30] of a longer, placebo controlled trial, where we can actually make more conclusive decisions and get more data in this population.

So these are the initial results that we have right now. Dr. Marcinek will be going to the American Aging Association meeting next week to present a more in depth findings, but encouraging data with all the caveats that we see. In terms of us for our next steps, Jamie, [00:15:00] Dr. Justice outlined the process for the XPRIZE. We've submitted our XPRIZE finals grant. We're hoping for the white smoke to come up if it's like electing the Pope. So we do have our XPRIZE final application now to do a one-year placebo controlled trial in older adults. I'll just close where I opened, and that is that we are enormously enthusiastic about the potential to treat aging and age related diseases by targeting mitochondria. We're really glad to be a part of this discussion [00:15:30] today as access to this therapy will certainly require clarity on the regulatory pathway forward for aging. So thanks again for having me today. I really appreciate it.

Susan C. Winckler:

I didn't imagine that we would be talking about white smoke nor basketball teams today, but that's okay. All fits in well. So now let's go to second presentation and so at our podium, Dr. Zahi Fayad, Lucy G. Moses, Professor of Medical Imaging and Bioengineering [00:16:00] at the Icahn School of Medicine at Mount Sinai. There you go.

Dr. Zahi Fayad:

It's a little bit ironic. The Cardinal's age that they can vote have to be less than 80 years old. So maybe they can reconsider that if we end up successful in our venture here. Okay. So it really gives me great pleasure to represent our team, part of the finalist to the XPRIZE Healthspan. So we are NYC-VITA 2030. This is a multimodal approach, as was alluded by Jamie. We're looking at exercise. [00:16:30] We're looking at spermidine, rapamycin and our basis of this whole idea is that we really need to work on the aspect related to the myeloid cells and the inflammation. This is how we can restore the aspect of aging and health span. So just very quickly, I mean, we are obviously going to go after this macrophage shift. We have a lot of data from our experimental work done in animal, but also looking at inpatient, looking also at cancer patient, [00:17:00] how we're able to change the milieu of that inflammatory system.

We are going to address the three different target that were imposed and put together beautifully by the Healthspan XPRIZE, so we're looking at the brain, muscle and immune function. And then we are

really going to put together a whole multimodal approach in terms of the composite scores in order for us to measure in the plasma, the different analytes. We have a lot of [00:17:30] experience with this OLink platform led by Miriam Merad, who's leading the study here through her many years of work in that space. We selected for the final, we had other ideas in the initial aspect, but we have the right to change according to what we've learned from the initial phase. We ended up continuing with the rapamycin dosing, as well as the spermidine. [00:18:00] Both of them have been selected in the right dose that we feel is appropriate for our study and also from the initial phase one that we have done.

And this has been really what drives us to go after in the finals, looking at this complementary approach to the macrophage shifting. We've lost also different, four independent signals, a chain into one story of restored resilience. I'm not going to go a lot into the detail. You can read them [00:18:30] into the slide deck that we provided. And these, again, have been very much driven according to what we've measured during the phase one study that we have taken. The final trial design ended up with 180 participant with a two to one randomization and a 12-month intervention. And then you'll see here we are looking at 60 controls and 54 valuable at [00:19:00] the end of the trial that will be matched according to the different visits that we have. We have lifestyle modification that we are undergoing.

So that's why we have that multimodal approach with exercise that's being driven with a design that we give to the people with instruction that's very specific. We have two week of high intensity interval training and then three weeks of resistance training within the [00:19:30] trial and achieving a certain level of activity and level that we will be measuring using the different devices that we will be deploying in the subjects. We'll skip that, yeah. So looking at the composite responders, we've selected as primary endpoint related to the muscle function, the VO2 max testing. We're looking at the brain processing speed by the cognitive testing that have been selected [00:20:00] also part of the trial that we're all going to be following, as well as an immune function where we have a reduction looking at this with a certain type of a threshold.

Again, the aspect of the different endpoint, we have other secondary endpoint that I think are very critical within the trial and they're very extensive. So divided obviously into muscle function, brain function and immune function. And I think we've been very much [00:20:30] guided by actually the biomarkers health span program that guided us into some of the selection of these endpoint that we will be measuring. So we are ready for the execution. During our first phase we finished the evaluation and then we have a whole aspect of approval from a regulatory point of view to move forward into the study. The infrastructure is there, the patient [00:21:00] are there and everything else and we gain the experience in how to deploy this in the real world. So we're really excited to be part of this. I think this is something that we've been all dreaming about and we hope that we will be able to deliver with you. Thank you so much.

Susan C. Winckler:

Excellent. So it's not part of your scoring mechanism, Dr. Justice, but being on time with presentations is [00:21:30] just brilliant. So thank you, Dr. Fayad. And now we have one more XPRIZE Healthspan presenter, and that is Dr. Blake Rasmussen, Professor and Chair UT San Antonio Long School of Medicine. Dr. Rasmussen, we can see you. Please proceed.

Dr. Blake Rasmussen:

Yes, thank you. I'd like to thank the organizers for the opportunity to present our work with the XPRIZE and we're going to switch gears a little bit. We're looking at a device this time, [00:22:00] so we're not looking at drugs or any kind of biologic. And so I wanted to give you just a brief history of how we came to look at low frequency ultrasound for the development of healthy aging. And so let me see here. Okay. So last year we published a paper in aging cell and we collaborated with the late Mike Sheetz on this project. Mike won the Lasker prize in 2012 for discovering [00:22:30] kinesin, the molecular motor with Ron Vale and Thomas Reese. And he was looking at low frequency ultrasound in an effort to look at actin filament dynamics and how those changed within a cell. We co-mentored a postdoctoral fellow, Sanjay Kureel, who's the first author of this paper. And he had an interest in senescence. And so this was a serendipity result. We took it, senescent cells, exposed them to low [00:23:00] frequency ultrasound and noticed that they were able to reverse induced and replicative senescence in these cells.

And we looked at a variety of different cell types. We also saw that this low frequency ultrasound could increase DNA methylation and telomere length. And then we took this a little bit further and we went into in vivo. And so we got a very old mice from the NIA and we created [00:23:30] a water bath where we had a low frequency ultrasound probe at the bottom of the water bath. And the reason we use a water bath is because these pressure waves that are generated by low frequency ultrasound travel best within water. So we placed these older mice in a little platform with the water up to their neck and they spent 30 minutes total time for 30 days in this ultrasound every day for 30 days in this bath. And we found some interesting things. And so we [00:24:00] discovered, and this is a relatively small study for lifespan studies, but we did see an increase in lifespan with low frequency ultrasound. As well an improvement in their physical activity as shown in the graph there on the right.

One thing I wanted to highlight is there's just a brief picture on the bottom, and panel D is the older mice and they look pretty haggard. But if you look on the bottom, these LFU treated older mice [00:24:30] moved a lot better, they looked better, their fur was better, they lived longer. And this is all I'm going to talk about for this particular preclinical study, but if you go to our paper and aging cell, we have a lot of videos online that show you how these change and how the cells move in response to a low frequency ultrasound. So how does this work? Well, this is still a [00:25:00] work in progress. We put in the paper a proposed mechanism and we are finishing some cell based studies right now to try to identify the cellular mechanism. What we do see is that if you take a senescent cell and expose it to a low frequency ultrasound, you get a reduction in SAS proteins.

We also see an increase in mitochondrial dynamics and actin dynamics. We see an increase in AMP activated protein kinase, an increase in growth activating factors that inhibit SASP. And we [00:25:30] are now working on the idea that this leads to an inhibition of mTOR mechanically and an increase in autophagy and perhaps a release of Sirtuin 1 to rejuvenate these senescent cells. This is still a work in progress, but this gives you the basic science background or preclinical background of why we propose to do this. So this led us to the XPRIZE semifinals where we proposed to do this first in human study. And in this study, we proposed to study [00:26:00] 20 older adults over the age of 70, and 10 would be a placebo control group and 10 would be the randomized group. Our placebo was that the people would sit in this tub without the ultrasound on and this is convenient because the ultrasound does not make a sound or they cannot feel the pressure waves that are generated.

And so they sat in this tub for three days per week, 45 minutes per day for two months. We did pre and post-testing physical. We did BIODEX for muscle strength, [00:26:30] DEXA for body composition, physical tests such as the six-minute walk and so forth, VO2 max. We looked at cognition using the NIH toolkit in this particular case, and then we looked at some immune markers of DNA methylation for age

as well as SAS markers. I'm not showing the preliminary data here, but because it's so preliminary, we've only completed 14 of the 20 subjects at this point. We'll finish all 20 by July. But the preliminary data is very [00:27:00] intriguing and somewhat supportive, we believe. So what are we doing for the longer trial? We've learned a lot from this trial. We've learned that this proposed tub, the hot tub, where we have the low frequency ultrasound. We've learned some things on how to improve it, how to improve the design. So we'll have more of these available for the long-term trial. We'll be doing this for a month or for a [00:27:30] full year, rather than two months.

And we'll be using the same design three days a week, 45 minutes per trial. We'll be doing a lot of pretesting and you can see all that there on the right. One of the big changes, we will no longer use the NIH toolkit. We'll use the COG state test instead, as proposed by the XPRIZE group. And we have the capacity to look at blood collection, all the different strength and physical function testing as well in addition [00:28:00] to all of these. And so I did want to just highlight our experience on these kind of studies. We're located at the Barshop Institute for Longevity and Aging Studies at UT San Antonio. We have three large NIA center grants within this institute. This institute is a brand new building with about 27 PIs and then on the first floor we have a large clinical trial space for first in human studies. [00:28:30] We have the Nathan Shock Center led by Dr. Adam Salmon. We have the Pepper Center led by Dr. Elena Volpi. And we also have in conjunction with the University of Michigan and JAX Labs, the interventions testing program.

We just completed the largest study the US government has ever done on health benefits of exercise, MoTrPAC trial, which is a very complex clinical trial that took place over a three-month period in all age groups and had [00:29:00] a lot of physiological phenotyping, muscle biopsies, adipose biopsies, blood collection, and multi-omics involved with that. Unfortunately, our entire clinical trials team has been retained from that MoTrPAC trial that just finished and we've put them to work on ARPA-H and the XPRIZE. We also have a GRECC VA center. We're a member of the ARPA-H and a program for PROSPR. We call our project VITAL H where we will repurpose [00:29:30] existing drugs for extending health span. Those drugs are semaglutide, rapamycin, and SGL2T inhibitor. And then this presentation was about this particular project for the XPRIZE. And our business partner is Novaquoustics, who we're working with to help us improve the design of this device. So thank you for your time.

Susan C. Winckler:

Great. Thank you so much, Dr. Rasmussen. Really helpful to have that snapshot of [00:30:00] looking at what I think about as more traditional drugs, the multimodal and then the device aspects. Let's turn to hearing about the ARPA-H work. Dr. Brack, would you remind us about the PROSPR awardees and your approach here?

Dr. Andrew Brack:

Sure. Hi again. So just as a way of introduction before we get into some of the performance of PROSPR, I just wanted to... We're only a few months in, [00:30:30] so we don't have those people running those trials yet as Jamie alluded to, but we've heard multiple times. We need to build the data. The data needs to be in place before to make any regulatory decisions. So I wanted a overview of the program, what the performers will be doing and highlight the regulatory, potential regulatory touchpoints. And so the first part of the tech... Oops. The first part is really the Stanford and THRIVE team. They're going to be using machine learning to integrate longitudinal [00:31:00] existing health data sets that contain IC metrics based and correlate them with 20 year real health outcomes. They're going to deliver on that and then

they're going to iterate based on other parts of the data that'll come in through PROSPR. For example, part of that THRIVE team will develop a lifestyle trial.

And so we're going to ask the question, how does intrinsic capacity change with lifestyle? That's going to give us our second version. There's two things that are going to come from that team though. One, as I mentioned earlier, is an intrinsic capacity [00:31:30] that is ready for clinical trial. Which looks very different than if you wanted to have intrinsic capacity for say for another purpose. We think it's critically important we can measure intrinsic capacity at home. When we think about health span, this is going to be healthcare at home. People are not going to go to the clinic. So can we have a predictive intrinsic capacity that is in every home of every person? So THRIVE have two roles, clinical trial, intrinsic capacity, and a kit for in home use that will be developed and commercialized. Columbia, as [00:32:00] mentioned by Nir Barzilai earlier on the left-hand side.

So Nir is going to develop and his team with Dambelsky is going to develop a blood-based biomarker using what we think is potential gerotherapeutics in diseased people. So now do those blood-based biomarkers that change with drugs, in diseased people, correlate with lifestyle and intrinsic capacity? That's the question. And then those sort of gerotherapeutics are going to be tested in non-diseased people as Blake Rasmussen just mentioned at UTH [00:32:30] San Antonio. So that's going to be a three-year health span trial. We're going to test rapamycin, SGLT2, GLPs, and ask, do we now show intervenability of intrinsic capacity in a clinical trial intrinsic capacity over that three year period? We're also going to model that with the intrinsic capacity kit. So that intrinsic capacity kit is going to be able to tell people at home, when you have this in your home, it's intervenable with exercise, it's intervenable with gerotherapeutics. And then finally, [00:33:00] what we're going to ask is there's four teams at the bottom.

They are the validation of intrinsic capacity. Can we now run instead of a 10-year health span trial, a year and a half phase 1B clinical trial where the endpoint is intrinsic capacity? That's the validation. And we're going to use what we call second generation therapeutics. Four teams, Cambrian, Nula, Linnaeus, and University of Rochester. So that's the program. We're going to talk about interaction of the touchpoints. [00:33:30] So right now, as I mentioned, a COA has gone in from the THRIVE team to the FDA to say, "Can we develop first generation intrinsic capacity?" They're also going to have an IND going in from UT San Antonio so we can begin that trial in about six months. And then finally the four teams with the second gerotherapeutics, IND enabling studies in approximately 18 months. So lots of touch points and so we want to find a place that we can put these sort of applications. Okay. Now I want to hand over to the three [00:34:00] people who are going to talk. We're going to have Brianna Stubbs from the THRIVE team who's going to talk about their touch points, followed by James Peyer, from Cambrian who is going to talk small molecule approaches for health span and finally George Kuchel, who's going to talk about repurposing approach using a potent HIV medicine to target fundamental mechanism of aging biology.

Susan C. Winckler:

Yep, go ahead.

Dr. Brianna Stubbs:

Okay. Okay. Hello. So you've already heard [00:34:30] from several of our speakers about what intrinsic capacity is. I'm going to give you an overview of how the THRIVE team is planning to develop intrinsic capacity scores, at home measurements for intrinsic capacity so we can start to roll this out at scale across the country and then also start to interact with the FDA starting this week when our COA goes in and is received.

So THRIVE is one team in the PROSPR consortium. Our collective efforts got underway in February, so we're just a few months in and we have five years, as Andrew just showed you, to get [00:35:00] this very, very ambitious program of work done. THRIVE is led by Mike Snyder out of Stanford, but it is really a multi-institutional effort. Mike Snyder leads our computational team along with David Furman at Buck. I lead our clinical team and we have participation from decentralized study experts at the California Institute of Stress and Resilience. And I'm particularly proud of the fact that we're also partnering with the YMCA to scale our recruitment and our intervention delivery across the US.

[00:35:30] There we go. Okay. Before I talk about our clinical plan, just wanted to center the conversation around our planned touchpoints with FDA. We've been designing this strategy in close collaboration with Andrew in the program office, close collaboration with other PROSPR consortium teams, but we would love your feedback. Dr. Newman is leading up one of our streams here, Dane Gobel, if you raise your hand. He's here in the audience. He's leading up our at-home test kit stream. So any feedback is welcome and we [00:36:00] want to start engaging with FDA and with the community early.

So we're developing two, let's call them assets for discussion with FDA. The first is our intrinsic capacity score suite. And so this has three different scores that will be submitted as clinical outcome assessments through the FDA drug development tool pathway. Firstly is, as you heard Kelly described earlier, are ready to go now clinic intrinsic capacity measurements. So this is using measurements that are already being used in clinical [00:36:30] trials. We think that's ready to go now. The second is the PROSPR intrinsic capacity score, which is going to be built by our computational team based on their large longitudinal data sets. And I'll say more about that shortly, but that's underway in development now. And then the third intrinsic capacity score will be our at-home test kit score and that will be again developed as we start to roll out our at-home test kit.

The at-home test kit itself is being reviewed under a separate pathway through the de novo classification [00:37:00] request pathway. The kit itself is still under development this year, but it's going to contain blood micro samples for targeted omic analysis, a wearable device that's going to collect continuous digital health data and then also a smartphone based web app where people will interact, complete patient reported outcomes, voice, video analysis, really next generation technologies that we hope will be sensitive enough to capture a whole range of function across the adult lifespan. And so data for all of these [00:37:30] submissions is going to come from THRIVE but also other PROSPR consortium teams and we're hopeful from elsewhere as the community starts to participate and use these technologies.

So to start off with, the first task for our collective team is building our PROSPR intrinsic capacity score. And I didn't know all that much about computational science until I started working with these teams, but this is a monumental task that they're trying to do in just one year. They're ingesting and harmonizing over 20 large international longitudinal data sets and they're pulling out data [00:38:00] that relates to all of the intrinsic capacity domains and looking at it for its power to predict these hard long-term health outcomes that really matter to FDA as well as also by their very nature telling us about

how people feel and function right now. So the ultimate deliverable is the PROSPR intrinsic capacity score that's going to be anchored to 20 year risk of disability, multimorbidity and mortality. We'll have sex specific scores within that as well as scores for each of the IC subdomains as well.

[00:38:30] And then once we have developed the first version of the score, as Andrew said, we'll continue to iterate, but the development of the score will allow us to move into the clinic. We start off relatively small with a pilot study, which is designed to evaluate the feasibility of use of our at-home kit and to look for its concordance with gold standard in clinic measurements. So a hundred participants will complete one at home measurement and one in clinic intrinsic capacity assessment. From there, we'll scale very, very quickly, as [00:39:00] a hallmark of APRA-H programs, into a decentralized study of 1200 participants, observational study where our goal is to look for a cross-sectional association between age and intrinsic capacity measured at home with this kit.

So it's important to point out, and it was on the other slide, but I'll say it now, that our participants in all of these studies are going to be between the ages of 35 and 75. So we're really looking across most of the adult lifespan. We're going to be recruiting people who are free of chronic disease and don't [00:39:30] have extreme NBMI. So we're already trying to look at the scores power to predict changes in health as people start to deviate away from where they should be on their adult health growth curve. We're going to be recruiting across the US. So as I mentioned, we have partnership with the YMCA. We'll be recruiting in the Bay Area, in San Diego, Minneapolis and Atlanta, really trying to cover the US and represent the whole US population.

From there, we scale again. We get even bigger. We're moving into a 1700 [00:40:00] person interventional study where people will participate for at least a year, up to 15 months measuring intrinsic capacity at home every other month. Again, the primary outcome of this study is that at home intrinsic capacity measurement with our at-home kit. We have three arms in our interventional group. Our active arm, they're going to receive the coached multimodal lifestyle intervention and they are going to be drawn from the participants we found in our observational study to have low intrinsic capacity and that's going to enrich [00:40:30] for participants who we think will benefit from receiving our lifestyle intervention. The lifestyle intervention itself will be based on that which has been used successfully in studies such as US Pointer, the Diabetes Prevention Program. We're not really trying to reinvent the wheel here. We're trying to take what's already been shown to be successful and implement it through community partners.

Our two control groups, we have a low intrinsic capacity control group, which is meant to match our active group and a high intrinsic capacity control group. And so the goal of [00:41:00] these two groups is to look for natural trajectories and intrinsic capacity across the year, whereas our active group, that's going to tell us is our at-home kit and is our PROSPR IC score sensitive enough to detect the changes that we expect should happen when people start to improve their lifestyle?

So those of you who run clinical trials are probably sitting there kind of having a heart attack because this is kind of a very ambitious series of studies for us to get done in a very short time. But I'm very, very optimistic that if we're successful or if we take small steps in the direction [00:41:30] of being successful, that the data that we generate here is going to inform the field, help academics, help pharmaceutical companies, biotechs to be thinking about how we run these next trials of gerotherapeutics. It's going to give us clinical outcome assessments and tools that we can all use to advance these endpoints at scale. And so thank you to APRA-H for taking this infrastructure bet, and I'm excited to be part of this program. Thank you.

Susan C. Winckler:

Thanks so much, Dr. Stubbs. Excellent overview and help us thinking [00:42:00] about advancements in this space that might be used by others. So our next case study from the ARPA-H side, we'll turn the podium to Dr. James Peyer, founder and CEO of Cambrian Bio. Go ahead.

Dr. James Peyer:

Okay. Wonderful. Thank you for having me speak and being here. This is a short presentation, right? We're just doing 10 minutes. So I thought it would be a good opportunity to kind of frame a little bit of why myself and Cambrian as a drug development player in this space thinks of [00:42:30] specifically what we're doing with PROSPR, with the XPRIZE as fundamentally important to this field.

And the way that I think about this is to start by asking the question, what is a gerotherapeutic from the perspective of the FDA? A gerotherapeutic is just a preventative medicine, but it is a preventative medicine for multiple different diseases. Now the FDA can already handle preventative medicines. This [00:43:00] is why we have preventative medicines today. And so when we think about the challenge, the market failure in preventative medicines, the market failure for preventative medicines is number one, it takes a really long time to run clinical trials to show prevention. And number two, because it takes a really long time, it's very hard to get for profit companies to do prevention as initial indications. I say that all to begin with because as a drug developer, that's how [00:43:30] I have to start facing this challenge of how do you develop gerotherapeutics.

So there are a lot of gerotherapeutics, 80 plus interventions that can extend healthy lifespan in mice. And the question is, how can we translate these discoveries to humans? I reached back and pulled this slide from seven years ago when I started Cambrian and this has been sort of the playbook that we've established as a company focusing on the biology of aging where you start with [00:44:00] mechanisms that have animal geroprotection and then every single drug that we take forward has to go through what we call a stepping stone indication, an acute disease that you test the molecule against before you would target its ultimate preventative case, what I like to call the highest and best use for a gerotherapeutic.

So this stepping stone indication could be, for example, the first company that I started way back 11 years [00:44:30] ago is called Aeovian Pharmaceuticals and Aeovian has a novel mTOR inhibitor. Their stepping stone indication is a rare disease called tuberous sclerosis that is caused by an over activation of mTOR Complex 1 and that would be kind of the proof point before moving to intrinsic capacity.

In order to do a trial in intrinsic capacity, you can do a long-term study with mortality or morbidity as an outcome. Again, FDA is equipped to handle those, but [00:45:00] certainly those studies are increased in their speed and the willingness of private actors to go after them if there's a biomarker involved.

And so one shortcut that we've been looking at that I won't talk much about here, but Cambrian's lead program is moving into phase two now, which is an AMPK and mitochondrial activator called ATX304, which uses what I call the metabolic shortcut [00:45:30] to preventative medicines because the FDA has established a bar in obesity that if you exceed 5% weight loss in a 52-week study, you can reach an NDA for weight loss.

And what is weight loss, right? Weight loss, obesity isn't a disease in its traditional sense, just like aging isn't a disease in its traditional sense, but it is a risk factor for multiple diseases. And so if a gerotherapeutic can hit obesity, you can be approved [00:46:00] immediately in this kind of preventative context and then expand from there to non-obese people. That's what I call the metabolic shortcut.

Most drugs don't have the opportunity for a metabolic shortcut. Most drugs for private actors to get in are going to need a biomarker to be developed and these biomarkers can fall into two categories that I separate into phenotypic and mechanistic. Phenotypic would be things like body weight, but also stuff like viral titer for HIV drug approvals and [00:46:30] intrinsic capacity would fall in that list. There are also mechanistic angles of going for biomarkers. And this is one that I think, especially as new categories of drugs are being developed, tend to be kind of embraced first by regulators.

Cholesterol is my favorite example here and we are going to be at least attempting to build the data sets for AMPK activation, mTOR inhibition and these other kind of, so let's [00:47:00] call it traditional mechanisms associated with geroprotection now that we have brand new tools to target them.

I'm going to focus on mTOR inhibition because this is the program that we're working with PROSPR on. Rapamycin, which we already heard about from a couple of groups, is this FDA approved mTOR inhibitor that has preclinically been demonstrated to deliver positive effects in almost every organ system in the body in mice. However, [00:47:30] what it's approved for in humans is as an immunosuppressive. It is a drug to be given along with kidney transplantation to keep a patient immunosuppressed. And that's because while mTOR Complex 1 is increased during aging and seems to have all these negative effects that come along with it, rapamycin and other approved mTOR inhibitors inhibit not only mTOR Complex 1, but also mTOR Complex 2. And by co-inhibiting those two complexes, [00:48:00] that's how you get the immunosuppression. So it's been an idealized notion for more than 10 years if you could make a compound that inhibited just mTOR Complex 1 but not two, you could have these pro longevity effects, these multi-organ benefits to intrinsic capacity without the negative effects on the immune system.

And jumping right into it, we generated this molecule. So what got us really excited after years of work, you can see on the left is [00:48:30] Novartis's rapamycin analog everolimus, which inhibits mTOR Complex 1 on the top as well as mTOR Complex 2 on the bottom. And we developed a compound called TOR-101, which is TOR-C1 selective at all doses. So it inhibits mTORC1 very strongly, but at no dose do you have any inhibition of mTOR Complex 2.

We've taken this molecule and showed that it can benefit cardiac health, cancer [00:49:00] prevention as well as cancer treatment, so both before cancer arrives and after it's already there, as well as immune decline, improving the responsive antibodies to vaccination. And importantly, it's not immunosuppressive at any dose. We've gone up 100 fold higher than when you start to see immunosuppression in rats and in primates with no signs of immunosuppression. So we've really nailed this novel [00:49:30] mechanistic angle.

And this allows us to take a pathway for our clinical development path thanks to PROSPR that will shave approximately five to 10 years off of the timeline that we would otherwise project to reach patients in a preventative kind of prophylactic sense versus my kind of baseline chart that I showed you earlier. So our stepping stone indication is still intact. [00:50:00] We go from animal geroprotection to a stepping stone improving vaccination in older adults, a little bit prevention-like, but in parallel because of the work that Dr. Stubbs just talked about, the development of this PROSPR IC score, we can move directly into a study for intrinsic capacity under the auspices of ARPA-H and that study allows us to go directly

for prevention in a way that could allow me as a drug developer [00:50:30] to do prevention in the short term. And that's my one point I wanted to get across, which is why this whole program and this whole conversation is so exciting. Thank you very much.

Susan C. Winckler:

Great. Thank you so much, Dr. Peyer. And we'll round out our use of slide decks today with Dr. George Kuchel, director of the UConn Center on Aging at the University of Connecticut. Take it away.

Dr. George Kuchel:

Hi. So we're running a bit late, so I'll be brief. [00:51:00] I'm here presenting on behalf of a wonderful multidisciplinary team. I want to give a shout-out first of all, our project is repurposing reverse transcriptase inhibitors to treat aging or RT age. I want to give a shout-out to Vera Gorbunova at University of Rochester, which is a prime site and John Sedivy at Brown, who've really done the seminal work showing that line one elements become incorporation is a hallmark of aging and accelerates aging and in fact drives [00:51:30] aging and therefore efforts to inhibit its incorporation represent a promising gerotherapeutic target.

Also, our colleagues at UConn, University of Texas Galveston, Alan Landay has many years experience working in the HIV aging field, testing these drugs in older adults, UT Houston, Nebraska and our commercial public industry partners at Transposon Therapeutics, who I'll talk about in a [00:52:00] few moments.

So basically the background, this is a PROSPR TA3 trial, which is really meant to go from mouse validation studies all the way to early human trials. In our case, actually not phase 1A, but actually phase 2 trials for reasons I'll mention in a minute. We're going to be testing ... So nucleotides reverse transcriptase inhibitors have been used for HIV for many, many years. And I talked about these line one elements, [00:52:30] which are the main retrotransposons in humans. There's a drug that was developed originally for HIV called TPN-101, censavudine, was developed in industry then was taken over by Brown and subsequently Transposon.

And the drug had been shown, was never taken to market for HIV for commercial reasons, but it was shown to be a much more potent inhibitor of line one reverse transcriptase than any other drug to date. [00:53:00] And so effectively we're talking about this being a second generation repurposed drug testing. The other advantage, other reason we can go so quickly is that there's considerable human safety and tolerability data already established and INDs have been obtained by retrotransposon for testing a drug for two neurogenerative diseases, progressive supranuclear palsy and ALS.

So this is the drug [00:53:30] here and basically the only thing to take home, the drug is on the right. On the bottom, you have four commonly used HIV drugs. The take home message that its ability to inhibit line one inhibitor activity is about at least 10 times more potent than generic HIV drugs. Its IC50 is 70 nanomolar. It also is highly 95% bioavailable, once a day dosing, low protein [00:54:00] binding, and excellent CNS penetration.

Now there's going to be the study, I'll show you the outline, it has two stages. Stage one is the mouse studies, which will be done at Rochester and Brown. Preclinical mouse studies testing the impact of

censavudine on intrinsic capacity in mice, two different doses tested in outbred mice, the same mice strains as used in the ITP program. The IC components as you can evaluate in mice will be tested. Also, general [00:54:30] health and molecular parameters, four time points studied between 15 and 24 a months and studies will be repeated at two independent sites.

Then stage two, there will be a no-go decision made in the second quarter of year two. And if we proceed, the human trials will be done at Yukon, Rochester and UT Galveston. Healthy women and men 60 to 65 years of age will be recruited. The drug will be randomized to 40 milligrams daily [00:55:00] or placebo over 48 weeks, 100 individuals in each arm. Effects will be tested then. By then we'll have hopefully the PROSPR IC will have been developed. We'll be able to tap into that. We're measuring sensory vitality, psychological, locomotion, cognitive domains and we'll be also able to implement some of the biomarkers of what comes from the PROSPR TA1 studies that you heard about earlier and the goal is to discern any potential effect to human health span.

And this is just [00:55:30] a general outline of ... The blue are the preclinical efficacy studies and IND enabling activities, manufacturer of the drug, and then testing in the last year and a half of the timeline. So in summary, it's an innovative approach to testing a second generation repurposed drug using multi-domain measures to measure impact on health span. We have the benefit of existing INDs for these indications. We can move quickly from mice to people. [00:56:00] There are potential pitfalls and challenges or timeline issues, human subject recruitment issues we can talk about later. Obviously clear communication both between teams and within teams is going to be absolutely essential. Thank you.

Susan C. Winckler:

Fabulous. That was such an intriguing review and immersion into different activity that's taking place. So let me invite [00:56:30] up to the stage, we not only get to move off from slides, but we get to sit down. So let's move a bit ... I hope to my colleagues that you found that fascinating and kind of what it is that we see that's moving here.

Regulatory Landscape: What Pathways Exist, Where They Break Down, and What Constructs Are Needed

Sandra Kweder, MD, Principal, Drug and Biological Sciences, Eliquent
G. Alexander Fleming, MD, President, Kitalys Institute

So let's talk about this panel. We're going to have a conversation about the regulatory landscape and to do this, we've turned to two former FDAers. It's one of the things [00:57:00] that I found after I left FDA that you then had an ability to speak more freely, although it doesn't matter. But it can be illustrative, right? Simply because ... You both matter. You know what I mean. But it can be illustrative just because you've sat in those chairs and thought about things and it can at least be constructive in thinking through these.

So we've [00:57:30] got two former regulators here to chat with us. I'm going to start, to my left this is Dr. Sandy Kweder. Now your experience at FDA, you were at the Center for Drug Evaluation Research in the Office of New Drugs and then I loved this quote in your bio. You said that you oversaw significant regulatory developments during periods of transformation in the landscape of science, policy and public health. And you didn't write that for this meeting. It existed already, but it sounds a bit [00:58:00] like what we are talking about today.

So imagine you are back at White Oak and a new drug application or even an IND request in this space came across your desk. What questions would you have?

Dr. Sandra Kweder:

Well, I would say ... Is this one?

Susan C. Winckler:

Yes. Yeah.

Dr. Sandra Kweder:

I would say that my first reaction would be, especially after sitting here this morning for the day, I'm on a packed 737. [00:58:30] They close the doors, we're taking off and someone just let loose a chicken.

Susan C. Winckler:

Again, that's a visual I did not expect but we'll run with it.

Dr. Sandra Kweder:

And all hell breaks loose. And what I mean by that is great uncertainty and the potential for chaos. A million thoughts racing at once. And then as we do, we say, "Okay, let's take a deep breath." And the first [00:59:00] thing that would come to my mind is, where is this going? Where is this company, this product, where are they trying to take this? And what I mean by that is what's the indication? And I was struck today by the fact that I only heard one person mention prevention and that was you. Everyone, yes, you did earlier this morning, but mostly people are talking about disease.

So what's the indication? How broad is it? [00:59:30] Who's this for? How will I write a label for this? What do we know about this drug? What's its mechanism of action? And how does that mechanism of action translate to where this company's trying to take this in an indication? What I heard very little about today, which would be one of my first questions as a regulator is, what are the risks? What's the safety profile? [01:00:00] And when I looked at all the slides in advance of this meeting, all I saw was well tolerated. That's not enough.

And what's the efficacy? What are they trying to claim and how do the endpoints that were studied support that claim and relate to it? And in particular, in what kind of population is this a narrow population [01:00:30] or a widely heterogeneous one, which I think most of the discussions today are focusing on is very heterogeneous population in people who bring a multitude of genetic variability and lifestyle variability with them to the clinical trial and how well has that been studied? And then of course, how does that benefit? How long do you need to take this stuff to achieve a benefit? And once you achieve a benefit, how [01:01:00] long do you need to continue to take it? And have the studies been designed in a way that can inform that and encompass general benefit risk? So that's after my deep breath.

Susan C. Winckler:

Yeah, that's all. If I hear it right, what I hear you describing is in whom do you want to use it? What do you intend to happen? What is it that delivers that happening? [01:01:30] And then from a safety perspective, I heard you say you want more than well tolerated. What does that mean?

Dr. Sandra Kweder:

And what are the off-target effects? What are the target effects that maybe aren't so great? Do you want a condition that both helps you respond to vaccines or that immunosuppresses? Which way does it go?

Susan C. Winckler:

Yeah. So a lot to think about.

Dr. Sandra Kweder:

A lot to think about.

Susan C. Winckler:

Okay. All right. [01:02:00] So now I'll turn to the other side. Dr. Fleming, you have experience at FDA too in the Center for Drug Evaluation Research and you have extensive experience in the private sector where you've been thinking about this very space. I'd like you to put both hats on, both what you've been learning since then and what you thought about in your FDA days and how do you think about the regulatory landscape?

Dr. G. Alexander Fleming:

[01:02:30] Well, first of all, great to be here. This is exciting. It's one of the first steps in the public process, which is long overdue and we're seeing all kinds of input that is being digested by FDA people who are here. That's a big step forward. Let me just say that the FDA is ready, willing and waiting for just what [01:03:00] Sandy was laying out. They want specific proposals and that involves the population, the drug, or the other intervention. And it could be a device or a biologic, or even a dietary supplement for that matter. But that's only part of what is needed here. And we can drill down a little more into just what [01:03:30] is needed to move the field.

But we can start by saying that FDA has been engaged from 2016, right near when you went with TAME. And then in 2019, Janet Woodcock, we featured in our conference and she said, "I think TAME or the endpoint looks perfectly good. What's wrong with reducing multiple chronic disease risk?" And [01:04:00] by the way, we don't prevent disease. We're never going to prevent a chronic disease. We reduce the risk of it and that's how we express a cardiovascular indication based on MACE. It's reduction of that risk. You don't eliminate it. It's just not going to happen in our generation.

And so FDA along the way has been very responsive. We had multiple people from review divisions, [01:04:30] Theresa Kehoe. We've had Jeff Siegel, Peter Stein and more recently, Rob Califf before he left. And what he said was, and he was speaking to the audience, he said, "You are the experts. Come and tell us what we should be thinking and what should be the endpoints that would move the needle." And

so this [01:05:00] is, coming back to our being together today, essentially responding to that invitation. And again, FDA is willing and able to respond to specific proposals, not grandiose proposals.

Susan C. Winckler:

Right. 737s with a chicken.

Dr. G. Alexander Fleming:

That's right. And what we need is a two pronged approach. One is groups like this, consortia [01:05:30] that get together to advocate for policy and for guidance. And the second prong is individual companies like BioAge, Cambrian and Stealth to come forward with specific proposals. And FDA can take them where they are. And let's be realistic, they're going to be stepping stone indications. Like James mentioned, it's a way to [01:06:00] address current unmet disease need but get to ultimately robust indications for products that actually can reduce the risk of multiple chronic diseases and disabilities.

Susan C. Winckler:

And so what I hear from both of you, two things, right? The agency likes to get ... Is intrigued right now. Intriguing can also [01:06:30] be challenging, but I hear some enthusiasm, right?

Dr. Sandra Kweder:

Absolutely. And I think this room is full of people who have a lot of knowledge to share, a lot of data to share and that's really exciting. FDA has a job to do and they need you to help them learn. And when you encounter skepticism on the part of FDA, that's okay. That's their job. That is their job [01:07:00] is to be skeptical. And quite honestly, whether I've been at FDA or I've been on the consulting side, which I am now, I've never seen a company that didn't think their product was beautiful.

Susan C. Winckler:

All our children are beautiful.

Dr. Sandra Kweder:

Yeah, exactly.

Susan C. Winckler:

It's understood.

Dr. Sandra Kweder:

No, I mean, that's just human nature, but it's a back and forth and that's what we want it to be. We want it to be a healthy discussion.

Susan C. Winckler:

Right. And that is something that I heard from you, Zan, that we should be thinking [01:07:30] about the agency that when you are a regulator, your job is to apply the regulatory structure and it's the companies that are bringing the, "Here's what my product does and here's what I'm pursuing." So that's part of the benefit of a shared learning like this is that we can talk about, all right, so what is emerging in this space? What are people studying? How are you studying it? And learn more about that.

Well, so what advice would you give product developers if [01:08:00] they're thinking about going to the FDA, I heard a couple of nuggets, but what else might you say to them? Zan, do you want to take that?

Dr. G. Alexander Fleming:

Well, I think Sandy spelled it out well in general, but it first comes with a discrete set of proposals that might be with a pre IND meeting or some other form of meeting that would get you started, and you come to some [01:08:30] kind of agreement for the next step. And as soon as you can, you get an understanding of what the end game is, what would be the phase three package that you need. And that doesn't include just efficacy, as Sandy said. It's demonstrated safety and it's actually having a product that you can manufacture reliably and a number of other things that never get mentioned in this kind of discussion, but it can definitely come back to bite you. So [01:09:00] this is all pretty plain vanilla in the development of therapeutics, but it does have extra challenges if you aspire to be a gerotherapeutic.

Susan C. Winckler:

How about you, Sandy, what would you add to that?

Dr. Sandra Kweder:

Yeah. I would add to that a few things. I think in this area that we're discussing, and I think it's more than one area, it's pretty broad, isn't it? And then there are some nice narrow lanes within it. I [01:09:30] think be very clear on where you want to go, and don't get yourself down too many rabbit holes. I have a lot of animal analogies.

Susan C. Winckler:

That's all right. We have had such a spectrum today, and I know it's just going to continue.

Dr. Sandra Kweder:

But no, I think it is. There's so much to think about, but pick a few things that are low hanging fruit to begin with and recognize that you will learn along the way. I [01:10:00] think one of the things for all of us, whether you're at FDA or you're in industry or you're in academia, is hold up the mirror and understand your biases. Be honest with yourself about them and force yourself to keep your mind open. And sometimes it's keeping your mind open to the excitement and sometimes it's keeping your mind open to the fact that maybe you didn't shine a light in all the dark corners where you need to. Like Zan mentioned, what's [01:10:30] your product? What is your product and how reliably can it be made? And also I think in this field, just like in any other therapeutic area, you've got to tend to some of the mundane.

I find that mundane. I'm not a chemist. The other is, what's your dose? What is your dose and how well have you tested a range of doses [01:11:00] that will get the effect you want without the off-target effects that you don't want? And FDA will press on that as they should, as they should. Don't assume that the dose that is used for one indication is likely to be equally wonderful in a different indication and the dose [01:11:30] may vary with the age of your population or the health of your population. And those are all things that matter because once you start talking about use beyond a small clinical trial, how are consumers or patients or prescribers to advise how best to use the drug? Those are kind of mundane things sometimes.

Susan C. Winckler:

Yeah. But important.

Dr. Sandra Kweder:

But they're really important for a product to have [01:12:00] a use and too often they're missed.

Susan C. Winckler:

And what you almost said, and I think Zan, you were talking about is that we haven't yet heard the phrase today, CMC or chemistry manufacturing and controls. That will matter at some point.

Dr. Sandra Kweder:

You're going to have to talk about it at some point.

Susan C. Winckler:

Yes. Okay. It matters.

Dr. Sandra Kweder:

It will. It will. Yeah.

Susan C. Winckler:

So then I want to ask a question. In some recent conversations I've been in, there's [01:12:30] conversation about how sometimes particularly in rare disease development, companies and patients get caught in pursuing precedent. So pursuing endpoints that others have pursued because that's the easier path, even if it's not going in the right direction. Is there though a flip side perhaps in this space where we could look at endpoints that are a precedent that might be used in this space so its [01:13:00] precedent could actually be helpful. Do you think there might be an opportunity there? Zan, I'll let you pick that one up.

Dr. G. Alexander Fleming:

Well, not just the opportunity. The necessity is that for now we have to focus on endpoints that have some kind of clinical relevance and value and so not biomarkers. We desperately need surrogates and part of this process, part of PROSPER can be to ultimately validate [01:13:30] specific tests that can be done at home or a cell phone in the clinic to manage disease risk, but that will come as a side benefit of PROSPER. To be clear, intrinsic capacity is not about surrogates. These are face valid, clinical endpoints. If you can walk further in a six-minute mile test, [01:14:00] that's a benefit. Now there's some details as to what is clinically meaningful and that's important. But the point is we for now, and Jeff Siegel will talk about this more in contrasting biomarker qualification with clinical outcome assessment, we've got to rely on what are things that people value, fetal function or survival.

And by the way, survival [01:14:30] is an endpoint that is in a way approachable, but I put it in the category and IC could be considered a survival endpoint in the sense that it ultimately can predict survival, but we're not going to be able to measure endpoints that involve some kind of formal lifespan evaluation.

Susan C. Winckler:

Sticking more-

Dr. Sandra Kweder:

Well, I'm not [01:15:00] sure I agree with that.

Susan C. Winckler:

Oh, all right.

Dr. Sandra Kweder:

I think that there are ways to test things over time. I thought we heard some really interesting presentation this morning on looking at short term survival and looking at longevity. I think there's a lot more work to be done in that field. The challenge is that over time life intervenes or rather things start to manifest. But nonetheless, I think it's quite interesting. [01:15:30] A couple of the other things that I think will be important as we think about this really exciting field going forward is when do you look to intervene? Some of the work that's been going on is focusing specifically on older age adults, but maybe in some cases the real benefits occur if you intervene earlier. And then also, and I mentioned this before, but I don't think it can be overemphasized is [01:16:00] how when we think about therapies in this space, how long do you need to take these products?

And I will say, I think in the whole world of drug development, whether it's regulators or developers, I don't think we've done a particularly good job at looking at chronic [01:16:30] interventions. We really have not. And I think there are in some therapeutic areas now, we're starting to see questions being raised about duration of therapies. I think in the psychiatry field it's really prevalent, but that's not the only one. So we need to be looking at that, particularly if we are looking at lifelong therapies regardless of when they begin.

Susan C. Winckler:

Yeah. All right, Zan.

Dr. Sandra Kweder:

You won't have to do [01:17:00] that. You won't have to look lifelong before for the first out the gate.

Susan C. Winckler:

Yes, yes. Yes. Final word from you and then we're going to turn to those developers.

Dr. G. Alexander Fleming:

Well, just to say, it is a balance between the health of the population and the event rate. We find that we have to do 16,000 people, obese people, who have high cardiovascular risk to be able to detect a benefit within five years. So it's that much [01:17:30] harder in a predisease population and that ultimately is what we're seeking to help. We're trying to make the would be, or the patient, not become a patient. We want to avoid becoming a patient.

Dr. Sandra Kweder:

Yeah. Exactly.

Industry Perspectives: What Product Sponsors Need from FDA to Bring Gerotherapeutics to Market

Joshua Diamond, MD, MSCE, Medical Director Clinical Development, Respiratory Early Pipeline Unit, GSK
David J. Glass, MD, Vice President, Research, Aging/Age-Related Disorders, Regeneron
Jill Lee, JD, Senior Director, Regulatory Policy & Intelligence, Novo Nordisk
Evan Mills, MA, VP Global Business Development, Olink, part of Thermo Fisher Scientific

Susan C. Winckler:

All right. Thank you so much to our regulators. They're going to leave their microphones and we're going to bring up four folks [01:18:00] who will help us turn from the former regulatory perspective to the industry perspective. And so as my four colleagues are coming on up to the stage, you can sit on your name card or drop it beneath your seat, whatever it is that you'd like to do. So we want to continue this exploration. I hope you're ready to talk about what it is that might happen here. And in particular, [01:18:30] we want to think about a product sponsor perspective, what perplexes you, excites you, interests you, all of those dynamics on the stage. Now I'll make one note for those of you who might have stalked the agenda and thought that you would see Cindy Lawley on the stage, this is Evan Mills. Cindy was unable to... Yeah, indeed, was unable to join us due to illness.

So thank you for stepping in to pick this up. But I'm going to start the conversation. Let's go down to my far right. [01:19:00] So Jill Lee is at Nova Nordisk where she leads US regulatory policy development and intelligence across a broad portfolio of areas. So Senior Director Lee, let's set the stage. Imagine you are at a company retreat and the primary agenda item is moving into the gerotherapeutic space. What

questions come to mind and what would you want to make sure the company is considering in that strategic move?

Jille Lee:

Yeah. I mean, I would have a lot of questions, [01:19:30] but first I'd be super excited because who doesn't want to live longer and healthier lives? So obviously a lot of excitement there. And then obviously the potential for moving into prevention or reducing the risk of disease. We're making a lot of progress when we're talking about that versus treating disease. So lots of questions. My first question, I guess, is what is our approach? We heard a lot this morning around, are we developing drugs to treat aging or aging related [01:20:00] conditions? So that would be the one, and obviously the goal is to get to an aging measure, but that's going to take some time. So obviously from our perspective, we'd want to take a much more practical, incremental approach to how we would tackle this. So obviously the aging related conditions would make sense. And then I think my second question is where's the science?

I mean, it's a lot of interesting science and I learned a lot this morning, but there's still a lot of discussions [01:20:30] around intrinsic capacity, functional endpoints, mortality, and it's clear that the science is still developing and evolving, so obviously trying to stay close to that. And then I think my next question is, what is the regulatory pathway to get us there? And there are obviously a lot of, there are existing pathways around biomarkers, COAs, but it takes time. And we heard a lot about the amount of time it takes too, especially in the area of prevention and delaying the onset of disease. [01:21:00] We were talking at lunch about bone mineral density and osteoporosis and that's really exciting news, but it took us 10 years to get there and that's talking about one domain. So how do we get there across multiple domains? That's going to be the tricky part.

And then I think also in the back of my mind, I'm thinking, this is a really noisy space potentially when you're talking about health span and longevity. When we do get to a place where we can develop a science-backed [01:21:30] drug that can treat this area, will patients, consumers understand kind of these types of drugs versus other things that might be happening kind of in the wellness space? But those would be a few things kind of pop into mind.

Susan C. Winckler:

Okay. Yeah. So then just so I understand, when you're saying noisy space, right, there's a lot of things already that we could all take to transform us that perhaps are not working, which gets us back to the earlier question today of how do we [01:22:00] know that these interventions might work. Very helpful. All right, let me turn to this side. Dr. Diamond, you are a relatively new entrant to FDA regulated industry and are now medical director in clinical development within the respiratory early pipeline unit at GSK. But let's apply your experience at Penn and at GSK and how are you thinking about that company retreat? And you may not have been to a company retreat yet, but that's okay, you can build it into the hypothetical.

Dr. Joshua Diamond:

I have not. I've only been at [01:22:30] GSK for a year. I did spend 20 years though in academics. I can think of at least four different questions that come up. So one is, how can we differentiate physiologic, normal aging from pathologic abnormal aging? Because I think the goal here is to try to impact

pathologic aging, but not necessarily physiologic aging. And the second is what is the population that we're actually interested in in evaluating? Do we need to enrich a patient population [01:23:00] for early disease, for disease risks that is a population that's at higher risk of developing disease? And then the last part is then what's the outcome of interest? Is it the development of disease? Is it a change in functional state? There needs to be some uniformity or acceptance of what that outcome measure might be. I heard a lot today about how to define what some of these outcomes might be.

I know in my time as an academic, I spent a lot of [01:23:30] time thinking about frailty. I actually was a lung transplant physician and so I spent a lot of time thinking about frailty both in people waiting for transplant and people who received organ transplants and was part of an attempt to put together a consensus statement about frailty within the transplant space, small group of people. It's a very small field in the US, 3000 patients a year, so very small. And even amongst us, we could not come to a consensus about what the correct measure or the best measure of [01:24:00] frailty might be. And then at GSK, I'm involved a lot in early discovery, so interacting a lot with my translational biology colleagues and my biology colleagues.

And to think about this from a mechanistic perspective, a lot of the things we heard about today impact immune function with the goal of trying to increase or augment immune function as people age. And the downside to that is immune related diseases like connective tissue disease, autoimmune disease, and then things like trying [01:24:30] to alter senescent states. There's a physiologic rationale for senescence and what's the off-target side effect of sort of altering senescence. So those are the things that I would be thinking about.

Susan C. Winckler:

So you're bringing the C-suite deep into that scientific exercise, which is helpful. They've got to think about it. Dr. Glass, I know you're going to be stunned by the question I'm going to ask you. So bring us your perspective from being vice president research at Regeneron Pharmaceuticals where you oversee a group that's specifically [01:25:00] exploring aging and age related disorders. You're at your own company retreat. Is your approach consistent with your colleagues, panelists, somewhat different, different things come to mind?

Dr. David Glass:

Well, surprisingly, we start exactly where Sandy said, which is first of all, what's the indication? And the way we view aging or the way I view aging is it sort of just gives you a different lens to think of a novel potential therapeutic. So for example, I'm a muscle biologist, [01:25:30] so I'm interested in the loss of muscle with old age or sarcopenia, which is now an actual disease as it has an OCD code. And the non-aging approach would be just like, what can improve muscle? And the aging approach is what are the particular mechanisms that are perturbed by age that makes sarcopenia so likely and makes frailty so likely?

That's the aging approach and that just gives you a different lens into that. But as you mentioned, you then have to say, [01:26:00] okay, so if sarcopenia is what we want to treat and we now have an aging mechanism into that, then we need to understand safety. We need to understand how we're going to use this potential medicine. So I mean, it's published as no secret. I've studied antimyostatin and anti-active mechanisms active in signaling goes up with age. So countering it is an age-related mechanism

and it gives you more muscle. [01:26:30] Now one thing that's frustrated me greatly over 25 years is people seem to be skeptical, including regulators, of whether or not more muscle means more benefit and there's requirements to show like how do you help people. But my pushback has always been everyone debates if more muscle is beneficial, no one debates, no one debates less muscle makes you weak.

No one debates that. And so if you have [01:27:00] a medicine that simply stops people from losing muscle mass, because that's physics, that if you have less sarcomeres, you're weaker. I would think that would be just as approvable as now we've saying for bone that just simple bone density after we've studied breaks for 20 years, that should be enough. So this is the kind of pushback or feedback I would give to the regulators. I mean, some things to me are common sense. Now maybe Sandy, this is what Sandy would say, because if [01:27:30] you're in the space, you're just very optimistic. But I think that's an example of the back and forth in terms of maybe making it a bit easier to get to regulatory approval.

Susan C. Winckler:

Which might be a series of conversations saying, and so here's what we see. And in fact, it doesn't yield a detriment because there may be, I imagine it might be safety questions or something, but to have that conversation and pursue it. Okay. I'm going to turn to our final [01:28:00] panelists and you actually, I would say in your role at Olink, which is part of Thermo Fisher, you lead business development and scientific strategy and I think of OLink as being a bit more in the gerotherapeutic enabling space. So why don't you give us a brief overview of where you sit in the ecosystem and then how you would address this company retreat question?

Evan Mills:

Yeah. Thanks so much for the opportunity to be here and Cindy gives her regards. She wishes she could be here, but [01:28:30] I was unable to speak clearly with a throat situation. So we are an enabler and the way I see our role in this really exciting space is to be a biological information layer that has been enabled by relatively substantial improvements in proteomic technologies over the last decade. So for 12 years, I've worked for proteomic companies that do not use mass spectrometry and we can all sit in this room [01:29:00] and say proteomics is a far better tool than genomics to look at aging or most disease processes, I'm not saying aging is a disease process, but most things that have a longitudinal component where one wants to measure how one reacts over time.

So actually from every company that's sitting here and 11 others, the UK Biobank project was something that we spearheaded from a technology perspective, but the pharma industry said, you know what? If we measure enough humans [01:29:30] and measure enough proteins in those humans and associate them with robust clinical records, we can get insights into disease, into biomarkers, into mechanism, and that has spurred this flood of activity around organ aging clocks and biological clocks.

And we heard earlier that while those might be cool, where are they really going to take us as a community? So the questions I'd be asking, and we literally just had one of these strategy meetings, so we asked these very questions [01:30:00] about aging is, what role do we want to play as a tool provider? Do we want to go into the worried well market of clocks and things that are very cool but maybe won't withhold the stringent... They just won't have the scientific stringency to pass anything towards a real diagnostic or a tool to help a therapy to market.

Or do we want to partner with our customers, partner with regulators [01:30:30] and understand, all right, what do we need to do for proteins to actually have the value that we all believe they should in terms of being a very sensitive, very specific way to understand aging response to therapeutics? So that's really, I think the core question for a tool provider is, where do we want to go and how seriously do we want this discipline to be taken as not just a biological entertainment, but more of a biological [01:31:00] tool to impact patients in the, hopefully, short term.

Susan C. Winckler:

Yeah. I didn't hear either of our former regulators talk about the cool factor, that that was anything that they wanted to see, but I can see that's part of the space here is there's the part of the space where there's a rigorous approach in saying, "What do we want to measure and how do we influence that?" And then the other part of the space that's, at best, less [01:31:30] rigorous and perhaps cool. Okay. Let's turn this into more of a conversation now that your C-suite is all set, which sure, that happens, right? So let's think about, as I listened to the conversation this morning, there was discussion we were talking about level of evidence requirements, multi-domain components, quantification. None of that is particularly unique to gerotherapeutics. So [01:32:00] are there lessons that we can apply from other therapeutic areas that help us think through that? Dr. Glass, do you want to pick that up first?

Dr. David Glass:

Sure. I mean, I think the thing that's in common is having a robust set of biomarkers that correlate with success or correlate with something that the patient cares is about. So the thing about all these epigenetic clocks is that they're not related to anything except for epigenetic [01:32:30] clocks. And in other words, what you would want from a biomarker is something that not just scores aging, but if you perturb age-related disease in a meaningful fashion, the biomarker would change. And so that linkage has to be very strict. And for me, I mean, it's very daunting to think about that for aging writ large, but again, for muscle biology [01:33:00] for sarcopenia, you can say, I've counter-regulated, for example, active in signaling, which I know goes up with age, and I can correlate that to muscle getting bigger.

Do you see what I mean?

Susan C. Winckler:

Yeah.

Dr. David Glass:

So that's a way that a disease process is directly correlated and that just shows you your aging mechanism might actually be causative or have a potential causative role in the actual disease, which is then you're on the best of both worlds. You have a biomarker of aging, which is demonstrably [01:33:30] linked to a phenotype, which you can perturb by counter-regulating that aging related mechanism. I think that's the best case and it's the cleanest case and that's a pretty rigorous approach because you're not just saying, "Oh, I'm perturbing aging." You're directly saying, "I have to link that to modifying a disease process in a way that's clear." And of course, blocking muscle loss with age, which is [01:34:00] important is just one example of that.

Susan C. Winckler:

And really helpful and in particular the idea that we're perturbing aging is I think just a great phrase to think about and how we disrupt that. Jill, any thoughts from your side about what lessons can we learn from other spaces?

Jill Lee:

Yeah. I mean, obviously from our company's perspective, we're thinking a lot about chronic disease and we have a long history in diabetes and I [01:34:30] couldn't help but think about the work we've been trying to do around pre-diabetes and kind of delaying the onset of type two diabetes. And I think there's a lot of connections there. Obviously, again, we're trying to reduce the risk of type two diabetes, the amount of data, how do you kind of establish that clinically meaningful endpoint? Prediabetes is one of those areas where it's clinically recognized, but there's still not yet kind of a regulatory definition for that. And so it's establishing or [01:35:00] generating the data within a reasonable period of time that can show that there's clinically meaningful outcomes associated with the preventing or the delaying the onset of disease. So it's one of those things where I do see some connection.

Susan C. Winckler:

I was even thinking about that, the slide, Brianna, where you talked about the work that you're doing with the Y and the kind of interventions there. It actually reminded me of the diabetes prevention program, which has a lot of those [01:35:30] kind of similar important lifestyle interventions that then have been recognized at least by payers and clinicians as saying, "Yes, this intervention makes a difference." Yeah.

Jill Lee:

Yeah. And then obviously there's been a lot of discussions around obesity and the GLP-1s and it's well recognized now that obesity is connected to 200 other comorbidities and there's a lot of work that we're doing kind of going indication by indication to kind of prove the benefits that we're seeing across multi-organ [01:36:00] connections in this cardiometabolic space. But the question is, can we do these trials more efficiently? We don't want to have to go outcome study by outcome study. So is there a way that we can move forward with more innovative trial designs to get there a little bit quicker?

Susan C. Winckler:

Which might help with tracking that perturbing of the aging process. Evan, any thoughts on this one of what we might be able to learn from other therapeutic areas?

Evan Mills:

Yeah, absolutely. I mean, when I think through the lens [01:36:30] of a tool provider, it's really how do you translate the research discoveries into something that's clinically actionable? When the genomics revolution took place, the thought of having polygenic risk scores or multi-gene panels with clinical utility was probably very farfetched and a bit hard for people to comprehend. I mean, traditional biomarkers, you're measuring a single thing that is very well validated and folks have the confidence to

use that clinically, polygenic risk scores, multi-gene panels, finding some traction. I think with proteins [01:37:00] and aging, it's going to have to be a very broad view of the biology since there's so many systems impacted that there's some confidence that there's a framework to go beyond just single biomarkers and single points of measurement that are going to be important. I mean, in terms of the surrogate piece, this morning I got a little nervous about the bars that would need to be crossed for surrogate endpoints to really gain traction, but it's happened in other areas.

I mean, obviously in cardiovascular risk, this is super common and it's just a matter [01:37:30] of the weight of evidence. I think the more we have these kinds of debates around, well, or conversations around the evidence needed. The debate hasn't started yet. I assume that may be later. This is what's needed really because I think we sit as a research tool provider primarily the weight of evidence is just so strong and so many people want to take action. It's just a matter of not having a very productive conversation with the folks [01:38:00] to make it happen. And that's what I think we're doing today, which is great.

Susan C. Winckler:

So then Dr. Diamond, you actually started to answer this question when you talked about your experience in the lung transplant community and looking at the different components and looking at frailty there. What else would you want to highlight as something that we could say, oh yes, it's been done there before or there are lessons we can learn and think about applying in the gerotherapeutic space.

Dr. Joshua Diamond:

I think a lot of it comes back to something that was brought up this morning, which is the [01:38:30] combination of therapies. It's not going to be one pill or one injection. It's going to be some combination of interventions, and it's hard to separate out the medication from the lifestyle changes that are going to be required to sort of meaningfully impact some of these endpoints as well. So within the lung transplant space, we spend a lot of time focusing on physical function. We use six-minute walk distance as a metric for success [01:39:00] for some of the things that we're doing. But we've tried things like app-based measures to improve physical function, ways of identifying changes earlier and earlier on in the disease process. This sort of gets back to the what are we trying to prevent? So can we identify problems before they sort of would have otherwise manifested, like digital tools that have the potential to be able to identify issues earlier and earlier?

Can some of those digital tools actually be utilized as an [01:39:30] outcome measure rather than just a diagnostic measure? For some real world experience? Again, I mentioned six minute walk distance. Six minute walk distance is a single point in time. I go to the gym, my leg is sore. I go for a six-minute walk test. The next day, my walk distance is going to be shorter, but I'm walking around my house or I'm going up and down my stairs. That's much more meaningful from a real world life experience at the level of a patient than walking up and down a 50-meter hallway for six minutes. Or [01:40:00] I can walk up and down that hallway, great. But then I go home and I have three flights of stairs to get up and I can't walk up those three flights of stairs because walking upstairs is quite different than walking on flat ground. But from a clinical perspective, these are things that we see in the clinic and patients all the time.

And so then how can we actualize that for a trial so that we're actually making meaningful changes for patients as opposed to sort of moving an endpoint for the sake of it being an endpoint.

Dr. David Glass:

And from that point, [01:40:30] everyone kept talking about six minute walk tests say, we don't lose endurance when we get older. We lose power. And so it's not the six-minute walk. It's going up the stairs. It's your fast fibers that you lose. It's not your slow fibers. So that's important.

Susan C. Winckler:

Yeah. Which I wa s quite heartened today that we heard a lot about, are we talking with patients? Do we understand what it is that the potential users of this would [01:41:00] want so that we're making sure that we aren't developing interventions that might have academically interesting endpoints that are regulatorily relevant that no one wants. I don't think that's what anyone is aspiring to. Well, part of what we've talked about during the day and Evan, you raised it, is that sometimes there's opportunities for industry to be collaborative. And so [01:41:30] I guess I want to put to each of you, are there areas where we should be thinking about collaboration in this space and what might be easier to accomplish collectively and then you would each be going to the agency with your individual component. So you get that one first, Evan.

Evan Mills:

Thank you for the opportunities. So I'm going to think back to the UK Biobank program where, as an American, I'm very excited that the UK government had the foresight [01:42:00] to build this huge biobank and now companies are measuring 600,000 humans across multiple different omic modalities, including proteomics, which is great. And that's a treasure trove of insights for drug development, causal biology inference, drug targets, biomarkers, et cetera, et cetera.

But the UK government actually stepped up and contributed quite a bit of money towards the multiomic analysis. And in America, I haven't seen that happen yet. I'm talking to all of us, we're talking to MVP, we're talking to a lot of these big cohorts, and it just feels [01:42:30] like we're a little behind there. And that's one thing. So that's the basis of knowledge that I think we can all build, to get at the molecular underpinnings of aging in multiple disease states. But then there's the longitudinal monitoring. And what came up a few times earlier that I keep thinking of is we can build the most beautiful biomarker, but if it's not responsive to change or interventions or real world, where's the utility?

So that's a partnership opportunity. I mean, right now, we're a company. We work with the pharma business and [01:43:00] well-funded academics and we do a handful of cool studies, but to do something with power, I think government could get involved more proactively to really get at a well-powered approvable set of biomarkers that could have real value for the field. So that would be my plea is I just think the data are going to become more and more impressive, but we can't just rely on pharma to spend for all of it. I think governments [01:43:30] should benefit and get involved in the creation of these data sets.

Susan C. Winckler:

Yeah. And maybe it's a possible collaboration following up from the ARPA-H work, things that are happening at NIH, but with a clear vision of where things are moving. Dr. Glass, you've worked in this space a lot. Where would you like to see more collaboration?

Dr. David Glass:

Well, just thinking of the four people on this stage, if there was an O-link based proteomic [01:44:00] signature that we got from the UK biobank and said, "Here's 15 proteins or so that are highly correlated as you get older going up or going down." And then each of these companies are testing different age-related diseases, it would be great to get together and say, "In each of these different conditions that we're all testing, how does this ..." In other words, to validate some kind of signature, or unvalidate [01:44:30] it and then try to or improve it or improve it. I mean, that's where you'd want all these different companies to ... Because we're not going to do what GSK does or what Novo does. No, hopefully they're not going to do what we do. But there are also, of course, there is overlap, but there's a lot of power, especially something like this, like validating a biomarker or validating and saying, "Okay, this is truly aging predictive." I mean, that's something that I think everyone wouldn't really [01:45:00] argue about getting together to do it. I think it'd be very valuable to everybody.

Susan C. Winckler:

And it strikes me as just such a natural outgrowth from the work that's being done to provide some infrastructure in this ecosystem that then you could all use. Dr. Diamond, where would you like to see some collaboration?

Dr. Joshua Diamond:

I agree with what you just said, specifically related to trying to come up with some precision for a surrogate outcome that we can agree on, [01:45:30] and an endpoint that we can all agree on, because I think it's hard to do trials to evaluate efficacy if we're all testing a different surrogate and a different final sort of registrational outcome. I think if we can come to some consensus or at least level of agreement about what is clinically meaningful, what is clinically actionable and then a surrogate that relates to those things and all be looking at the same thing, we can then at least be doing comparative studies that can sort of come to some sort of uniformity,

Susan C. Winckler:

[01:46:00] Which I would think would help in other conversations at the regulator, if it's like, "Oh no, this is what we've seen." It might have been in a different unit, but that there starts to be some familiarity with the concepts, if there's a broader understanding.

Dr. Joshua Diamond:

We've done that in other disease states, right? Pulmonary hypertension, everybody knows we want to change six minute walk distance, as poor an outcome as it might be, but that's the outcome that we all have agreed upon. And the regulators have agreed upon, [01:46:30] so that we all know what we're testing and we all know what the thresholds we need to meet in order for that to be meaningful to a patient.

Susan C. Winckler:

Yeah. I just have to say, having had a conversation in the rare disease space, where they eschewed the six-minute walk test, it's just delightful to have ... When it works, it can be great, but it's a measure you're looking for. Jill, what would you add here as we think about collaboration?

Jill Lee:

Yeah, I fully agree. There's no way one sponsor is going to get there, and especially with the amount of data [01:47:00] that would need to be generated. And obviously, in order to make sure that we're all kind of moving in the same space, fully agree that there has to be some sort of agreement so that we're generating data that can also kind of support the same in the same direction. And that means there has to be some sort of agreed, harmonized way that we're collecting the data, measuring the data, kind of all shooting for the same, or agreeing on certain endpoints or biomarkers. Again, I fully agree with your [01:47:30] point on the biomarkers as well. We have to see that biomarker change across different mechanisms and show that there's clinically meaningful endpoints across certain thresholds. So that's all important to do as a scientific community so that we're all kind of generating evidence towards that direction. So fully agree.

Susan C. Winckler:

And it strikes me then that that collaboration helps us get to a point where you're measuring something that helps break through [01:48:00] the noise, and isn't just cool. Yes, make sure that we do that.

All right, let's close out with, and you can actually each take a little bit of time for this, but let's pivot to a regulatory lens. And if there were one regulatory question that you could have answered in this space, what would it be?

Dr. Diamond, do you want to pick that up first? You can toss it to somebody else if [01:48:30] you want, but that's all right.

Dr. Joshua Diamond:

Well, one thing that was brought up by our regulatory colleagues just before was dose selection, right? So I think this is a big challenge when we're talking about an outcome that might be years down the line. So how does one figure out a dose effect relationship for something that's so hard to measure within the timeframe of what we typically think of as a [01:49:00] trial that can be designed with a reasonable number of patients at a reasonable cost is figuring out those dose levels, which means that we have to figure out some other effect outcome that we can utilize because it's not going to be a mortality that's going to be sort of the dose effect. So I think some guidance at the level of the regulator about how to pick out the dose when aging is the outcome that we're thinking about.

Susan C. Winckler:

Okay. Evan, what do you [01:49:30] think about in that space if there was a regulator and recognizing ... Like we're not going to put any of these questions to the regulators this afternoon, but rather thinking about what might that be?

Evan Mills:

So I was having a conversation with one of David's colleagues, and I've had this conversation with a lot of scientists. The big, big question I think in our space and ours being tools that measure lots of things at once is, will the FDA ever move towards approving [01:50:00] algorithmic AI-enabled data points versus a reductionist view, which is the current standard of, "Okay, we're going to measure one to three things or one or two things," right?

The utility being for something like aging where one would imagine you want to measure and capture a lot of human biology, and with many other diseases, you want to capture a lot of human biology. I think we're short-changing our opportunity to build sensitive tools if we're just reducing everything down to [01:50:30] maybe one, two or three things. But today it's impossible to get any diagnostic or a test approved that measures 5,000 things and can spit out algorithms for 100 different conditions. I feel like in the future, that might make sense, but how do we get there? So that's my question, is as AI evolves, as measurement technologies evolve, do we see a path to approve different kinds of data if it's robustly correlated with clinical [01:51:00] outcomes and all the things one would need to do? Because it's just so much more efficient. It'd be so much more efficient to run one test and get a lot of different outputs than having to build 10. That would be my question.

Susan C. Winckler:

Yeah. Which seems like a space where there would need to be quite a lot of shared learning. I mean, absolutely I am aware that one thing that tends to strike at least, I was going to say fear, I mean aversion into regulators is [01:51:30] what are often called black boxes. So like not knowing what's happening, and I don't think you want that either, right?

Evan Mills:

No, the onus would be on the provider to provide as much validation evidence as possible, but I still think both can exist at the same time. I don't think it has to be a black box.

Susan C. Winckler:

And certainly, it's a piece we've certainly seen a lot of forward leaning at the agency, and thinking about where AI might be appropriate and also being like, "Yeah, and maybe not in that space yet." But this [01:52:00] seemed like a space perhaps for a collective exploration. Jill, do you have a regulatory question that might be helpful to explore?

Jill Lee:

Yeah. I mean, I think for me it's, are you open to continuing the dialogue? Because I do think the regulatory approach has to move with the science and as the data is being generated. So I'm kind of heartened by the fact that there's a lot of interest and openness to kind of going and exploring this [01:52:30] pathway or kind of moving in this direction. So for me, it's ensuring that there's kind of open lines of communication to kind of continue the discussions and get the FDA or regulators thoughts around the ideas that are already being put forward, like what is the thinking around intrinsic capacity?

What are the pros and cons of it? What about the other domains? And so kind of moving together with regulators as we continue to develop the science [01:53:00] and as we continue to learn more.

Susan C. Winckler:

And then it's probably also a question that's not just happening in the United States. I mean, our foundation is quite US-centric because we are for the FDA, but imagine there's global regulatory conversations where they have similar exploration of how to move this forward. But yeah, the shared learning environment here I think shows some of that. Yes, there's interest in pursuing it. All right, Dr. Glass, we'll give you the final [01:53:30] word on a regulatory question that you want answered.

Dr. David Glass:

So I have about 25 years of PTSD over these very short term, like six minute walk. As you were saying, these are motivation based. We all go to the gym on different days, and I can tell you my six-minute walk changes. And the first time I ever did a grip strength, the dude who was testing me said, "You have the strength of an 85-year-old," and that's-

Susan C. Winckler:

And were you like, "That is [01:54:00] in no way motivating."?

Dr. David Glass:

And that's made me go really much ... So we have the six-minute walk, and we have stair climb, and this is where we are. And this has killed more muscle drugs than I can tell you because I can tell you about trials we've done where in one site, we showed force and we showed benefit, and then you go all over the world where different stairs all over, and the error bars all of a sudden get to be like this. So in terms of talking about AI and now it's 2026, [01:54:30] can we evolve to looking at people over two months or three months, and aggregating data, and seeing what they do? Because the other thing is like when you're older and you have a drug that makes people potentially stronger and maintains their muscle, it takes time to build confidence, because you have to figure out what you can do that you couldn't do.

Because the thing that scares old people more than anything is if they've had a fall or they've suffered weakness, and now all of a sudden you think you're helping them. So [01:55:00] for me, either accept that preventing muscle loss is by itself approvable or if you insist you have to show a benefit. We need to do better in terms of showing a benefit. And I think with these more modern tools we can. And then if you extrapolate that to aging with large, it's the same story for all of these things, aggregated measures, putting different criteria together for different phenotypes, [01:55:30] this is I think where the future is. So I think that is an evolving conversation with the regulators.

Susan C. Winckler:

Yeah. I mean, I was so heartened by the at home kind of clinical test that might monitor the activity in the home because that's really ... Improving grip strength in front of the grip strength tester is one thing, but being able to open a jar or use that railing on the way up the stairs is really where we want to make [01:56:00] a difference.

Dr. David Glass:

Or keep walking up the stairs. I was just trying to sell my condo that has two flights, and all these older people come and say, "I don't want to go up the stairs." And I'm like, "You're going to save your life by going up the stairs."

Susan C. Winckler:

Yes, indeed, right? You're like, "No, let me show you the data that shows actually living there, you will live longer."

Dr. David Glass:

Buy my condo.

Susan C. Winckler:

We just have to collaborate on the writeup for your condo, and how we deliver that. With that, [01:56:30] I want to thank each of you for providing some illumination as we think about the sponsor perspective. So let's thank this group. And we're going to do a quick change.

Next Steps to Designing Workable Regulatory Constructs for Gerotherapeutics

Andrew Brack, PhD, Program Manager, PROactive Health Office, ARPA-H
G. Alexander Fleming, MD, President, Kitalys Institute
Jamie Justice, PhD, Executive Director, XPRIZE Healthspan, XPRIZE Foundation
Jill Lee, JD, Senior Director, Regulatory Policy & Intelligence, Novo Nordisk
Justin Penzenstadler, PharmD, Acting Associate Director, Office of Cardiology, Hematology, Endocrinology, and Nephrology, Office of New Drugs, CDER, FDA
Jeffrey Siegel, MD, Office Director, Office of Drug Evaluation Sciences, Office of New Drugs, CDER, FDA
Lisa Yanoff, MD, Deputy Director, Office of Cardiology, Hematology, Endocrinology, and Nephrology, Office of New Drugs, CDER, FDA

Susan C. Winckler:

Jill, you actually get to stay in the exact same seat. Everything is going to move around you, including me. I'll put the right microphone up because there's not room for me on the stage for the final panel, [01:57:00] but we want to pivot here, and thank you all for coming right on up. There you go. We blocked your stairs a little bit.

Kari Barrett:

Same place. You're next to Jill. Justin, Lisa, you're down here.

Susan C. Winckler:

No, no, no. No, you don't have to do this one. Yeah.

Dr. Justin Penzenstadler:

Hey Sam, do you want to switch?

Susan C. Winckler:

Justin, you're at [01:57:30] that end. You're at that end, unless Dr. Yanoff set that end?

Dr. Lisa Yanoff:

[inaudible 01:57:36].

Susan C. Winckler:

Oh, okay. That fine.

Kari Barrett:

So maybe ... If you don't mind-

Susan C. Winckler:

So this is where, you know, when you get on the airplane, we're back to your 747 standing. We've got a seat map, and then they all decided to change where they're sitting. So I'm just going to turn this way while they figure out where they're sitting, and then I will see from the other side where we are.

Kari Barrett:

All right, perfect.

Susan C. Winckler:

I'm [01:58:00] glad that you all agreed to adjust your chairs and sit elsewhere. Almost. Although we lost Andrew. We lost Andrew.

Speaker 2:

He just went to the restroom.

Susan C. Winckler:

Oh, well that's not allowed. Actually, it's just fine. All right. So are we all settled? Everybody have a microphone? Should each have your own. Yes. Excellent. [01:58:30] It'll turn on when we get to it. Now with the seat change, it just means that AV might take a little bit longer, but you should each have your own microphone, and they'll control it that way. Yeah, there we go.

Some of these people you've seen before. Some of them, you have not seen them on the stage yet. And so this is our panel where we want to reflect on the day, and I'll remind you that today's meeting is about shared learning. [01:59:00] It's not about regulatory decision making or making any sort of regulatory commitment, but I want to speak to the feedback that we want to gather now from our new faces who are all coming to us from FDA.

So Dr. Yanoff, I'm going to turn to you first.

Dr. Lisa Yanoff:

Is it ... Oh.

Susan C. Winckler:

Yep, it'll work. So in your role at the Office of New Drugs at FDA's Center for Drug Evaluation and Research, at least part of your daily activity is thinking about [01:59:30] the FDA requirements for approving a drug, including the benefit risk profile, which we heard a bit about. Would you give us a few thoughts on the evidence needed to navigate FDA review?

Dr. Lisa Yanoff:

Navigate a review or an approval?

Susan C. Winckler:

Well, a review because then that yields either approval or not, so yes.

Dr. Lisa Yanoff:

Well, it sounds like you're jumping into the NDA stage when we finally come in for a deal. And I think there's a-

Susan C. Winckler:

You can start earlier, it's just fine.

Dr. Lisa Yanoff:

Yeah. I think there's a lot to be learned in the earlier stages, and early engagement [02:00:00] is very important, and the IND stage might even be more important for this area because of the uncertainty and the development pathways and the endpoints and things. And once we get to the point of the review, hopefully everything's tied up. So that's our goal, by engaging early with stakeholders.

I've been asked to just kind of very briefly at a high level outline kind of the way to engage with FDA in case people don't know, and I'm sorry if this is redundant for a lot of people here. But [02:00:30] I mean, there's multiple mechanisms to engage with FDA. If you're an industry sponsor, and you have a specific drug, of course, you can come in with an IND, and we are happy to engage with you on your specific

product and ideas for development. And the way it works is there's a package that you submit, and there are specific questions that are asked. So it's a very targeted meeting. So you really have the ability to bring up ... [02:01:00] Typically, the questions should be appropriate for this stage of development so we wouldn't be getting into some of the endpoints until later, but all of these things that have been coming up today, we do have a mechanism to engage directly.

And even if you are not an industry with a new product and you are thinking about maybe repurposing an old product, you can still come in with an IND and talk to us, even if you don't necessarily have a patent on that product, so to speak. [02:01:30] And then there's another layer of that is if there's not really a specific product but you have more of a concept that you want to discuss, we also have mechanisms for that. I think one that comes to mind is CPM, critical path initiative meetings, where general concepts about endpoint developments or other regulatory interests can be brought to us for a general discussion. It can be multi-sponsor, multi-stakeholder, non-industry can be included. And, of course, now we have with Jeff, these new biomarker qualification [02:02:00] programs that is relatively new, and I know has had a rough start and there's some, I would say understandable concern about how long that first one took. I think that there's been a lot learned, and it's not going to be always like that way in the future.

Susan C. Winckler:

So that's great in reminding us that there are structures for agency interaction and sometimes I will hear from industry or others who [02:02:30] are like, "Well, we're not sure we want to talk to the FDA." And then sometimes they'll say, "Because we'll have to listen to them." Yes. Yes, indeed. Correct.

Dr. Lisa Yanoff:

You may not want to hear what we have to say.

Susan C. Winckler:

Yeah.

Lisa Yanoff:

I wish sometimes we'd be more willing to say we don't know. That's the other thing. Instead of skirting questions, "premature" is something that we say that a lot when we don't really know the answer. I think we need to do a little better and being upfront about what we know and what we don't know, and the [02:03:00] fact that, really, it's you all developing the science that we're reacting to, and it's really not the other way around.

Susan C. Winckler:

Right, right. Because your expertise is in the regulatory construct that you're applying to the science that's brought to you. Great. That's very helpful in just reminding us about opportunities to interact. So now let me turn to Dr. Pezenstadler, also in OND at CDER, I had to use some acronyms or people wouldn't believe it was an FDA meeting, but you are the acting associate [02:03:30] director in the office of cardiology, hematology, endocrinology, and nephrology. So building from Dr. Yanoff's baseline

information and then reflecting on today's discussion, what comes to mind for you? What insights would you share?

Dr. Justin Penzenstadler:

Sure, thanks. Dr. Yanoff is the big picture person. I'm the nuts and bolts. I've just gathered a few things from hearing folks today. First, I'm super encouraged by the discussions that are [02:04:00] regulatory focused or the regulatory considerations, like fields function survives. I haven't heard that discussed so much outside of an agency room ever. So I think that's very positive. I'm very encouraged with that, and also a consideration for biomarker validation and various aspects of that. I'm an optimist in this field. I think our [02:04:30] regulatory framework does exist, and I've heard that echoed from multiple people today. I think if we can identify ... Sandra had a point to this earlier. I think if you can identify a population clearly, very, very clearly identify a population, ascertain risks and benefits reliably using robust technology or trial methodology and so on, I don't see any impasse towards getting this across [02:05:00] the finish line.

Just a few, I want to go a little bit deeper into the nuts and bolts on endpoints here. I really agree. Listening to doctors Allison and ... Kritchevsky.

Susan C. Winckler:

Kritchevsky, yes.

Dr. Justin Penzenstadler:

Thank you. As a regulator, I always try to find things I disagree with. That's just how we operate. I couldn't find very much in their talks. I think their framing for [02:05:30] clinical endpoints was spot on. I think overall survival, I think disease or disability free survival, I think the hard endpoints are achievable and we've seen that with the proposed TAME study. So I think those are ready for prime time. I understand, I did hear a little hesitation that it doesn't actually represent longevity, right? Clinical endpoints and time [02:06:00] to event measures, hazard ratios and relative risks and things of that nature. Dr. Yanoff and I have dealt with this in the diabetes space, extrapolating hazard ratios for clinical endpoints to years of increased survival, lifespan and stuff and so on.

So I think there are model-based approaches to get where you really want to go, but using traditional clinical trial metrics that are well validated [02:06:30] and easily measurable. I do understand ... I'm checking my time. Sorry.

Susan C. Winckler:

That's okay. That's my job.

Dr. Justin Penzenstadler:

I do understand the attraction towards things such as the IC, survival heart endpoints. Those aren't often feasible for small biotech or for phase two studies. I get it. I understand. I heard something I really liked about the framing of the IC is that it is a face-valid endpoint. [02:07:00] As you consider developing

the IC, I think that should be your prime directive, not to bring Star Trek stuff in here. But really when you measure things that are face value fields, functions and survives, there's much less validation that's needed. And someone earlier mentioned bone mineral density, or you might know LDL, hypertension or blood pressure. Those are challenging [02:07:30] to validate, and they take years to validate. And often, you have to run the trials first to fully validate them. I think sticking to keeping the prime directive in the IC as things that directly measure fields function survives a great idea. And I also encourage folks to interface with the FDA to talk about these points. One more thing.

Susan C. Winckler:

Sure.

Dr. Justin Penzenstadler:

I'm hearing about a lot of repurposing [02:08:00] of drugs. I think ICH E19 is underutilized in this space. ICH E19 describes selective safety data collection. I do not think we need a Q3 month creatinine measurement for patients taking metformin with good renal function at baseline. Okay. Using these sort of selective [02:08:30] safety data approaches can remove logistical barriers and pragmatic barriers for folks considering developing these drugs. And I encourage folks to interface with the review divisions at FDA when they have a proposal ready. And I should stop there. Thank you all very much.

Susan C. Winckler:

Yeah, yeah. That was great. Thank you. And just so the ICH, international Conference on Harmonization, E19, which gets a bit at what you raised, Sandy, about safety and beyond well-tolerated, but what [02:09:00] do we know and what might we need to gather?

All right, our final new face for this panel, Dr. Siegel, you head up the Office of Drug Evaluation Science, which is in a different area in the review organization, but you focus on clinical outcome assessments and endpoint qualification. So tell us, what sparked your interest today?

Dr. Jeffrey Siegel:

So I heard a lot today that makes me very encouraged about the field. [02:09:30] I think that there have been advances in the last couple of years that really indicate there is a path forward for advancing the field. You mentioned that the office that I am office director for is in a different area than Dr. Yanoff and Dr. Pezenstadler. My office is also in the Office of New Drugs, but it oversees qualification of biomarkers and clinical outcome assessments [02:10:00] across all of the therapeutic areas in the office of new drugs. So let me discuss each of them in turn. I also thought intrinsic capacity was a promising way of evaluating potential benefit for a drug that can retard the aging process. The different domains that are incorporated in intrinsic capacity, cognition, mobility, sensory capacity [02:10:30] are all things that I think matter to patients. And in many ways they fit the paradigm that we have for developing clinical outcome assessments.

This is all described in the patient focused drug development guidance series, which recommends that to develop a clinical outcome measure, you want to interview patients with a disease or condition and find out all the ways that the disease impacts them, what matters to them about their condition. And

then you put together [02:11:00] a clinical outcome assessment that demonstrates that it can impact these things that matter to patients in their day-to-day lives. So you start with a meaningful aspect of health and then look at individual concepts of interest. Those would be the five domains in the intrinsic capacity, and then see how much of a change in the score represents something that would be a meaningful change for patients. So I think that was on the [02:11:30] right track. The difficulty is with clinical outcome assessments and biomarkers, we always look at the thing that's being measured and the concept of the COU, the-

Susan C. Winckler:

Context of use.

Dr. Jeffrey Siegel:

The context of use, so would be using the IC in a particular condition. And that's the situation that Sandy was pointing out, that we don't really know I know [02:12:00] exactly what that is. Once we have a definition of the condition or disease have a way of diagnosing it, understanding exactly what the population is it narrow or broad? Then we can understand how to make sure that intrinsic capacity really does measure something meaningful, and how much of a change would be important.

The other thing that I wanted to address development of biomarkers in this [02:12:30] area. We often use the term biomarkers in a very loose way. But biomarkers can be used in many different ways. One of the ways is to see if the drug hits the target. So if you have a drug that hits a particular signaling pathway, and you see less signaling there, then you know that the drug has hit the target.

Or if you know a mechanism of disease, and the biomarker represents that mechanism of disease, and it's impacted by [02:13:00] the treatment, it tells you something about whether you're impacting the mechanism of disease. So those are many different uses, but often what industry means when they talk about a biomarker is a surrogate endpoint. And to use a surrogate endpoint in drug development, you need to show that a change in the biomarker predicts a particular later clinical outcome. And it's going to be a long time before we get [02:13:30] there. In most situations, you need to have randomized clinical trial evidence showing that a particular change in the biomarker predicts a particular improvement in the later clinical outcome. I don't think that we have therapies that are effective yet to be able to do studies like that.

But nonetheless, you can assess whether your biomarker is on the causal pathway of disease. And [02:14:00] as we're learning more about what causes aging, what causes aging-related disorders, I think we can better understand whether a biomarker represents the causal pathway of disease. And if you have a treatment that impacts that biomarker, you may be able to say something about whether the drug is hitting the causal pathway of disease. When we try to correlate biomarkers [02:14:30] with later clinical outcomes, that's generally correlational evidence, and correlation does not indicate causality. But if you have a biomarker that's on the causal pathway of disease, that can help put an evidence package together that, together, can show that the drug is hitting something important in the disease process.

Susan C. Winckler:

Yeah. Very helpful. And particularly that reminder to make sure that we're thinking about biomarkers and surrogate endpoints and clinical outcome assessments in the right order, which I probably [02:15:00] didn't put them in the right order there, but I did hear you on those. So let's turn ... Dr. Fleming, welcome back to the stage. That's a great seat. I was there.

Dr. G. Alexander Fleming:

I'm right in the middle.

Susan C. Winckler:

Yeah, there you go. So we heard your thoughts earlier about multi-domain endpoints and some of the challenges that you think about as a former regulator. So reflect on the data as a whole, what would you highlight?

Dr. G. Alexander Fleming:

Well, I do think we understand that we've got to crawl before we [02:15:30] walk and before we run. And it will mean seeking approvals for disease indications to start with. But we can quickly, I hope, move towards less diseased or even non-disease populations. And frailty is a great example, or sarcopenia, of a stepping stone indication. It's a huge public health issue, frailty [02:16:00] and sarcopenia. And God knows we need effective interventions for that. And so let's go for those. And some of these agents will turn out to be candidates for actually preventing or reducing the risk of sarcopenia or frailty. And they may turn out, as Jeff has talked about, to be involved with mechanisms which are intertwined [02:16:30] with the pathogenesis of the disease. Let's call it the disorder. So it will be a process, a stepwise process, but one that we can relentlessly stay at. And by the way, you mentioned ICH, and I'm glad you did because I do believe this should be an ICH topic. This is not a US problem, obviously. It's a global problem, and we can move that much faster by collaborating [02:17:00] with other regulatory authorities and the emerging scientific communities outside the US. So I would put a pin on that idea to make this an ICH topic.

Susan C. Winckler:

Yeah. And I'll give Dr. Penzenstadler credit for that in saying, "Look at the ICH piece." But it sounds like you're seeing too this idea that there's a stepwise approach. There's steps we know to follow in the interaction with the agency, and [02:17:30] that there is a pathway for progress to be made. Okay. The two folks who we've spent a lot of time talking about the agenda for today and what it is that we're talking about. So Drs. Justice and Brack, you are facilitating efforts in this space every day and you're thinking about context for domain-specific intrinsic capacity composites as endpoints or other endpoints, biomarkers. We heard from your [02:18:00] PRIZE competitors and your awardees earlier today. Which one of you wants to jump in first with thoughts about what we should do next?

Dr. Jamie Justice:

Okay. I'm being told to go.

Susan C. Winckler:

All right.

Dr. Jamie Justice:

So we'll start here. First, again, just want to issue a huge, huge thank you is that it's great to be here and to hear some of the thoughts reflected. I too also think that Steve [inaudible 02:18:28] does no wrong. Steve was my [02:18:30] mentor for over 10 years, so I think I'm obliged to say that, and worked on some of those with him. And again, I'm really, really happy to see this. Again, I don't need to go on too much about the construct of the PRIZE. A few things that come out about this is, again, have been working in this space for some time and we're just using this as a model to create impact. Because we had no guidance, we've made some explicit choices, and some of those choices were actually making the decision to allow our teams to develop. [02:19:00] And so I think it's very much when we've sought guidance before, it was, "Well, proceed. Let the teams submit their own applications. They have to figure out their own context of use, their patient population, make sure they're making intelligent choices."

What's really reflected, I think as Sandy mentioned that earlier, is really thinking about safety, risk profile, doing all of the matching, and respect the teams and allow them the autonomy to do that and put those applications forward. But while also providing [02:19:30] certain structure and guidance so that we can build the longitudinal evidence base that's necessary. And I think that's one of the key aspects there. And so in developing that longitudinal database, what is really needed? And that we had to make some explicit choices, again, multi-domain endpoints, functional assessments being really important, composite constructs. I'm going to go through... We actually, in advance of this... Again, the competition is, it's a way to invite collaboration. [02:20:00] And so we allow the teams, our advisors, our judges, our partners to be part of the conversation. Building up to this meeting, we did, within our PRIZE ecosystem, ran a modified Delphi consensus process.

So we had a survey that went out. It's actually still in process. It'll go out beyond the PRIZE community after this meeting. But just with our teams and some of our key senior investigators in the competition, we had about median of 20 years experience. These are actually [02:20:30] from 17 countries. So again, very much global. We actually have 73 countries represented in the competition, so there's a pretty good pool to choose from. But those that completed the survey, they're really talking about regulatory frameworks. And I just want to pull out a couple of signals from that. It's in progress, so these were not on slides earlier. About 90% of our senior investigators respondents reject an aging as disease classification. So I think that's a good start. We also had about [02:21:00] identical right around 90% that endorsed a functional non-disease framework centered on measurable biologic and functional decline or intrinsic capacity.

So again, that's a signal, a readout that we're getting. 87% of our respondents identified the absence of an FDA or regulatory approved surrogate endpoint as the single most significant regulatory barrier. So not funding, not alternative trial designs, is that really looking for partnership on what [02:21:30] endpoints and what pathways could be approached. So I thought that was great. And about 85% have requested a formal multi-stakeholder working group to be convened as a potential pathway. And back to the international perspective, that they also wanted to include within that multi-stakeholder group was an international perspective. Probably not surprising because we're global. Of course, we're going to get that from both folks close to the PMDA and EMA as well.

Now onto a couple of endpoints. [02:22:00] Again, using my scientists, the folks around us, I'm going to start because again, we're prioritizing early stage trials. So these are really these phase two trials. And so I'm going to start with some endpoints around that. And when we queried our groups around this, what's important to our scientists as trialists, 96% said immune function and inflammation biomarkers as being very important constructs. Physical [02:22:30] performance and mobility at 92% agreement. Cognitive assessment at 84% agreement. Right around 70 to 75% agreement were intrinsic capacity as a composite or wearable digital biomarkers.

And so those are important call-outs because they had zero or non-zero disagreement across all five of those as potentially important as secondary endpoints for large scale trials or as important for early stage phase one, phase two trial [02:23:00] readouts. For phase three primary endpoints, which again, if we're going into this, those are great early reads, no go, no signals for developers, but for a phase three primary endpoint, our group was clear. They actually came in at 76% lowest disagreement on a phase three endpoint was around time to disability or time to new disease, closer to that [inaudible 02:23:27] end point.

So I thought that was also really telling. [02:23:30] Intrinsic capacity was also a strong leader with 72% support. All of those had very low levels of disagreement, which is also critical. And so the field, I would say, outside of that and the open-ended responses, they're explicitly comfortable with composite functional constructs as the locus of regulatory and clinical decision making. It's an open question about where do we go from here and again, what is missing [02:24:00] from that survey that I had was patient voice. I think that's a very strong consideration of what's meaningful to people, not just what's meaningful to scientists and drug developers.

And a couple of things around what the field rejects. There was a lot of strong opinions on both sides around mortality as a primary endpoint. In our current survey, only about 32% support mortality as the primary endpoint. But again, I think there needs to be deeper study on why. And second is [02:24:30] that there was some concern about using things like an epigenetic clock as a single biomarker with only about 50% support for that as a lot of respondents had caution about over-reliance on circuit biomarkers in the absence of functional validation.

So again, I think that these are some critical concerns. And they're not concerns. I think they're really important. They contribute to a larger conversation that's really part of my ask today is that as a steward to this group and to this work, we know that biomarker qualification takes time. That's not a problem [02:25:00] and it's not a criticism. It just talks about sequencing and what's needed. And so that means we need to build the functional endpoint infrastructure and do the biomarker development with longitudinal data sets and work on it together now so that we have approval pathways that can rest on solid ground when we're ready to move forward. And I think that's what Andrew and I are both here really petitioning and working on. We have tandem programs. We have a lot of momentum. We can partner with folks at NIH and other locations.

Evolution has been a huge supporter of this globally [02:25:30] as well, is to think about how do we drive this forward? And so a couple of asks just based on the feedback from our group would be, again, as I would love to find a pathway towards a formal multi-stakeholder convening, to think about the evidentiary requirements for health span and aging as an approvable non-disease indication perhaps, and what that might look like. I don't have the answer, but I'd like to work towards it. And then two, I would love to see a workshop, again, not [02:26:00] just those stakeholder work group, but also a workshop to think about those clinically meaningful multi-domain endpoints and what they are, and

then how do we develop surrogates or biomarkers around those Because really I think our perspective is that it's not whether the field is ready, the field's ready for in testing. The real question is whether the regulatory infrastructure gets built in parallel or if we have to work afterwards to retrofit. And I think that's a situation none of us really want.

Susan C. Winckler:

Well, and I think we've heard too from the regulatory perspective, there are ways to have [02:26:30] the discreet conversations-

Dr. Jamie Justice:

Absolutely.

Susan C. Winckler:

... and then figure out broader conversations that might be helpful for that shared learning.

Dr. Jamie Justice:

Yeah. And our teams, the discrete questions are going to be coming from the teams. If they have not started submitting, they will be.

Susan C. Winckler:

Yeah. And actually Dr. Siegel wanted to jump in here, Andrew. Yeah. Yeah.

Dr. Jeffrey Siegel:

Yeah. I just wanted to make a comment in that regard. So it's important to understand that the biomarker qualification program and the clinical outcome assessment qualification program [02:27:00] are in a separate area than the clinical review divisions, but we work hand in glove with them. We don't ever make a decision about something without bringing in our colleagues from the clinical review division. And in particular, I could think of two examples where biomarkers went forward more quickly because there was a push from the review division to move forward with them. One example is osteoporosis and qualifying bone mineral density as a validated surrogate [02:27:30] endpoint. It did take a long time to qualify that. A lot of that had to do with getting the data, but there was full support from the review division, so that made it very easy for us to help move the project forward.

The other example is for MASH. The approvable endpoint now is a reasonably likely surrogate endpoint, which is improvement in liver histopathology. This is metabolic disorder-associated steatohepatitis. And the review division felt that there was a need [02:28:00] for non-invasive tests, so patients wouldn't have to undergo liver biopsy multiple times. That would allow larger trials to happen more easily. So we put out a paper together about the process that would be required to qualify a non-invasive test as a reasonably likely surrogate endpoints. And now we have two submissions in the ISTAND program for proposals for recently likely surrogate endpoints for MASH. I think a similar paradigm might work here.

[02:28:30] Once there's agreement on what the disease is, what the disorder is, then we can begin to have discussions about clinical endpoints and biomarkers.

Susan C. Winckler:

Yeah, go ahead, Dr. Yanoff. Yeah, that's all right.

Dr. Lisa Yanoff:

I also want to emphasize that it doesn't have to be a one size fits all.

Susan C. Winckler:

Yeah. Mm-hmm. Mm-hmm.

Dr. Lisa Yanoff:

I'll give you a secret how the sausage is made. Companies come in with specific questions, with a proposal, and we are [02:29:00] given a set amount of time based on FADUFA to respond. And in my experience, that is what moves things forward the fastest. I've heard a lot about public... I support all the ideas of general consensus and international meetings and public workshops, and I even heard the word perfect. We haven't found the perfect endpoint.

Susan C. Winckler:

Anything. Right.

Dr. Lisa Yanoff:

And I don't think that's what FDA [02:29:30] is expecting.

Susan C. Winckler:

Right.

Dr. Lisa Yanoff:

The perfect... I think if you come in with proposal and you make a reasonable justification, you'd be surprised at how often you're going to get a yes. And somebody's got to start, right? And then we have precedent and then the next person, the next sponsor benefits from the work that the first sponsor did. I think sponsors in general are not necessarily always collaborative, right? There's competition.

Susan C. Winckler:

Right.

Dr. Lisa Yanoff:

And I haven't seen a lot of areas where [02:30:00] the first thing sponsors wants to do is join together, share all their secrets and all their data and come up with something everybody else can use, right? So... What?

Susan C. Winckler:

Well, but I think that's part of what both XPRIZE and ARPA-H are trying to flip that on its head a bit.

Dr. Lisa Yanoff:

So that is a huge endeavor and very important, but we are not waiting for that.

Susan C. Winckler:

Right.

Dr. Lisa Yanoff:

We want you to come talk to us now.

Susan C. Winckler:

Yeah. Yeah. That's [02:30:30] a very helpful reminder about the user fee clocks and what drives some of the interaction. And that it's probably, if I may, a combination of the discrete sponsor requests that drive agency response and the broader efforts that are supporting that. Okay. Andrew, now you may go.

Dr. Andrew Brack:

Thank you. This has been a great discussion. So if I reflect on the day and what PROSPR is trying to build, we're trying to be that convening [02:31:00] force to build that data, because in the absence of data, it's all speculative. And so we thought we're betting on intrinsic capacity because it's face validity, build the data sets to say, "Here's our case that'll be presented by the performers and the team." And so that's what we think about when we build PROSPR. The drugs, the intervenability is all a case to make that this could be an endpoint of clinical relevance for the health span. Now healthspan is broad, and to Sandy's point, no one's [02:31:30] going to give us a label for a decrease in healthspan. So we talk about thresholds. So what threshold is meaningful? 20%, 30%, because we can get to that, which says, "At 30%, my risk of diseases increases." John Beard has already got that data. And now can we intervene in it? So what would that look like? It's still not health span. It is in the case of frailty or sarcopenia, threshold of intrinsic capacity has been reached.

We could reach for that. That could be an endpoint. It could [02:32:00] also be a prescribed drug for that if you can now revert it. So we're thinking about this intrinsic capacity as our North Star, but in bite size stepping stones, I think, to use Zan's phrase. And so I really think the point was made of frailty. So frailty is associated with low intrinsic capacity. It's also a serious condition with an unmet need. That's a path to an accelerated approval. And so now we're using the language of intrinsic capacity with [02:32:30] a relatively short space of time. I'm ideating here, by the way, if you haven't noticed. And so why is that relevant? Well, frail people have a five-year survival rate that matches ovarian cancer, about 40%. So

there's your mortality experiment. And I would take a point that with drugs of frailty, it's not going to be the same as healthspan.

Diabetes prevention is exercise and diet. Diabetes reversal is insulin. It's a drug. So [02:33:00] I would not assume one drug that fits early health span versus frailty are going to be the same. Different experiments, different intrinsic capacity thresholds. But that's the way we're thinking about this with bite size pieces towards that gold star, towards that moon, that North Star. I do think digital measures, we need to improve so much more on that, how we can predict a meaningful improvement. And part of the decentralized trial through PROSPR will get us there. We don't need to get a validation, but we'll be able to [02:33:30] correlate that with drug responsiveness.

And finally, I'd like to make the point that we've gone all in on PROSPR. And it seems, in this room at least and maybe on virtually, that people are excited about this. To consider putting this into all your trials that you're running as an exploratory endpoint, it's going to take a village. It took 10 years for BMD. So we think about putting this money in for five years, we're going to make rapid progress, large scale studies, but everyone out there, put IC in your exploratory endpoint, you're running [02:34:00] a trial. It could be after kidney transplant and recovery. How long does it take my IC to restore? As David mentioned, people, when they have a fall, you get nervous. So what if intrinsic capacity to say, "You're good to go back into the gym now?" Things like that. So a way to score recovery and back to vitality, back to meaningful workplace. I will leave it there. [inaudible 02:34:29]

Susan C. Winckler:

Lots of [02:34:30] ideating, which is very helpful. Jill, I am not going to ask you about adding IC to all of your trials, but I do want to come back to you. We haven't forgotten you, but you're a primary user of all of this information, right? You take things to the agency, you work in this ecosystem. So what do you see as a primary area for follow up, recognizing there are some things you'll need to go alone, some things where you might collaborate, but help [02:35:00] us weave some of that together.

Jill Lee:

Yeah. I mean, it's exactly those things. I mean, I think there's things we can definitely take back and think about how we're designing our trials, what are we including as exploratory endpoints, functional endpoints, intrinsic capacity in terms of how we can start generating that data to develop that body of evidence. And then I do think it is continuing to engage in the broader conversation around how we can move these composite endpoints or these new endpoints forward. And I do think even from a sponsor perspective, we do recognize [02:35:30] something like this is going to take collaboration with other stakeholders, and it is something that we'll have to make sure that we're continuing in that dialogue, but absolutely I think there's a lot to take back. I think I'm definitely heartened by some of the directions or some of the potential for certain directions, especially when it comes to these new endpoints, certainly around functional endpoints also. That's something that we can certainly include pretty easily as exploratory endpoints and trials. So [02:36:00] definitely lots to think about and take back, and things that we could potentially do.

Susan C. Winckler:

Very helpful. And to your point, we recognize sometimes that will be individual conversations with the regulator in the structured manner, and then sometimes it's the broader conversations where there can be collaboration. So I want to open this up a little bit more for back and forth, which thankfully you already started. That's exactly what we want to do there. But recognizing there's [02:36:30] some places where collaboration works and some places where coming to the agency is a one by one enterprise, are there spaces where you think that the collaboration has the greatest impact? Andrew, I think you already put the marker down that's saying, can we work on these endpoints? Jamie, you added into it with gathering the expert opinion. And that expert opinion will be published later in the year?

Dr. Jamie Justice:

Yes. Yeah.

Susan C. Winckler:

Yes.

Dr. Jamie Justice:

It's in [02:37:00] progress. We're going to send out the Delphi survey. It's going to go out again to a larger pool of participants. So not just our teams, but we need more perspective.

Susan C. Winckler:

Okay.

Dr. Jamie Justice:

And then it will come forward.

Susan C. Winckler:

Yeah. So thoughts on where collaboration, beyond that, where is collaboration helpful? Lisa, go ahead. Yeah.

Dr. Lisa Yanoff:

Probably in areas where there is no universal, to use Dr. Allison's term, no universal accepted criteria for a disease. That's where FDA isn't really... We were happy to participate in the conversations, [02:37:30] but we really can't be the only ones there giving sponsors recommendations of what we want, how we want them to define diseases. We can say if you do a test of six minute walk, and VO2 max, and some cognitive test, then we can give you a label that says this drug is indicated to improve VO2 max, [inaudible 02:37:57] six minute walk and cognitive, but [02:38:00] we're not going to go ahead and call that aging in a vacuum.

Susan C. Winckler:

Right.

Dr. Lisa Yanoff:

So that's where I think it's...

Susan C. Winckler:

Yeah, that's helpful.

Speaker:

Sorry to jump in, Lisa, but-

Susan C. Winckler:

So just... Yep. I need you to write it down just because for the microphone and everything else.

Speaker:

I'll write down something [inaudible 02:38:20]

Susan C. Winckler:

Yes.

Speaker: Okay. I will-

Susan C. Winckler:

Yeah. Sorry. Sorry. It just helps with the recording because we do a recording and a transcript and the virtual audience.

Dr. Lisa Yanoff:

[02:38:30] Who was bringing up sarcopenia?

Susan C. Winckler:

Ah, yes. So that's come up a couple of times.

Dr. Lisa Yanoff: That was a good one where I think for... I don't even know if there's still a unified definition of sarcopenia, but that's one where I think FDA has been well involved in the conversations.

Susan C. Winckler:

Yes.

Dr. Lisa Yanoff:

So that's a good example of where we're not there, but we're close enough where we have meaningful input to provide. And I think some of this stuff is so in the basic science realm still that I'm not sure where FDA fits in.

Susan C. Winckler:

[02:39:00] Yeah. Yeah. Other thoughts? Jamie, I think your piece there. Yes, go ahead, Jeff.

Dr. Jeffrey Siegel:

So the question is about areas where cooperative ventures would be helpful.

Susan C. Winckler:

Yes.

Dr. Jeffrey Siegel:

So the one that comes to mind for me is collaborating on longitudinal epidemiologic studies where you follow patients over time, perhaps collect biomarkers to see how they change over time, and then see occurrence of particular [02:39:30] clinical outcome events and see what predicts them and how they progress over time. In the MASH space, there are several groups who've collected multi-year data relating liver stiffness, for example, to liver related outcomes like cirrhosis and varices and so on. And those data are going to be essential for qualifying liver stiffness potentially [02:40:00] as a reasonably likely surrogate for MASH. I think similar studies in the aging space could serve the same purpose, but it means coming together and pooling resources to conduct such a study.

Susan C. Winckler:

Yeah. Yeah. Zan or Jill, anything you want to add in that space? Or Justin?

Dr. G. Alexander Fleming:

Well, I think it brings us back to the very first question that came up today and that is if we had an agent that could slow [02:40:30] the aging process with some kind of associated benefit, how would we know it? And that really is our predicament because it takes time and lots of resources to be able to measure that benefit in a larger population, particularly one that doesn't have disease yet. And so that's really going to be an ongoing challenge with a lot of devil in the details. The technology just for [02:41:00] measuring some kind of benefit in a large population, something you could do with a cell phone, for example, if we could imagine a trial of a hundred thousand people, relatively healthy people with a cell phone based endpoint, well, that sounds pretty farfetched, but that's one kind of approach we should be visualizing.

How would we bring that off? What kind of [02:41:30] technology would be convincing to experts both at FDA and outside that it's a meaningful benefit, and that the product can be shown to be safe and effective in that large simple trial setting.

Susan C. Winckler:

Yeah. That sounds like an excellent opportunity for that collaboration. So I'll reflect, and we had a little bit of laughter when Lisa, you said you could approve [02:42:00] something that was a key endpoint like around VO2 max or something else. And the question that came in is some companies might be happy with that. Does a happy company make... Is that a possibility?

Dr. Justin Penzenstadler:

I got this. That would be a review issue.

Susan C. Winckler:

There you go. Well said. Well said. Well said. Yeah.

Dr. Lisa Yanoff:

[02:42:30] Happy as in accepting of that advice? Yes, absolutely. I think that we have some experience in companies who do want a claim for something broad like aging, and the one that comes to mind is cachexia. And we are working to figure out how to consider multifactorial [02:43:00] diseases don't really have a clear definition. And the best we've come up with is similar to where you were going, Zan, is to get an indication for cachexia, you need to show that you're affecting multiple aspects of the disease. You're affecting appetite, you're affecting body weight, you're affecting some functional capacity that's making a difference to patients. [02:43:30] The only reason we get caught up in the details is because we're regulators just as much as we're scientists.

Susan C. Winckler:

Right. Right. And details matter.

Dr. Lisa Yanoff:

And details matter, especially when it comes to competition among industry. And if you did a study and you only looked at body weight, and somebody else did a study and looked at body weight and appetite and functional capacity, and you both got a claim for cachexia, how would you feel if you were the one that did all the work? [02:44:00] We try to be fair. We try to treat similarly situated sponsors fairly and make sure that the playing field is fair in terms of drug development, and transparent that what the claim you're getting is supported by data, and that the claim is extremely clear about what the data are showing that the benefit is.

Susan C. Winckler:

And that clarity is helpful then for patients and clinicians who are then using [02:44:30] an approved product in what is it that they might expect as an effect. Yeah. Okay. So we have time for a lightning round, which for that I am actually looking for a response of less than a minute from each of you. And I will... Actually, let me give you the question, then I'll give you the order because it gives you time to think about it. The question. What is the single word, phrase, or concept you want people to remember from today? So we'll [02:45:00] go Brack, Lee, Yanoff, Justice, Penzenstadler, Siegel, Fleming. So Brack, Lee, Yanoff.

Dr. Andrew Brack:

Age associated decline in intrinsic capacity.

Susan C. Winckler:

Okay. Lee. Well, excellent brevity, however. What's this-

Jill Lee:

Repeat the question one more time.

Susan C. Winckler:

Yes. The single word, phrase or concept you want folks to remember from today? It's all right. [02:45:30] She's got a minute and a half. You ceded your time.

Jill Lee:

Practical next steps in moving forward in gerotherapeutics.

Susan C. Winckler:

Excellent. Yanoff, Justice, Penzenstadler. So Dr. Yanoff.

Dr. Lisa Yanoff:

Our ultimate goal is a benefit risk assessment and that involves a lot more than evaluating a PD effect and whether something has an effect on aging, but the whole picture and what we're doing to help patients.

Susan C. Winckler:

Brilliant. Justice, Penzenstadler, [02:46:00] Siegel.

Dr. Jamie Justice:

Okay. My word is proactive. So again, I think being proactive, I think it's multifaceted. So we're used to developing and thinking about drugs and we're thinking about diseases and treating things once they're

here. I think a theme that went throughout, even though it was mentioned that it was only brought up a couple of times is prevention, and so alternative solutions. And so I think that's really where we're at is we're thinking about, what proactive solutions can we use? [02:46:30] How do we embrace this? How do we not use, just try to retrofit old data sets, but actually look proactively about how do we define, how do we test, what do we do? How do we build these longitudinal data sets and endpoints together? So again, I would say proactive.

Susan C. Winckler:

All right. Penzenstadler, Siegel, Fleming. Yes.

Dr. Justin Penzenstadler:

Focus on the patient. Feels, functions, survives.

Susan C. Winckler:

We'll highlight that in the slide deck as well. [02:47:00] Siegel, Fleming.

Dr. Jeffrey Siegel:

So Justin anticipated what I was going to say. I think that the focus on the patient is the most important thing. And in the end, patients care about how they feel, function, and survive. But that doesn't mean that biomarkers aren't important, but the biomarkers should predict or reflect the way patients function, feel, or survive.

Susan C. Winckler:

Excellent. Zan, you get the last word.

Dr. G. Alexander Fleming:

I love it. After all, it's people who don't want to be patients [02:47:30] that we're ultimately working for and they want evidence that the product works and is safe.

Susan C. Winckler:

Yeah. So as you've all spoken about, are we listening to the individuals and what is it that they're looking for that we can have something in the feel, function, survive and an endpoint that matters that's safe? Yes. Thank you for the reminder earlier. All right. Let's thank this panel for that excellent [02:48:00] reflection, and I'll just note thanks to everyone in the room and online. The recording transcript and slide deck will be posted at Reaganudall.org next week. Thank you all so much. Take care and be well.

Adjourn